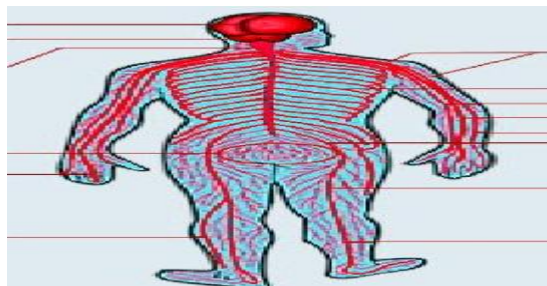




INTRODUCTION TO HUMAN PHYSIOLOGY FOR MEDICAL STUDENTS



By

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Preface

With recent advances in the field of human physiology, it has become urgent to provide an up to date review in the subject of human physiology.

This book to help medical student in understanding modern human physiology. It presents the whole subject in brief comprehensive and up to date form.

I hope this book will be a real help to undergraduate medical students, as well as to postgraduate and candidates of higher degree, in the field of human physiology.

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**Contents**

No.	Title	Pages
1	Chapter I General Principles in Medical Physiology	7
2	Systems of human body include	12
3	Types of transportation through cell membrane	14
4	Chapter II Physiological Organization of Autonomic Nervous System	15
5	Functions of ANS	19
6	Receptors	22
7	Resting membrane potential[RMP]	24
8	Neuromuscular transmission	28
9	Chapter III Physiology of muscle	31
10	General mechanism of muscle contraction	33
11	Excitation- contraction coupling:	36
12	Properties of Neuro-muscular Transmission(N . M .T)	36
13	Molecular mechanism of muscle contraction	43
14	Simple muscle twitch and factors affecting it	46
15	Chapter IV Blood, Immunity and Lymph	54
16	The function of the blood as a tissue:	54
17	Plasma	55
18	Anemia	58
19	Haematostasis	63
20	The mechanism of blood coagulation	63
21	White blood cells	66
22	Immunity	68
23	Chapter V Cardiovascular system	71
24	CELLULAR EVENTS OF THE HEART	72
25	THE HEART AS A PUMP	76
26	CARDIC CYCLE	78
27	The Electrical activity of the heart and the ECG	81
28	The control of the cardiac output	84
29	Cardiac arrhythmias	87
30	Pressure and flow in systemic circulation	93
31	Cardiac reserve	97
32	Special circulations	102
33	Edema	107
34	CHAPTER VI RESPIRATORY SYSTEM	110
35	Pressure-Volume relationship in the respiratory tract	113
36	Surfactant	114
37	Neural Control of Breathing	118



38	Gas Diffusion & Blood flow to the lungs	120
39	Physiological significance of the oxyhemoglobin dissociation curve:	123
40	The transport of CO ₂ in the blood	124
41	Chemical control of Breathing	126
42	HYPOXIA	130
43	CHAPTER VII KIDNEY	133
44	Renal Blood Supply	137
45	Mechanisms of autoregulation of renal blood flow	139
46	Renal function: Glomerular filtration and its control	142
47	Glomerular Filtration	143
48	Renal function	146
49	Na ⁺ reabsorption in the different segments of the renal tubule	150
50	Plasma clearance	154
51	Regulation of renal water excretion	157
52	Role of the kidney in long term regulation of arterial blood pressure	158
53	Counter current system	160
54	Physiology of Micturition	162
55	CHAPTER VIII DIGESTIVE SYSTEM	166
56	Function of Saliva	168
57	Hormonal Regulation of GIT	170
58	Vomiting	172
59	GIT Secretion	173
60	Physiology of THE GALL BLADDER & PANCREAS	175
61	PHYSIOLOGY OF THE LARGE INTESTINE	176
62	GIT Hormones	177
63	CHAPTER IX Endocrinology	180
64	Hypothalamic Hormones	184
65	Feedback control of hormone secretion	186
66	Anterior pituitary hormones	187
67	Disturbances of GH function	189
68	ADH: Vasopressin	191
69	Physiology of Thyroid Hormones	192
70	The Physiology of the Adrenals gland	195
71	Physiology action of cortisol	196
72	Actions of Aldosterone	198
73	Role of estrogen on growth of breast ductal system	201
74	Hypothalamic Control of Prolactin Secretion	202
75	Functions of oxytocin	204
76	The Physiology of Pancreatic Hormones	204



77	Physiological effects of insulin	205
78	Glucagon and Its Functions	208
79	Somatostatin Inhibits Glucagon and Insulin Secretion	210
80	Diabetes mellitus	211
81	CHAPTER X Reproduction	213
82	Male Reproductive System	214
83	Congenital abnormalities	216
84	Placental Functions Diffusion of nutrients	217
85	Puberty	218
86	Progesterone	220
87	The Ovarian (reproductive)Cycle	222
88	physiological control of ovarian hormones	223
89	Parturition(Labor)	227
90	Lactation	228
91	Menopause	230
92	CHAPTER XI CENTRAL NERVOUS SYSTEM	232
93	Thalamus	235
94	Sensory areas (cortex)	235
95	Physiology of the eye (Anterior chamber accommodation)	238
96	Accommodation	240
97	physiological role of the external and middle ear	245
98	Functions of the Middle Ear in Hearing	246
99	SYNAPTIC TRANSMISSION	248
100	Role of the Brain Stem in Controlling Motor Function	252
101	Types of the Stretch reflex	255
102	Neural connections of basal ganglia Functionally important pathways	259
103	Division of the cerebellum	261
104	Vertigo	264
105	Limbic system	265
106	Reticular activating system(RAS)	266
107	physiology of the speech	267
108	Aphasia	268
109	Functions of the hypothalamus	269
110	PHYSIOLOGY OF SLEEP	270
111	Mechanisms of sleep	272
112	Cognitive function of the brain	272
118	CHAPTER XII Skin and Immunity	280
119	Immunity	281
120	References	282

Chapter I



General Principles in Medical Physiology

In unicellular organisms, all vital processes occur in a single cell. As the evolution of multicellular organisms has progressed, various cell groups organized into tissues and organs have taken over particular functions. In humans and other vertebrate animals, the specialized cell groups include a gastrointestinal system to digest and absorb food; a respiratory system to take up O₂ and eliminate CO₂; a urinary system to remove wastes; a cardiovascular system to distribute nutrients, O₂, and the products of metabolism; a reproductive system to perpetuate the species; and nervous and endocrine systems to coordinate and integrate the functions of the other systems. This book is concerned with the way these systems function and the way each contributes to the functions of the body as a whole.

In this section, general concepts and biophysical and biochemical principles that are basic to the function of all the systems are presented. In the first chapter, the focus is on review of basic biophysical and biochemical principles and the introduction of the molecular building blocks that contribute to cellular physiology. In the second chapter, a review of basic cellular morphology and physiology is presented. In the third chapter, the process of immunity and inflammation, and their link to physiology, are considered.

General Principles

The Body as an Organized "Solution"

The cells that make up the bodies of all but the simplest multicellular animals, both aquatic and terrestrial, exist in an "internal sea" of extracellular fluid (ECF) enclosed within the integument of the animal. From this fluid, the cells take up O₂ and nutrients; into it, they discharge metabolic waste products. The ECF is more dilute than present-day seawater, but its composition closely resembles that of the primordial oceans in which, presumably, all life originated.

In animals with a closed vascular system, the ECF is divided into two components: the interstitial fluid and the circulating blood plasma. The plasma and the cellular elements of the blood, principally red blood cells, fill the vascular system, and together they constitute the total blood volume. The interstitial fluid is that part of the ECF that is outside the vascular system, bathing the cells. The special fluids considered together as transcellular fluids are discussed in the following text. About a third of the total body water is extracellular; the remaining two thirds is intracellular (intracellular fluid). In the average young adult male, 18% of the body weight is protein and related substances, 7% is mineral, and 15% is fat. The remaining 60% is water. The distribution of this water The intracellular component of the body water accounts for about 40% of body weight and the extracellular component for about 20%. Approximately 25% of the extracellular component is in the vascular system (plasma = 5% of body weight) and 75% outside the blood vessels (interstitial fluid = 15% of body weight). The total blood volume is about 8% of body weight. Flow between these compartments is tightly regulated.

Units for Measuring Concentration of Solutes

In considering the effects of various physiologically important substances and the interactions between them, the number of molecules, electric charges, or particles of a substance per unit volume of a particular body fluid are often more meaningful than simply the weight of the substance per unit volume. For this reason, physiological concentrations are frequently expressed in moles, equivalents, or osmoles.

Moles

A mole is the gram-molecular weight of a substance, ie, the molecular weight of the substance in grams. Each mole (mol) consists of 6.022 × 10²³ molecules. The millimole (mmol) is 1/1000 of a mole, and the micromole (μmol) is 1/1,000,000 of a mole. Thus, 1 mol of NaCl = 23 g + 35.5 g = 58.5 g, and 1 mmol = 58.5 mg. The mole is the standard unit for expressing the amount of substances in the SI unit system.

The molecular weight of a substance is the ratio of the mass of one molecule of the substance to the mass of one twelfth the mass of an atom of carbon-12. Because molecular weight is a ratio, it is dimensionless. The dalton (Da) is a unit of mass equal to one twelfth the mass of an atom of carbon-12. The kilodalton (kDa = 1000 Da) is a useful unit for expressing the molecular mass of proteins. Thus, for example, one can speak of a 64-kDa protein or state that the molecular mass of the protein is 64,000 Da. However, because molecular weight is a dimensionless ratio, it is incorrect to say that the molecular weight of the protein is 64 kDa.

Equivalents

The concept of electrical equivalence is important in physiology because many of the solutes in the body are in the form of charged particles. One equivalent (eq) is 1 mol of an ionized substance divided by its valence. One mole of NaCl dissociates into 1 eq of Na⁺ and 1 eq of Cl⁻. One equivalent of Na⁺ = 23 g, but 1 eq of Ca²⁺ = 40 g/2 = 20 g. The milliequivalent (meq) is 1/1000 of 1 eq. Electrical equivalence is not necessarily the same as chemical equivalence. A gram equivalent is the weight of a substance that is chemically equivalent to 8.000 g of oxygen. The normality (N) of a solution is the number of gram equivalents in 1 liter. A 1 N solution of hydrochloric acid contains both H⁺ (1 g) and Cl⁻ (35.5 g) equivalents, = (1 g + 35.5 g)/L = 36.5 g/L.

Water, Electrolytes, Acid/Base

The water molecule (H₂O) is an ideal solvent for physiological reactions. H₂O has a dipole moment where oxygen slightly pulls away electrons from the hydrogen atoms and creates a charge separation that makes the molecule polar. This allows water to dissolve a



variety of charged atoms and molecules. It also allows the H₂O molecule to interact with other H₂O molecules via hydrogen bonding. The resultant hydrogen bond network in water allows for several key properties in physiology: (1) water has a high surface tension, (2) water has a high heat of vaporization and heat capacity, and (3) water has a high dielectric constant. In layman's terms, H₂O is an excellent biological fluid that serves as a solute; it provides optimal heat transfer and conduction of current.

Electrolytes (eg, NaCl) are molecules that dissociate in water to their cation (Na⁺) and anion (Cl⁻) equivalents. Because of the net charge on water molecules, these electrolytes tend not to reassociate in water. There are many important electrolytes in physiology, notably Na⁺, K⁺, Ca²⁺, Mg²⁺, Cl⁻, and HCO₃⁻. It is important to note that electrolytes and other charged compounds (eg, proteins) are unevenly distributed in the body fluids pH and Buffering

The maintenance of a stable hydrogen ion concentration ([H⁺]) in body fluids is essential to life. The pH of a solution is defined as the logarithm to the base 10 of the reciprocal of the H⁺ concentration ([H⁺]), ie, the negative logarithm of the [H⁺]. The pH of water at 25 °C, in which H⁺ and OH⁻ ions are present in equal numbers, is 7.0

For each pH unit less than 7.0, the [H⁺] is increased tenfold; for each pH unit above 7.0, it is decreased tenfold. In the plasma of healthy individuals, pH is slightly alkaline, maintained in the narrow range of 7.35 to 7.45. Conversely, gastric fluid pH can be quite acidic (on the order of 2.0) and pancreatic secretions can be quite alkaline (on the order of 8.0). Enzymatic activity and protein structure are frequently sensitive to pH; in any given body or cellular compartment, pH is maintained to allow for maximal enzyme/protein efficiency.

Molecules that act as H⁺ donors in solution are considered acids, while those that tend to remove H⁺ from solutions are considered bases. Strong acids (eg, HCl) or bases (eg, NaOH) dissociate completely in water and thus can most change the [H⁺] in solution. In physiological compounds, most acids or bases are considered "weak," that is, they contribute relatively few H⁺ or take away relatively few H⁺ from solution. Body pH is stabilized by the buffering capacity of the body fluids. A buffer is a substance that has the ability to bind or release H⁺ in solution, thus keeping the pH of the solution relatively constant despite the addition of considerable quantities of acid or base. Of course there are a number of buffers at work in biological fluids at any given time. All buffer pairs in a homogenous solution are in equilibrium with the same [H⁺]; this is known as the isohydric principle. One outcome of this principle is that by assaying a single buffer system, we can understand a great deal about all of the biological buffers in that system.

Diffusion

Diffusion is the process by which a gas or a substance in a solution expands, because of the motion of its particles, to fill all the available volume. The particles (molecules or atoms) of a substance dissolved in a solvent are in continuous random movement. A given particle is equally likely to move into or out of an area in which it is present in high concentration. Osmosis

When a substance is dissolved in water, the concentration of water molecules in the solution is less than that in pure water, because the addition of solute to water results in a solution that occupies a greater volume than does the water alone. If the solution is placed on one side of a membrane that is permeable to water but not to the solute, and an equal volume of water is placed on the other, water molecules diffuse down their concentration (chemical) gradient into the solution Osmolal Concentration of Plasma: Tonicity

The freezing point of normal human plasma averages -0.54 C, which corresponds to an osmolal concentration in plasma of 290 mOsm/L. This is equivalent to an osmotic pressure against pure water of 7.3 atm. The osmolality might be expected to be higher than this, because the sum of all the cation and anion equivalents in plasma is over 300. It is not this high because plasma is not an ideal solution and ionic interactions reduce the number of particles free to exert an osmotic effect. Except when there has been insufficient time after a sudden change in composition for equilibrium to occur, all fluid compartments of the body are in (or nearly in) osmotic equilibrium. The term tonicity is used to describe the osmolality of a solution relative to plasma. Solutions that have the same osmolality as plasma are said to be isotonic; those with greater osmolality are hypertonic; and those with lesser osmolality are hypotonic. All solutions that are initially isosmotic with plasma (ie, that have the same actual osmotic pressure or freezing-point depression as plasma) would remain isotonic if it were not for the fact that some solutes diffuse into cells and others are metabolized. Thus, a 0.9% saline solution remains isotonic because there is no net movement of the osmotically active particles in the solution into cells and the particles are not metabolized. On the other hand, a 5% glucose solution is isotonic when initially infused intravenously, but glucose is metabolized, so the net effect is that of infusing a hypotonic solution.

Physiology is the science of life. It studies the functions in all living organisms. Human physiology is concerned with the specific characteristics and mechanisms of human body that make it a living human being. Cells of similar structure and functions are grouped together to form a tissue.

- Human tissues include :
- 1-Epithelial tissue.
 - 2-Connective tissue.
 - 3-Muscular tissue.
 - 4-Nervous tissue .

Different tissues enter in the formation of different organ : e.g. heart ,stomach ,liver.....Several organs having similar or complimentary functions form a system. Each system is designed to perform a specific function for the benefit of all the body



Systems of human body include

1-Digestive system :

Formed of mouth , pharynx , esophagus ,stomach ,small and large intestine and the glands which open in the gastrointestinal tract as salivary glands , liver and pancreas. It is important in digestion and absorption of food.

2-Respiratory system

Formed of nose ,pharynx ,larynx , trachea , bronchi and the lungs, it supplies the body with oxygen ,and removes CO₂ and volatile waste products.

3-Urinary system

Formed of the kidneys , ureters , urinary bladder and urethra. It helps in excretion of non-volatile waste products e.g. urea, uric acid , creatinine and excess water

4-Cardio vascular system:

It includes a central pump(the heart) and closed system of blood vessels; as arteries , arterioles, capillaries , venules and veins .These contain the blood which distributes oxygen and nutrients to all body cells and take away the waste products to be excreted.

5-Locomotorsystem:

Formed of muscles, attached to bones and joints. It moves the body as a whole or part of it in relation to others.

6-Reproductive system

Responsible for maintenance of species

7-Endocrine & nervous system

Which regulate and co-ordinate various functions of all other systems of the body .

Homeostasis: Means keeping the conditions in the internal environment constant .

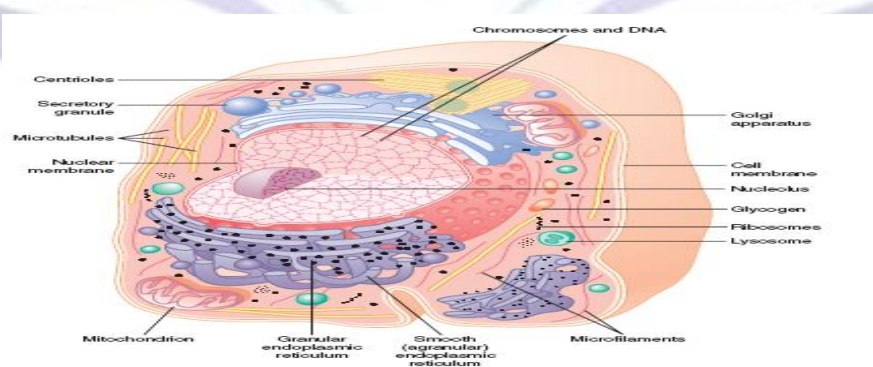
The cell

Is the structural unit of various tissues & organs in the human body. The cell consists of: *A mass of protoplasm surrounded by the cell membrane *The protoplasm = The cytoplasm + Organelles + nucleus -The structure of the cell varies according to the function it performs .

Cell membrane:

That surrounds the cell completely. Semipermeable , thin ,& elastic . Transport through the cell membrane Substances can pass through cell membrane in 3 ways:

(1)Diffusion (2)Active transport (3)Vesicular transport.



The cell

Types of transportation through cell membrane

Diffusion: It is the movement of molecules , in liquids or in gases, from regions of higher concentration to regions of lower concentration.



a-Simple diffusion. [without energy or carrier]

b- Facilitated diffusion. [with concentration gradient - need a carrier]

(2)Active transport: Transport of substance across the cell membrane against an electrochemical gradient .

(3)Vesicular transport: It means movement of macromolecules.

A - Endocytosis: It is the movement from outside the cell to the inside .

B - Exocytosis : It is the movement from inside the cell to the outside.

Function of the cell membrane :

1-It protects the protoplasmic mass & bind its components together.

2-It regulates ionic& non- ionic fluxes in or out of the cell.

3-It contains receptors for chemical messengers which would activate or inhibit various cellular functions

Chapter II

Physiological Organization of Autonomic Nervous System

The Autonomic N .S. Divided into:

1- Sympathetic N. S.

2-parasympathetic N. S .

[1]Sympathetic Nervous System Originate from:

The lateral horn cells of all thoracic & upper 3 lumbar Segments of the spinal cord .

A - Functions of sympathetic N . S

(A)Head and neck: Origin: 1st & 2nd thoracic segment .

Functions :

(1) Eye : elevation of upper eyelid to increase the field of vision .

-Relaxation of ciliary muscle to decrease power of the lens to see the far objects

(2)Skin: secretory to sweat glands& Erection of hairs (contraction of piloerector muscle).

(3)Salivary glands: secretion of saliva .

(4)Cerebral circulation: Increase arterial blood pressure more rapid cerebral blood flow .

(B) On thoracic viscera: Origin: Lateral horn cells of the upper 4 thoracic segments.

Functions:

(1)Heart : increase excitability and rate of conduction .

(2)Lungs: Dilatation of bronchial tree.

(C)On abdominal viscera: Origin: lateral horn cells of the lower six thoracic segments .

Function:

(1) Gastrointestinal tract : inhibition of the plain muscles(stomach – small &large intestine).

(2)Liver: increase blood glucose .

(3)Spleen: contraction of splenic capsule .



(4) Adrenal medulla: increase secretion of adrenaline 80% and noradrenaline 20% .

(D) On pelvic viscera : Origin: 12th thoracic segment and upper 3 lumbar segments .

Functions:

(1) Gastrointestinal tract: contraction of the internal anal sphincter retention of stool .

(2) Urinary bladder: contraction of the internal urethral sphincter retention of urine.

B - Function of the parasympathetic N. S.

Parasympathetic division is the cranio-sacral outflow: The cranial outflow: -

-Oculomotor nerve.

-Facial.

-Glossopharyngeal.

- Vagus.

The Sacral outflow: 2, 3 & 4 sacral spinal nerves .

Head and neck: The Oculomotor nerve

Origin: nucleus in midbrain

Function: contraction of ciliary muscle to increase power of lens in near vision .

Facial nerve

Origin: nucleus in lower pons .

Function: vasodilator , Secretomotor . [salivary & nasal glands]

(B) ON thoracic & abdominal viscera :

Origin: Vagal nucleus in medulla.

Function:

(1) Heart: Inhibition of all arterial properties.

(2) Lungs: Stimulation of bronchial glands .

(3) Gall bladder: evacuation of gallbladder .

(C) On Pelvic Viscera:

Origin: 2, 3, 4th Sacral segment.

Function: Defecation due to contraction of the wall of the rectum . Vasodilatation of female genital organs .

Autonomic Ganglia

Definition Collection of nerve cells (neurons) outside the CNS.

Function Act as distributing centers . [Mother neurons of post ganglionic nerve fibers]

A-Preganglionic Neurons.

B-Postganglionic Neurons .

There are 4 types of autonomic ganglia:



- 1-paravertebral sympathetic chain .
- 2-Collateral ganglia .
- 3-Terminal ganglia.
- 4-The adrenal medulla :(secrete catecholamines directly In the blood).

Chemical Transmission at Autonomic Junction

The two main chemical transmitters are:

- [1]Acetyl choline : cholinergic fibers &receptors
- [2]Catecholamines: (adrenaline&noradrenaline)

Adrenergic fibers & receptors.

Acetylcholine:

Synthesis: In the terminal endings of cholinergic nerve fibers (Rich in ATP). Acetyl CoA +choline choline acetyl transferase Acetyl choline Which is stored in vesicles ,and released by exocytosis .

Cholinergic receptors:

- A)Central receptors[=Nicotinic receptors]
- B)Peripheral receptors[=Muscarinic]

Noradrenaline:(Norepinephrine)

Chemical transmitter released by adrenergic fibers(post ganglionic sympathetic fibers).

Synthesis:

- It occurs in the terminal endings of adrenergic nerve fibers
- Secreted from the adrenal medulla with adrenaline.
- Released by exocytosis as in acetylcholine .

Adrenergic receptors

- A)Post synaptic receptors.(Alpha & Beta).
- B)Presynaptic receptors(Alpha & Beta).

EFFECT OF SYMPATHETIC STIMULATION

Innervation of Body Organs

In the body there are organs which are innervated by both sympathetic and parasympathetic systems:

- Heart - Digestive tract
- Pupil of the eye - Salivary glands, etc

There are organs with only sympathetic innervation:

- Adrenal medulla - Sweat glands - Most blood vessels

Functions of ANS



1- Sympathetic system: Mass discharge of sympathetic system prepares the body for activity (Fight/Flight). Excitation of sympathetic centers will cause increase in heart rate, increase in blood pressure, - blood glucose is elevated - increase in the rate of metabolism - mental activity is also raised, - blood is diverted to skeletal muscle.

2- parasympathetic system: usually has opposite effects to those of sympathetic system.

Excitation of parasympathetic causes:

- Decrease in heart rate,
- Increase blood flow to the digestive system,
- Increase activity of the digestive system.

Sympathetic and Parasympathetic Tone

Normally both sympathetic and parasympathetic systems continuously transmit action potentials (signals) at low rate throughout their nerve fibers. By doing this the ANS can have both positive and negative effects on its effector organs: e.g control of blood vessel diameter by sympathetics

Blood flow to muscle in exercise: Sympathetic nervous system causes blood shift to muscle during exercise by vasoconstriction of blood vessels of all other organs except heart and brain.

Neurotransmitters of the ANS

1- Acetylcholine (ACh)- the transmission is said to be cholinergic.

- ACh is the transmitter released by:
 - All preganglionic fibers (in both sympathetic and parasympathetic)
 - Most parasympathetic postganglionic fibers
 - Some sympathetic postganglionic fibers

2- Norepinephrine (noradrenaline)- the transmission is said to be adrenergic.

- Norepinephrine is the transmitter released by: - Most postganglionic sympathetic fibers,

3- Non-adrenergic non-cholinergic (NANC)- - The transmitter is neither ACh nor NE

- Proposed candidates are: ATP, VIP, and NO.

Receptors

NE causes excitation to some tissues while it inhibits others.

This is due to the presence of different receptors on the target cells.

- There are two types of adrenergic receptors:

α -adrenergic receptors

β -adrenergic receptors

ACh also has two types of receptors:

- Nicotinic - Muscarinic

Resting membrane potential[RMP]

-It is the potential of the membrane during rest



-It is the difference in electrical potential(voltage) Between the inside and outside.

Causes of R.M .P.

It is due to unequal distribution of ions on both sides of the cell membrane.

(1)Selective permeability of membrane.

-K⁺ concentration is very great inside the membrane.

-Na⁺ ions accumulate outside the nerve fiber.

-K⁺ diffuse out & Na⁺ diffuse in .

*The net result: more +ve ions on the outer surface,and more -ve ions inside the membrane.

-The resting membrane potential of ions is -86mv(95% of RMP).

2)Sodium-Potassium pump mechanism:

-Na⁺ is pumped out against:concentration gradient & electrical gradient .

-K⁺ is pumped in against: concentration gradient only .

Importance of Na⁺ K⁺ pump:

(1) Keep Na⁺ outside & K⁺ inside.

(2) R. M .P.as the outer surface is more positive 3Na⁺ outside , and 2 K⁺ inside .

(3) Make about -4 mv(5% of R.M.P.)

Action potential

-Rapid changes in the membrane potential following stimulation of the nerve fiber by a suitable stimulus .

-It results from change in membrane permeability for Na⁺ & K⁺

Phases and shape of action potential:

(1)Stimulus artifact : Indicate the time of application of The stimulus .

(2) Latent period: corresponds to the time it takes the impulse to travel along the axon from the site of stimulation to the recording electrodes .

(3) The action potential wave:[Spike potential]

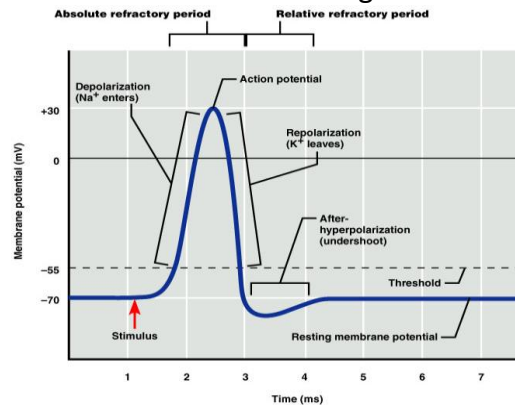
(A)Depolarization phase(Ascending limb)is produced by Na⁺ entry.

(B)Repolarization phase(Descending limb)is produced by K⁺ exit .

(4)Hyperpolarization(small but prolonged)



The membrane become more $-ve$ than resting membrane potential (R.M.P.)



Excitability changes during nerve stimulation

[A] Absolute refractory period [A.R.P.] - It is the period during which action potential can not occur .

[B] Relative refractory period [R.R.P.] - Is the period during which stronger stimuli can excite the nerve . - Begin at the end of absolute refractory period & ends when the membrane potential returns to resting membrane potential (R.M.P.)

Muscles are divided into 2 types:

-Striated muscles: [Include skeletal & cardiac muscles]. -Smooth muscles: [They are involuntary muscles & found in blood vessels and viscera]. Smooth muscles thinner than cardiac muscles. Not divided into sarcomeres. No interdigitating: thick & thin filaments.

Smooth muscle fibers lack of troponin . The sarcoplasmic reticulum (SR) is poorly developed & no T tubules.

Cardiac muscle fibers:

-Represent 75% of total volume of the myocardium

-Contain contractile proteins in myofibrils. -Are rich in mitochondria (30% of cell volume).

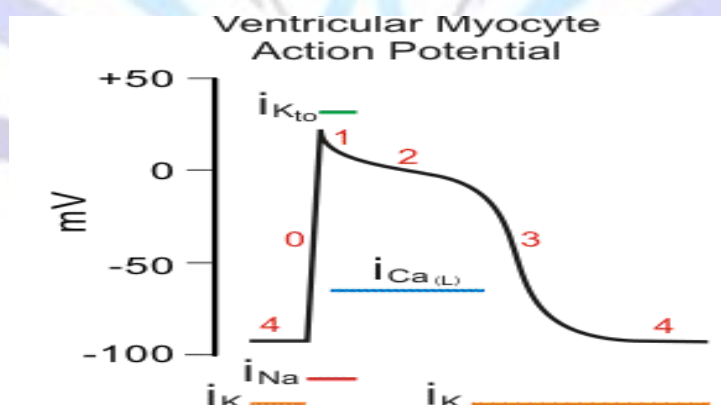
-Contain mature sarcoplasmic reticulum SR in which release Ca^{++} during contraction.

-Act as functional syncytium because of their intercellular connection [Intercalated discs]

Phases of the ventricular Action potential

Phase 0 (Rapid depolarization and overshoot). Phase 1 (Rapid repolarization to $+10mV$)

Phase 2 (Plateau). Phase 3 (Repolarization). Phase 4 (Resting membrane potential).



Aim of the Ventricular action potential: Maintain entry of Ca^{++} during long plateau forced contraction Proper ejection of the blood . Changes of excitability during the action potential

(1) Absolute refractory period: It is the interval of time during which normal cardiac impulse can't reexcite an already excited as of cardiac muscle . -During which the fiber does not respond to any stimulus. -Contain phases 0, 1, 2 and about half of phase 3 (whole period of systole) .



(2)Relative Refractory Period (R.R.P.): During which the excitability (muscle contraction) of cardiac membrane is subnormal. Cardiac muscle remain relative refractory until phase 4 (first half of diastole).

(3)Vulnerable or dangerous period: -A critical interval with the last half of diastole time -In which the excitability is supernormal *Stimulation at this time ventricular fibrillation (Fatal). Action potentials in smooth muscle -Membrane potential are small waves which can not cause muscle contraction

The action potentials occur in 2 forms: Spike potentials: similar to skeletal muscle. The action potential with plateau. Ca^{++} channels open very slowly slow action potential.

Excitation-Contraction coupling in smooth muscle: There is no troponin-tropomyosin complex: inhibit cross bridge cycling. Myosin cross-bridges can not bind to actin. Ca^{++} initiate a sequence of reactions ending in phosphorylation of myosin.

Neuromuscular transmission

--Transmission of impulses from motor neuron to skeletal muscle fibers .

*Sequence of Events during Neuromuscular transmission:

(1)Action potential (A.P.) reaches the nerve ending: increase the membrane permeability to Ca^{++}

(2) Ca^{++} enters the nerve endings Release of acetylcholine(Ach) by exocytosis .

(3) Ach diffuses to muscle to bind to nicotinic receptor in motor end plate increase Na^{+} & K^{+} conductance of the membrane.

*The amount of Na^{+} entering the cell > the amount of K^{+} leaving the cell The cell depolarizes End-plate potential (E.P.P.)

(4) The E.P.P. depolarizes the membrane , and act as a stimulus & depolarizes adjacent muscle membrane

- Action potentials A.P. are generated on either side of the end plate.

-The muscle action potential in turn initiates muscle contraction .

(5) Ach is degraded rapidly by choline- esterase to prevent multiple muscle contraction .

Properties of Neuromuscular Transmission

[1]Unidirectional : one direction only from the nerve to the muscle.

[2] Delay : about 0.5 m sec. for release of Ach

[3]Easily fatigued: due to repeated stimulation

[4]Effect of ions: The number of rupture vesicle is directly proportional with Ca^{++} ions. The number of rupture vesicle is inversely proportional with Mg^{++} ions .

[5] Effect of drugs : (a)drugs that block neuromuscular transmission ex: curariform drugs. (b) drugs which stimulate neuromuscular transmission by inactivating cholinesterase: ex : Neostigmine. (c) drugs that stimulate muscle fiber by acetylcholine -like action. Ex : Methacholine.

Molecular basis of muscle contraction [4 steps]

A- Release of Ca^{++} The propagation of A.P into T tubule Open Ca^{++} channels on the terminal cisternae TC Ca^{++} flows out into cytoplasm .

B- Activation of muscle proteins Ca^{++} binds to troponin on the thin filament. Troponin: causes tropomyosin to move away from its position. Uncovered, the binding site on actin Actin combines with cross-bridges from thick filament and contraction begins.

C-Generation of tension: Tension(the force developed when a muscle contracts)

(1)The first step : Binding of actin and myosin.

(2)The second step: Bending of cross-bridges

[Energy is obtained from hydrolysis of ATP].

(3)The third step: detachment of the cross from the thin filament(actin)

(4) The final step: The cross bridge returns to its original position .



RelaxationCa⁺⁺ is removed from cytoplasm by Ca⁺⁺pump located on SR membrane which lead to: Troponin returns to its original state .Tropomyosin cover the myosin binding site on actin Cross-bridge cycling stops.

Chapter III

Physiology of muscle

Muscle shortens and develops tension so that movement is brought about . Muscles are divided into two types : Striated muscle - Smooth muscle

Striated muscles: Include skeletal and cardiac muscles. -Characterized by alternating light and dark band. -40% of the body is skeletal muscle. -10% of the body is smooth and cardiac muscles..

Skeletal muscles: -Attached to bones. -They are under voluntary control. -When contact=move the body or part of the body -Their contraction depends on its nerve supply. -The human body contains over400 voluntary skeletal muscles.

Functions:

- 1-Force production for locomotion and breathing.
- 2-Force production for maintaining posture and stabilizing joints.
- 3-Heat production.
- 4-Help venous return.

Physiologic Anatomy of the skeletal muscle and motor end-plate

Structure of the end-plate region:

I-Axon terminal(end feet): -The alpha motor neuron axon terminals(end feet) skeletal muscle fibres . -Each skeletal muscle fibre receive only one axon terminal . -Containing Acetyl choline vesicles (A.ch).

II-Motor end plate(MEP): -Thickened muscle membrane . -Is rich in Ach receptors .-Contains junctional folds .-The extracellular space between the nerve terminals and muscle membrane called basal lamina .-It is occupied by connective tissue -The basal lamina bound to acetylcholine- esterase(AchEase) .Sequence of events during neuromuscular transmission

(1) As the nerve impulse(action potential)reaches the nerve ending : lead to opening of voltage-gated Ca⁺⁺channels increases the membrane permeability to Ca⁺⁺.

(2) Ca⁺⁺enters the nerve endings which lead to a marked increase in exocytosis of Ach vesicles .

(3) Ach diffuses to the muscle to bind to its receptor in the motor end plate (MEP) . which lead to-open the channel . -Increase Na⁺ & K⁺ conductance of the membrane Na⁺ (inside) Influx and K⁺(outside) Efflux . -Then depolarization occure i.e the cell depolarized which lead to EPP .

(4)The EPP depolarizes the muscle membrane to threshold:-EPP is a local response-non propagated response .-EPP act as a stimulus and depolarizes the adjacent muscle membrane to its firing level . -AP (action potential) are conducted away from the end plate in both directions .-The muscle action potential initiates muscle contraction .

(5)Ach is breakdown rapidly -After binding to the Ach-receptor . -Degradation of Ach is necessary to prevent the multiple muscle contractions .

6-The AP depolarizes the muscle membrane ,and much of the AP electricity flows through the center of the muscle fiber .Here it causes the sarcoplasmic reticulum to release large quantities of Ca⁺⁺ ions That have been stored within this reticulum

7-The Ca⁺⁺ ions initiate forces between the actin and myosin filaments ,causing them to slide ,which is the contractile process .

8-After a second ,the Ca⁺⁺ ions are pumped back into the sarcoplasmic reticulum and remain stored untill a new muscle action potential comes This removal of Ca⁺⁺ ions from the myofibrils causes the muscle contraction to stop .

General mechanism of muscle contraction

1-An AP travel along a motor nerve to its endings on muscle fibers .

2-At each ending ,the nerve secrete a small amount of the neurotransmitter substance Ach .

3-Ach acts on a local area of the muscle fiber membrane to open multiple Ach gated channels through protein molecules floating in the membrane



4-Opening of Ach gated channels allow s large quantities of Na⁺ ions to diffuse to the interior of the muscle fiber membrane .This initiates an AP at the membrane .

5-The AP travels along the muscle fiber membrane in the same way that action potentials travel along nerve fiber membranes .

Excitation–Contraction-Coupling of skeletal muscles

Membrane potential : the basis of excitability There is a marked difference in the ionic composition of intracellular fluid (ICF) and extracellular fluid (ECF) as: Large amounts of K⁺, protein ,Mg⁺⁺& phosphate ions inside the cell .Excess Na⁺ , CL⁻ ,& HCo³⁻ , ions in the ECF .-Such variation creates electrical potential called membrane Potential which is responsible for excitability in all living cells .

-Excitability: It is the ability of living tissues to changes in its environment

Stimuli : They are the changes which excite an organism. -Responses:They are the resultant effects .

N.B Nerves & muscles are the most excitable tissue in the body .

Factors that affect the membrane potential and excitability

(A)Role of Na⁺

1-Any condition increase muscle permeability to Na⁺ increase excitability. vertarine. -low Ca⁺⁺ in ECF

2-Any condition decrease nerve permeability to Na⁺ decrease excitability. -high Ca⁺⁺ in ECF -Cocaine (local anesthetic).

3-Hyponatremia decrease size of AP(little effect on RMP)

4-Blockade of Na⁺ channel by Toxin tetrodotoxic (T.TX) no AP.

(B)Role of K⁺

-1-Hyperkalemia (increase K⁺ in ECF)

-2-Hypokalemia (decrease K⁺ in ECF) Hyperpolarization.

3-Blockade of K⁺ channels by tetraethyl anonium (T.E.A) longer AP (prolonged repolarization) Absent hyper -polarization .

(C)Role of Na⁺-K⁺pump

At rest: the muscle membrane is relative impermeable to Na⁺ During depolarization: Na⁺ enters the cell . Mebrane excitation, the neuromuscular junction When a motor nerve is stimulated: An action potential arrive at the neuromuscular junction (NMJ). Depolarization of nerve terminal, Opening of voltage gated Ca⁺⁺channels. Calcium ion diffuse from extra cellular fluid into nerve terminal, Ca⁺⁺ cause rupture of acetylcholine (ACh) vesicles, Release of (ACh) into synaptic cleft. ACh bind to the specific nicotinic receptors [Ach-gated ion channels] in muscle membrane,

-Influx of Na⁺ ions and efflux of K⁺ ions from muscle membrane, but the permeability to Na⁺ is more than K⁺. -Local depolarization of muscle membrane which is known as end plate potential (E.P.P.). -Under normal conditions, this potential reaches the firing level (-40mv) which start an action potential along the muscle fiber. -Once ACh produces its action, it is rapidly hydrolyzed by cholinesterase enzyme,to prevent. re-excitation of the muscle so, single stimulation of nerve lead to one excitation of the muscle and no more.

Excitation- contraction coupling:

It is the process by which an action potential initiates the contraction .

(1)Release of Ca⁺⁺ :The propagation of the action potential into the T tubule.

_Open the Ca⁺⁺channels on the terminal cisterne(TC)

_Ca⁺⁺flows out of the TC and into the cytoplasm.

(2)Activation of muscle protein:

Ca⁺⁺binds to troponin in the thin filament. Troponin undergoes a conformational change causes tropomyosin to move away from its position. Uncovered, the binding site on actin. Actin combines with the cross-bridges from the thick filament & contraction begins .

(3)Generation of tension



Tension [the force developed when a muscle contracts] it takes 4 steps :-

1-The first step: binding of actin and myosin.

2-The second step : binding of the cross-bridges (energy is obtained from hydrolysis of ATP [both the ATP & ATPase are attached to the cross-bridge]

3-The third step: detachment of the cross-bridge from the thin filament .-For detachment to occur: .ATP → ADP + inorganic phosphate (pi) .ADP + pi must be removed from the cross-bridge .New molecule of ATP put in their place . .This new ATP reduces the affinity of the cross bridges for the active site . .If no ATP is available , thick , & thin filaments can not be separated (Muscle contracture) .

4-The final step : the cross-bridge returns to its original upright position . Once there , it can participate in another cycle. *The force developed by the binding of the cross-bridge is transmitted through : The actin filament → Z disk → sarcolemma → tendinous insertion → bones .Relaxation:[active] Ca⁺⁺ is removed from the cytoplasm by Ca⁺⁺ pump Located on the SR membrane: decrease intracellular Ca⁺⁺ troponin returns to its original conformational state.

Mechanical changes There are two types of muscle contraction: isotonic & isometric contractions.

Mechanics of single fiber contraction:

(1) Contraction refers to the turning on the cross- bridge cycle, change in muscle length depends upon the external forces acting on the muscle.

(2) Three types of contractions can occur following activation of muscle fiber-1-an isometric contraction : the muscle generates tension but does not change length ; -2-an isotonic contraction: the muscle shortens , moving a load; -3-a lengthening contraction: the external load on the muscle is greater than the muscle tension, causing the muscle to lengthen during the period of contractile activity.

(3) Increasing the frequency of action potentials in a muscle fiber increases the mechanical response (tension or shortening), up to the level of maximal tetanic tension.

(4) Maximum isometric tetanic tension is produced when there is a maximal overlap of thick and thin filaments, that is at the optimal length. Stretching a fiber beyond its optimal length decreases the filament overlap and decreases the tension produced , decreases the fiber length also decreases the tension generated for several reasons .

(5) The velocity of muscle fiber shortening decreases with increases in load. Maximum velocity occurs at zero load .

Whole muscle contraction :

A) The tension produced by whole-muscle contraction depend on the amount of tension developed by each fiber and the number of active fibers in the muscle.

B) Muscles that produce delicate movements have a small number of fibers per motor unit.

C) Fast-glycolytic motor units not only have large-diameter fibers but also tend to have large numbers of fibers per motor unit .

D) Increases in muscle tension are controlled by increasing the number of active motor units in a muscle, a process known as "recruitment" .Slow- oxidative motor units are recruited first during weak contractions then fast-oxidative motor units , and finally fast-glycolytic motor units during very strong contractions. Increasing motor unit recruitment increases the velocity at which a muscle will move a given load .

F) The strength and tolerance to fatigue of a muscle can be change by exercise .

(1) Long-duration , low -intensity exercise increases a fiber's capacity for oxidative ATP production by increasing the number of mitochondria and blood vessels in the muscle .

(2) Short-duration ,high-intensity exercise increases fiber diameter as a result of increased synthesis of actin and myosin resulting in increased strength. Tropomyosin moves back to cover the myosin binding site on actin .cross -bridge cycling stops .

Properties of Neuro-muscular Transmission(N . M .T)

1) Unidirectional (one direction only from the nerve to the muscle)

2) Delay :- about 0.5 m.sec (time needed for) -The release of A-ch. -Change in the permeability of muscle fibre membrane -Inflow of Na⁺ -Building up of depolarization to the firing level .

3) Easily fatigued : due to -Repeated stimulation . -Exhaustion of acetylcholine vesicles .



4) Effect of ions -The number of ruptured vesicles \propto Ca^{++} . Ca^{++} rupture of A.ch. vesicle increase of A.ch. Release -The number of rupture vesicles \propto Mg^{++} Mg^{++} stabilization of A.ch. vesicles decrease A.ch. Release decrease N.M.T. K^{+} have anti curare action on motor end plate .

5) Effect of drug : a) Drugs that stimulate muscle fibre by acetylcholine-like action:-

-Are not destroyed by cholinesterase .-Their action persists for many minutes to several hours . -E.g. methacholine ,carbachol ,and nicotine in small dose .

b) Drugs that block neuromuscular transmission (curariform drugs) : -Can prevent passage of impulses at motor-end plate .-Curare competes with acetylcholine for the receptor .

c) Drugs which stimulate neuromuscular transmission by inactivating cholinesterase -Thus extreme amounts of A.ch. Can accumulate and stimulate the muscle . -E.g. neostigmine ,physostigmine ,and di-iso-propylfluorophosphate .

When muscle is stimulated either directly or indirectly through its motor supply the following changes occur :-

1-Electrical changes . 2-Excitability changes . 3-Metabolic changes . 4-Thermal changes .5-Mechanical changes .

1)The electrical changes

They are similar to those occurring in nerves except for quantitative differences in timing & magnitude :-The resting membrane potential is about -90 m v. -The action potential is last 2-4 m sec. -The firing level is reached about -40 m v(it is about - 55 m v in nerves) .-The velocity of conduction of action potential on the surface of the muscle fibres is 3-5 m sec(it is variable in nerves depending on their diameter)-Muscle contraction follows action potential in muscles by about 2 m sec .(no contraction occur in nerves). -The duration of - ve & +ve after potentials are relatively longer in muscles than in nerve fibers .-The chronaxie is generally longer in skeletal muscles than in nerves .

(2)Excitability changes

The Excitability changes which occur in the muscle are identical to those which occur in the nerve .Phases of muscle excitability:- a- Absolute refractory period. b-Relative refractory period. c-Supernormal phase of excitability. d-Subnormal phase of excitability.

N.B 1-Under resting conditions ,all Na^{+} channel are ready for stimulation.

2-At beginning of depolarization , Na^{+} channel start opening(activation).

3-At firing level ,all Na^{+} channels are opened & inactivation of Na^{+} channels starts .

4-AT top of spike ,all Na^{+} channels are inactivated .

5-At depolarization , Na^{+} channels start to return to resting state ,

(3)Metabolic (chemical) changes

Chemical composition of skeletal muscle :- Water : 75 - 80%. Proteins: 20%(actin ,myosin ,troponin ,tropomyosin & other). Energy-producing substances :- a)ATP : 0.33% b) Creatin phosphate (phosphagen) 0.5 % . c)Glycogen : 0.1 – 1.0 % Inorganic ions : a)Cations: Na^{+} , K^{+} , Ca^{++} , Mg^{++} . b)Anions : HCO_3^{-} , Cl^{-} , SO_4^{-} , PO_4^{-} .

Metabolism of muscle :

During rest : -Muscles consume about 60 ml O_2 l min . Which accounts for 25% of total Basal metabolic rate (B.M.R). -The resting energy is used for the following: (1) Maintenance of the Resting membrane potential(Na^{+} - K^{+} pump). (2)Keeping the electrolyte composition of muscle fiber constant. (3)Chemical synthesis of muscle proteins , glycogen & other organic compounds . (4)Supply energy for muscle tone .

During activity 1- breakdown of ATP into ADP and liberated energy 2 – rapid regeneration of ATP and formation of creatinine so ATP remain constant and decreased CP but creatinine increased and anaerobic energy give contraction

C)During recovery : 1) Fate of lactic acid **A)Oxidation during recovery** period Lactic acid Pyruvic acid $CO_2 + H_2O +$ Energy (used for resynthesis of ATP & CP.

B)Diffusion to the blood stream Then to liver where it is converted to glycogen through (The Cori cycle) .c)It is used as a fuel PH changes in muscle contraction



During contraction The PH of the muscle pass in 3 phases : **(1)Acidic phase** : Due to H_3PO_4 formed during the breakdown of $ATP \rightarrow ADP + H_3PO_4 + E$.**(2)Alkaline phase** : Due to accumulation of creatine during resynthesis of ATP from $CP + CP + ADP \rightarrow ATP + creatine$. **3)Acidic phas** Due to accumulation of pyruvic & lactic acids formed from breakdown(oxidation)of the muscle glucose .Glucose +Pyruvic acid \rightarrow Lactic acid **(4)Thermal changes** The heat produced as a result of a single muscle twitch occurs in 2 main stages :-

1)Initial heat : Which occurs during the contraction & is divided into :

a-Activation heat : produced due to conduction of the action potential along the surface of the muscle .

b-Shortening heat : produced by contraction and sliding of actin over myosin .

c-Work heat : produced by lifting a weight & performing work .

d-Relaxation heat : produced by the active Ca^{++} pump ,recollecting Ca^{++} back into the sarcoplasmic reticulum relaxation .

Cause of the initial heat : It is due to heat produced by the anaerobic reactions responsible for muscle contraction .

Recovery (delayed) heat : It is nearly equal to the initial heat .It is released immediately following the twitch and continues for a much long time (several minutes)

Cause of the recovery heat : .Waste heat produced mainly by the aerobic oxidative processes that resynthesize glycogen , CP ,&ATP .Avery small amount of this heat is produced anaerobically .

Molecular mechanism of muscle contraction

Excitation-contraction Coupling(E .C) It is a process by which an action potential initiates the contractile process -The contractile response takes place in 4 steps .

1)Release of Ca^{++} :-The propagation of the action potential into the T tubule .-Open the Ca^{++} channels on the terminal cisternae(TC) - Ca^{++} flows out of TC and into the cytoplasm .

2)Activation of muscle Proteins:- Ca^{++} binds to troponin on the thin filament . Troponin undergoes a conformational change *causes tropomyosin to move away from its posit ion . *Uncovered ,the binding site on actin. *Actin combines with the cross-bridges from the thick filament & contraction begins .

3)Generation of tension:- Tention (the force developed when a muscle contracts) . (1)The first step: binding of actin and myosin . (2)The second step: binding of the cross bridges(energy is obtained from hydrolysis of ATP) . Both ATP & ATP ase are attached to the cross-bridge }

(3)The third step : Detachment of the cross -bridge from the thin filament . For detachment to occur :- $-ATP \rightarrow ADP + inorganic\ phosphate(Pi)$ - $ADP + Pi =$ must be removed from the cross bridge . -New molecular of ATP put in their place . -This new ATP reduces the affinity of the cross bridge for the active site -If no ATP is available ,thick & thin filaments can not be separated (Muscle contracture) .

(4)The final step :- The cross bridge returns to its original position . Once there , it can participate in another cycle . *Cycling continuous as long as : Ca^{++} is attached to troponin and energy is available . *The force developed by the bending of the cross-bridges is transmitted through The actin filament.

Relaxation :- (Active) Ca^{++} is removed from the cytoplasm by Ca^{++} pump located on the sarcoplasmic reticulum membrane : Intracellular Ca^{++} troponin returns to its original conformational state . Tropomyosin moves back to cover the myosin binding site on actin Cross-bridge cycling stops .

ALL or NONE LAW :

A single skeletal muscle fibre obeys the all or none law .{A single skeletal muscle fibre contracts maximally or does not contract at all }A skeletal muscle DOSE NOT obeys the all or none law

Components of skeletal muscle fibre :-Muscle shortens and develops tension so that movement is brought about . -Muscles are divided into 2 types : striated & smooth .-

Striated muscle :-Include skeletal & cardiac muscles .-Characterized by alternating light & dark bands .-40% of the body is skeletal muscle .-10% of the body is smooth & cardiac muscles .

Skeletal muscles : -Attached to the bones .-They are under voluntary control .-Their contraction depends on its nerve supply .-When contract move of the body or part of the body .-The human body contains over 400 voluntary skeletal muscles .



*Function of skeletal muscle:

(1)Force production for locomotion . (2)Force production for maintaining posture and stabilizing joints . (3)Heat production . (4)Help venous return .

Skeletal muscle fiber :--Bundled together by connective tissue . -Arranged parallel between the tendinous ends . -Each muscle fiber is a single cell . -Made of many parallel myofibrils .

Myofibrils:--They are threadlike structures that contain the contractile proteins . Embedded in the cytoplasm of the fiber (sarcoplasm) . -Contain thick (myosin) & thin (actin) protein filaments . -Divided into functional units (sarcomere) by transverse protein sheet (Z Line) Banding pattern(filaments) :[cross striations]

There are 2 types of filaments : 1-Thin actin filaments . 2-Thick myosin filaments .The interdigitating thick &thin filaments create the pattern of light &dark bands :-

(1)The dark area(A band) -In the center of the sarcomere . -These contain the thick filaments & thin filaments ,which overlap to some extent . -While the area without any thin filaments is called H-Zone -At the center of the H- Zone there is a region does not contain any cross bridges ..

(2)The light area(I-band) -The light areas on either side of the Z- disk . -They contain the thin filaments .

The cross-bridges : -Projection from the thick filaments(myosin) extend toward the thin filaments (actin) . -Play a fundamental role in muscle contraction . -The amount of overlap between myosin & actin varies with sarcomere length determines the force of muscle contraction . *When the muscle is stretched or shortened :- -The thick and thin filaments slide past each other . -The I- band increases or decreases in size . Tubular System :- There are two tubular networks are present in skeletal fibers: (1)Transverse (T) tubule . (2)The sarcoplasmic reticulum (SR) . Transverse T tubule:- Invagination of the surface of muscle membrane . -Located at the junction of the A & I bands . -The space of T tubules contain extracellular fluid

The Sarcoplasmic Reticulum(S R):- -It is the endoplasmic reticulum of the muscle fiber . -It has high concentration of Ca^{++} . The muscle proteins :-Contain : I-Myosin protein :- -They are arranged in the middle of each sarcomere . -It is about 300 myosin molecules form myosin filament . -Cross bridges = head + arm . II-The thin filament protein : (1)Actin:It has specific active site combin with myosin filaments during muscular contraction . (2)Tropomyosin : It cover active site to prevent combination between actin & myosin at rest . (3)Troponin :- -Troponin I :It has strong affinity to bind with actin . -Troponin T :It has strong affinity to bind with. Tropomyosin Troponin C :It has strong affinity to bind with Ca^{++} .

Sarcolemma : Is the cell membrane of the muscle fibre (plasma membrane) At each end of the muscle fibre ,the surface layer of the sarcolemma fuses with a tendon fibre collect into bundles to form the muscle tendons that then insert into the bones .

The sarcomere :- It is the portion of muscle fibre that lies between two successive Z lines. It is the contractile unit of the skeletal muscle fibre. The contractile proteins that make up the myofibrils are formed of thick myosin & thin actin filaments .

Activation of skeletal Muscle : -A contraction of the whole muscle is produced by nerve impulse (Action potential) arriving at the neuromuscular junction . -Action potential spreading through out the membrane of the muscle , in which lead to contraction of the whole muscle .

SIMPLE MUSCLE TWITCH AND FACTORS AFFECTING IT

Motor unit: Motor unit =motor neuron +the nerve fibre + the muscle fibers. The number of the muscle fibers in motor unit varies. In muscles which perform fine and graded movements. ex :hand muscles – ocular muscles. Each motor unit contains few muscle fibers 3 -6 muscle fibers. In big muscles which perform gross movements. ex : muscles of the leg and back. Each motor unit contains 100 – 200 muscle fibers.

Simple Muscle Twitch: It is the short contraction followed by relaxation produced by a single maximal stimulus to the muscle . It consists of 3 phases:-

1)Latent period. It is the time between the application of the stimulus &the start of the contraction. It is normally about 0.01 sec.

2)Contraction phase During which the muscle shortens(in isotonic contraction) or its tension increase (in isometric contraction).



3) Relaxation phase During which the initial length of the muscle is restored (in isotonic contraction) or the muscle tension drops again to the resting level (in isometric contraction) It is about 0.05 sec.

Factor affecting muscle twitch: 1-Types of muscle fibers. 2-temperature of muscle. 3-Fatigue of muscle. 4-Initial length of muscle. 5-Stimulus(single- two- successive)

Temperature of muscle : Warming of the muscle=Strong contraction of a higher amplitude than normal. -The effects of warming is due to: a-Acceleration of the metabolic reactions in the muscle. b-Reduction of its viscosity =facilitating the process of contraction(easy sliding of actin & myosin). Cooling the muscle : =has an opposite effect. Slowing contraction ,or prolonged - Excessive heating of the muscle-----Coagulates its proteins & destroys the muscle maintained shortening of the muscle called heat contracture or heat rigor.

Fatigue of muscle: Continuous indirect stimulation of the muscle (neuromuscular fatigue) Continuous direct stimulation of the muscle (muscular fatigue) fatigue & the muscle relaxation becomes incomplete (contracture)

Fatigue of the muscle: -Prolonged and strong contraction of muscle leads to accumulation of metabolites (lactic acid). Decrease Acetylcholine (ACh) Decrease ATP, glycogen and creatine phosphate. Decrease blood & O₂

Decrease force of contraction. Decrease velocity of shortening. Increase duration of contraction. Incomplete relaxation (contracture).

Evidence that nerves are not easily fatigued :-- In a nerve-muscle preparation, if a segment of the nerve between the stimulating electrodes & the motor end plate is blocked (e.g. by cocaine) & the nerve is repeatedly stimulated for several hours then the block is removed, nerve stimulation still produces muscle contraction this indicates that the nerve is not fatigued in spite of its continuous activity for several hours -In the body: ,fatigue occurs due to failure of synaptic transmission in the central nervous system (synaptic fatigue) due to depletion of chemical transmitters at the nerve endings.

Initial length of muscle :-

The contraction of the muscle depends on the initial length of the muscle fiber

- 1) Maximal contraction is obtained when the sarcomere length equals 2.2μ
- 2) At sarcomere length greater than 2.2μ the force of contraction decreases.
- 3) At sarcomere length less than 2.2μ the force of contraction increases.

Muscles can contract both isometrically and isotonicly in the body; but most contractions are actually a mixture of the two.

During running : Isometric contractions when the legs hit the ground Isotonic contractions to move the limbs. When a person lifts a heavy weight using the biceps: the contraction starts isometrically and completed isotonicly

The skeletal muscles contain- Contractile element (C.E.) - Elastic and Viscous elements Series elastic component (S.E.C.)

Tetanus: Complete Tet.----no relaxation between stimuli. Incomplete Tet.---there are periods of incomplete relaxation between stimuli summation of contraction.-

Staircase(=Treppe)phenomenon: If the effective stimuli of equal strength are successively applied to a resting muscle at a rate which does not produce fatigue The first few contractions become progressively stronger.(progressive increase in contraction to a plateau value.)

The cause of staircase phenomenon:- a) Reduced K⁺ ions inside the fibres: increase the release of Ca⁺⁺ from S.R. better contraction. b) Increased Ca⁺⁺ ions conc. Inside the muscle fibres: more binding of Ca⁺⁺ to troponin stronger contraction. Effect of stimulation of skeletal muscle by two successive stimuli c) Warming up of the muscle: i.e. heat liberated from the preceding contraction. Facilitates the second contraction. The effect of two successive stimuli will depend on the time of the application of the second stimulus as follows:

1) If the second stimulus falls during the latent period or the early contraction phase of the muscle twitch of the first stimulus ineffective.

2) If the second stimulus falls during the late contraction phase of the first twitch a stronger contraction is obtained due to summation of the mechanical responses of the two stimuli.



3) If the second stimulus falls during the relaxation phase of the first twitch incomplete relaxation of the first twitch then, the muscle passes immediately into a second contraction stronger than the first produced by the second stimulus.

4) If the the second stimulus falls at the end of relaxation phase of the first twitch two successive complete muscle twitches are obtained; the second is stronger due to staircase phenomenon. Effect of stimulation of skeletal muscle by several successive stimuli (Genesis of tetanus) The response of skeletal muscle to multiple successive stimuli depends on the frequency (or the rate) of stimulation as follow :**If the frequency of stimulation** is low so that the stimuli fall soon after the relaxation phases of the preceding twitches separate muscle twitches show the staircase phenomenon. If the frequency of stimulation is increased so that the stimuli fall during the relaxation phases of the preceding twitches incomplete tetanus (which consists of successive muscle contraction). If the frequency of stimulation is further increased so that the stimuli fall at the contraction phases of the preceding twitches complete tetanus (i.e. continuous contraction). These stimuli cause persistent release of Ca^{+} ions continuous cycling of the cross-bridges continuous contraction .

Length Tension Relationship:

Starling law: The more the initial muscle fiber length the more the active tension developed during muscle contraction within limits .

Total tension tension that a muscle develops when stimulated to contract isometrically .

Passive tension exerted by the unstimulated muscle .

Active tension Total tension –passive tension .

Tension varies with the length of the muscle fiber :

Maximal force obtained when the sarcomere length = 2.2μ -This is the resting length of the muscle inside the body .-Every cross – bridge from the thick filament is opposite an actin molecule .

Load –Velocity Relationship In isotonic contraction:-

a) For the muscle to shorten (contract) , it must lift a weight called after load,which is applied after the muscle begins to contract .Increasing the after load has the following effect :As the muscle shortening(contract) below a sarcomere length of 2.2μ The amount of shortening (force of contraction) decreases The velocity of shortening decreases The ability to generate force decreases The maximal velocity of shortening (V_{max}) occurs with zero load V_{max} is theoretical ,because load can not be zero Muscle with predominant fast fibres have a greater V_{max}

b) At sarcomere length greater than 2.2μ -Decrease in the force development .-The overlap between thick and thin filament is decreased .-Some cross- bridges do not have actin filaments to combine with

C) At sarcomere length less than 2.2μ -Decrease in the force development .-The ends of the two actin overlap each other ,in addition to overlapping the myosin .-Making it more difficult for the muscle to develop force .

Chapter IV

Blood, Immunity and Lymph

Introduction to blood system

Blood is a mobile tissue because its function is transportation. It moves in a network of blood vessels. Like any organ it has cells and interstitial fluid. The interstitial fluid has been expanded to help mobility of the blood and is named plasma.

The composition of the blood:

1- cellular compartment: RBCs (red blood cells or erythrocytes) : transport O_2 and CO_2 . Platelets : play a role in haemostasis. leukocytes (white blood cells): are concerned with cellular defense function. They are: **Neutrophils**, - **Lymphocytes**, -**Monocytes** , - **Eosinophils** & - **Basophiles**.

2- fluid compartment (plasma) Plasma transports soluble components e.g. plasma proteins, nutrients, metabolites, coagulation factors, antibodiesetc., with different sites of action.

The function of the blood as a tissue:



- 1 - Transport of oxygen and nutrients to the tissues for use and storage.
- 2 - Transport of metabolic wastes to the kidney, liver and skin for elimination.
- 3- Transport hormones from the endocrine glands to the target tissues.
- 4 - Transports heat to the skin for exchange.
- 5- Blood provides a barrier that protects the internal environment.
- 6- Homeostasis and clotting seal the any disruptions of the vascular system
- 7- Vascular injury initiates a sequence of responses that limit blood loss from the site of the injury.
- 8- Platelet adhesion and coagulation seal the site of injury.
- 9- Maintenance of proper concentrations of other ions in the tissues.

Normal values of blood and plasma volume :

In an adult, blood makes up to 8% of the total body weight. (5 to 6 L) in a young male 70 Kg. (4 to 5L) in a young female 60 Kg. Blood volume decrease with the age. Approximately 45% of the blood volume is RBCs (48% for males & 42% for females). Less than 1% WBCs & 55% is plasma.

Hematocrite function and its normal values

The average RBC count is 5,500,000 cell/mm³ of blood. Hematocrite: is the proportion of blood that is cell, normally 48% for men, 42% for women. Hematocrite is determined by centrifugation of heparinized blood. Normal hemoglobin values are: 16 g/dl for men and 14 g/dl for women. RBCs are heavier than water so, the density of blood can be used as an estimation of hematocrite. Density of blood can be used as an estimation of hematocrite, they also can be influenced by osmotic changes in red cell water. In human: the liver is the primary organ that sequesters RBCs and releases them during times of enhanced sympathetic nervous system activity. This release of stored RBCs, along with changes in plasma volume, can produce changes in hematocrite that are unrelated to RBCs synthesis or destruction.

Plasma

Plasma is separated from blood by addition of an anticoagulant and subsequent centrifugation. Fresh plasma is a straw- colored fluid decanted from the top of the centrifuge tube and is 92% water. Plasma contain clotting protein. Serum is a cell- free fluid decanted from clotted blood. Serum lack the clotting protein.

The composition of plasma:

Plasma consists of water, electrolytes, nutrients, wastes and protein. Normal concentration of plasma protein: Blood proteins, also called serum proteins, are proteins found in blood plasma. Serum total protein in blood is 7g/dl, which in total makes 7% of total blood volume.

Plasma protein components include: Albumin, alpha, beta & gamma – globulins , collecting factors, complement, enzymes, precursors and their substrates, hormones, specific carrier proteins, apolipoproteins. The plasma proteins consist of approximately 88% normal human albumin, 12% alpha and beta globulins and not more than 1% gamma globulin.

Types of plasma protein: Acting together, the three type of plasma proteins keep the body healthy. They are the building blocks of all the body's cell and tissue, including antibodies, hormones, and clotting agents. They transport a variety of substances, including drugs, hormones and vitamins. They control osmotic pressure between blood and tissues and help control the acid-alkaline balance of the blood. They are also a source of energy for muscles and tissues when not enough energy-producing foods are ingested. Plasma proteins form three major groups and these have various functions.

The three groups are : albumin (60% of total plasma protein) fibrinogen (4% of total plasma protein) globulins (36% of total plasma protein) further fractions (alpha, beta and gamma) can be distinguished within the globulin group. - Most of the plasma proteins are produced by the liver. The gamma globulins are produced by cells of the body's immune system. Normal values Serum albumin: 3.5-5.0 g/dL. Serum total protein: 6.0-8.0 g/dL. Site of synthesis and function of plasma proteins: All the plasma proteins are synthesized in liver except gamma globulins. 60% of plasma proteins are made up of the protein albumin, which are major contributors to osmotic pressure of plasma which assists in the transport of lipids and steroid hormones. Globulins make up 35% of plasma proteins and are used in the transport of ions, hormones and lipids assisting in immune function 4% is fibrinogen which is essential in the clotting of blood and can be converted into insoluble fibrin. Plasma proteins circulate in the blood and between the blood and the extracellular tissue spaces. Their movement occurs not only by passive diffusion through junctions between capillary endothelial cells, but also by active transport mechanism and by pinocytosis and exocytosis. Because of this movement, most extravascular fluids normally contain small amounts of plasma proteins. Regulatory proteins which make up less than 1% of plasma proteins are proteins such as enzymes, proenzymes and hormones.



Hypoproteinemia → edema Hypoproteinemia occurs mainly due to hypoalbuminemia. Normal albumin concentration maintains the plasma osmotic pressure. Hypoalbuminemia results in edema.

Causes of Hypoalbuminemia

a - Impaired synthesis: (e.g., due to diminished protein intake, liver disease)

b - Increased catabolism: As a result of tissue damage and inflammation.

c - Reduced absorption of amino acids: Caused by malabsorption syndromes.

d - Protein loss: In urine, due to: nephrotic syndrome, chronic glomerulonephritis, diabetes mellitus, or systemic lupus erythematosus. In feces, due to: protein-losing enteropathy arising from inflammatory or neoplastic disease; or from the skin itself through burns.

Red blood cells, anemias and polycythemias

The functions of red blood cells : The major function of red blood cells, also known as erythrocytes, is to transport hemoglobin, which in turn carries oxygen from the lungs to the tissues. The red blood cells have other functions, they contain a large quantity of carbonic anhydrase, an enzyme that catalyzes the reversible reaction between carbon dioxide (CO₂) and water to form carbonic acid (H₂CO₃), increasing the rate of these reaction several thousand fold. The red blood cells are responsible for most of the acid- base buffering power of whole blood.

The requirements for RBCs production: RBCs requires functional bone marrow, erythropoietin, thyroid hormone and adequate supplies of iron, vitamin B12, folic acid, pyridoxine and protein and traces of copper. The absence of any these components leads to either an impaired rate of RBCs production or to the formation of a typical cells. The regulation of RBCs production - The hormone erythropoietin controls the rate of RBC formation. - Erythropoietin is synthesized primarily in the kidneys. - Tissue oxygenation controls erythropoietin release. - Anemia or prolonged exposure to altitude (hypoxia) increases RBC synthesis. Impaired cardiac or pulmonary function also increases RBC synthesis as does pregnancy.

Anemia

Anemia: is the condition caused by the lack of dietary iron in the body, which reduce the count of the erythrocytes, i.e. blood corpuscles in the blood. An anemic person has poor quality of blood, which leads to circulatory problems in various organs in due course of time. People who take less iron sources in the diet will have a poor hemoglobin quality. The major cause of anemia is the deficiency of iron in the diet which causes various problems with the quality of the blood, the most important being the reduction in the number of red blood corpuscles. Anemia results from an imbalance between the rate of RBC synthesis and the rate of RBC loss. Anemia also result from RBC loss that accompanies hemorrhage and from the increased fragility characteristic of the sickle cell mutation.

Anemia classification according to cause:

1- Iron deficiency anemia: This is caused due to gross deficiency of iron in the body. Iron is essential for the building of hemoglobin and the red blood corpuscles of the blood. A low count of iron can be due to one or more of the following : Less intake of iron in the diet – Ulcers - Colon condition such as colon polyps or colon cancer. -Heavy periods.

2-Megaloblastic anemia: Megaloblastic anemia is caused due to the deficiency of water- soluble vitamins in the blood of the person, especially vitamin B12 and folic acid. This is a dietary deficiency. The amount of B12 in the blood can be lowered due to: Crohn's disease, an autoimmune disease which is responsible for reducing the count for red blood corpuscles in the blood.

3- Anemia due to underlying diseases: Some diseases can lower the count of the red blood corpuscles in the blood. Diseases such as kidney disorders and hormonal imbalances can lose their erythrocytes. Kidney patients lose large amounts of red blood corpuscles during dialysis.

4- Aplastic anemia: -This is a metabolic disorder in the body when the blood is unable to make an adequate amount of red blood corpuscles. This can occur due to a large number of factors such as: drugs used for rheumatoid arthritis. Diseases where the immune attacks the body, like lupus. Radiation and chemotherapy treatments for cancer. Bone marrow diseases. Some toxic chemicals.

5- Genetic anemia: Genetic anemia is a deficiency of red blood corpuscles in the blood caused due to inherited factors. Anemias classification according to red cell size



Blood loss anemia: After rapid hemorrhage, the body replaces the fluid portion of the plasma in 1 to 3 days, but this leaves a low concentration of red blood cells. If a second hemorrhage does not occur, the red blood cell concentration usually returns to normal within 3 to 6 weeks.

Microcytic hypochromic anemia: The red cells grow too large, with odd shapes and are called megaloblasts, these cells are mostly oversized, have bizarre shapes and have fragile membranes. These cells rupture easily leaving the person in dire need of an adequate of RBCs.

Hemolytic anemia Hereditary spherocytosis: The red cells are very small and spherical rather than being biconcave discs. On passing the splenic pulp and some other tight vascular beds, they are easily ruptured by even slight compression.

Sickle cell anemia: The cells have an abnormal type of hemoglobin called hemoglobin S. when this hemoglobin exposed to low concentrations of oxygen, it precipitates into long crystals inside the red blood cells. The precipitated hemoglobin also damages the cell membrane, so that the cell become highly fragile, leading to serious anemia. Once the process starts, it progress rapidly, eventuating in a serious decrease in red blood cells within a few hours and often death.

Effect of anemia on function of the circulatory system:

In sever anemia, the blood viscosity may fall, which decrease the resistance to blood flow in the peripheral blood vessels, due to increased the quantities of blood flow through the tissues and return to the heart, thereby greatly increasing cardiac output. Also, hypoxia causes the peripheral tissue blood vessels to dilate, allowing a further increase in the return of blood to the heart and sometimes three to four times normal. Thus one of the major effects of anemia is greatly increased cardiac output, which increased pumping workload on the heart. The increased cardiac output in anemia partially equalize the reduced oxygen- carrying effect of the anemia, because even though each unit quantity of blood carries small quantities of oxygen are actually delivered to the tissues. When a person with anemia begins to exercise, the heart is not capable of pumping. Consequently, during exercise, which greatly increases tissue demand for oxygen, extreme tissue hypoxia results and acute cardiac failure ensues. There are two populations of red cells present. One is normocytic, and the other is microcytic. This occurs either because an iron-deficient patient has been transfused or treated with iron, or in the Sideroblastic Anemias This high magnification view is of a peripheral blood smear in a patient with iron deficiency anemia, whose hemoglobin was in the 5 to 6 gram / deciliter range. A normal lymphocyte is seen for comparison purposes. The red cells are markedly hypochromic and microcytic. Increased platelets are also seen. peripheral blood in a patient with iron deficiency anemia who has been transfused. A double population of red blood cells is seen. One population is intensely hypochromic and probably microcytic, although there is no lymphocyte for comparison purposes. A population of normochromic normocytic red blood cells is seen, which represent the transfused erythrocytes. Some of those transfused cells appear spherocytic

Iron deficiency blood - One monocyte, 1 small lymphocyte

Iron Deficiency Anemia

The red cells are hypochromic and microcytic. One cell stands out as larger than the others and is stained a "slate" blue colour, i.e. shows polychromasia, the hallmark of a newly released red cell. Iron deficiency anaemia is commonly a symptom of chronic blood loss and this cause always requires consideration before any other. Young red cells inappropriately but universally referred to as reticulocytes complete their maturation in the hours following release into the circulation. There is loss of residual cytoplasmic RNA and consequently loss of basophilic staining. The remains of organelles are removed and the cell membranes are remodelled by the spleen, with some decrease in cell size.

When the tissue become hypoxic because of too little oxygen in the breathed air, such as at high altitudes, or because of failure oxygen delivery to the tissues, such as in cardiac failure, the blood- forming organs automatically produced large quantities of extra blood cells. This condition is called secondary polycythemia. The red cell count commonly rises to 6-7 million/mm³, about 30% above normal.

Physiologic polycythemia : A common type of secondary polycythemia, occurs in native who live at altitudes of 14,000 to 17,000 feet, where the atmospheric oxygen is very low. The blood count is generally 6- 7 million/mm³, this allows these people to perform reasonably high levels of continuous work even in a rarefied atmosphere.

Polycythemia vera (Erythremia) : In addition to those people who have physiologic polycythemia, others have a pathologic condition called Polycythemia vera. In which the red blood cell count may be 7-8 million/mm³ and the hematocrite may be 60-70% instead of 40-45%. polycythemia vera is caused by a genetic aberration in the hemocytoblastic cells that produce the blood cells. The blast cell no longer stop producing red cells when many cells are already present. This causes excess production of RBCs, also causes excess production of WBCs and platelets. not only the hematocrite increase, but the total blood volume also increases, on some occasions to almost twice normal. As a result, the entire vascular system becomes intensely engorged. In



addition, many blood capillaries become plugged by the viscous blood; the viscosity of the in Polycythemia vera sometimes increases from the normal of 3 times the viscosity of water to 10 times that of water.

Effect of polycythemia on function of the circulatory system:

Increases blood viscosity in polycythemia, decreases the rate of venous return to the heart. Conversely, the blood volume is greatly increased in polycythemia, which tends to increase venous return. The cardiac output in polycythemia actually is not far from normal, because these two factors more or less neutralize each other. The arterial pressure is also normal in most people with polycythemia, although in about one third of them, the arterial pressure is elevated. This means that the blood pressure-regulating mechanisms can usually offset the tendency for increased blood viscosity to increase peripheral resistance and, thereby, increase arterial pressure. Beyond certain limits, however, these regulations fail, and hypertension develops. A person with polycythemia vera ordinarily has a ruddy complexion with a bluish (cyanotic) tint to the skin.

Haematostasis

Haematostasis: Is the formation of the platelet plug and activation of the coagulation cascade. Haemostasis is the balance between clot formation and clot lysis. The main aim of this balance is to prevent bleeding without causing thrombosis. - The main mechanisms that prevent blood loss after an injury (the mechanism of blood coagulation): Normal haemostasis seals a break in the vascular system to limit blood loss. This repair process is attenuated by anticoagulants and fibrinolytic agents so that the clot is restricted to the damaged area of the circulation. Damage to the endothelial cell lining initiates platelet formation and possibly clotting. Platelets adhere to the exposed subendothelial (collagen) surface. Formation of a platelet plug depends on the presence of fibrinogen and is enhanced by clotting factor VIII. Platelet granules containing ADP, serotonin and thromboxane A cause platelets to adhere and also cause vasoconstriction. Simultaneously, the clotting mechanism is activated and thrombin promotes further platelet aggregation and release reactions. The fibrin mesh helps trap additional platelets and RBCs and complete the haemostatic plug.

The role of platelet in hemostasis Platelets alone control hemostasis when a damage involves a small area of the blood vessel. If the damage involves a large area, coagulation factors must join with platelets to form permanent clot. Coagulation depends on the sequential activation of number of clotting factor enzymes, most of which circulate in plasma in an inactive state. The fibrin mesh is formed by the action of thrombin or fibrinogen. The extrinsic pathway for fibrin formation is triggered by the release of tissue thromboplastin. The intrinsic pathway for fibrin formation uses clotting factors that are normally present in the blood. Hemostasis is enhanced by emotional stress, strenuous physical activity, epinephrine, pyrogens and vasopressin. All of these probably work through endothelial plasminogen activators.

The mechanism of blood coagulation (cascade mechanism): The clotting cascade is a series of enzymatic reactions leading to fibrin polymerization. Activation of either intrinsic or extrinsic pathway leads to the formation of prothrombin activator. Prothrombin activator catalyzes thrombin formation. Thrombin catalyzes fibrin formation. Fibrin polymerizes into a network of strands that traps cells and forms a clot. The extrinsic pathway is activated by disruption of the vascular endothelium and contact of blood with thromboplastin in the tissue spaces. Intrinsic pathway activation occurs following blood stasis or contact with negatively charged surfaces such as glass or collagen. - Factors required for blood coagulation: Clotting factors are synthesized primarily in liver except factor VIII, Von Willebrand factor, which comes from endothelial cells and megakaryocytes

Calcium and vitamin K role in blood clotting: Calcium is necessary co-factor for many of the clotting enzymes. Hepatic synthesis of clotting factors requires vitamin K and can be blocked by dicumarol and warfarin. These agents diminish the tendency for a new clot to form.

Fibrinolysis definition: Fibrinolysis is the dissolution of clots, primarily due to action of the enzyme plasmin.

Mechanism of fibrinolysis:

The fibrinolytic mechanism is activated a few hours after clot formation. Plasmin is formed by the action of tissue plasminogen activator on the plasma protein plasminogen. Plasmin is a proteolytic enzyme that dissolves fibrin, fibrinogen and factor V and VIII. Fibrin degradation products produced by clot lysis also act as anticoagulants. Plasmin is formed from plasminogen by streptokinase, staphylokinase and urokinase as well as intrinsic pathway components.

Natural intravascular anticoagulants: The ability to create clots to limit loss from sites of vascular injury is balanced by systems designed to limit clot formation and to dissolve existing clots. The blood contains natural anticoagulants that are continuously to inhibit clot formation. Fibrinolytic agents dissolve existing clots. In doing so, blood flow through the vascular system can be maintained.

The major anticoagulants in clinical use: Anticoagulants reduce the ability of clots to form and also prevent unrestricted clot growth. Natural anticoagulants prevent clot formation in the normal vascular system. Clinically, heparin, warfarin and aspirin are the most commonly used anticoagulants. –



Heparin: Act immediately to potentiate antithrombin III action and prevent clot formation.

Warfarin: Interferes with the vitamin K- dependent hepatic synthesis of clotting factors. Consequently, treatment with warfarin has little immediate effect but is useful for chronic suppression of clotting ability.

Aspirin: Is classified as an anticoagulant, but it acts on platelets to reduce their clotting ability by blocking thromboxane production rather than acting on the clotting cascade.

In vitro: Clot formation can be prevented by chlators citrate, EGTA & EDTA. Protein C which is activated by the clotting factor thrombin. Can prevent further clot growth and thus the normal clotting cascade produces an enzyme that helps stop the clotting process. **How blood clotting is prevented in normal vascular system :** Disorder can occur due to insufficient clotting activity. Which can be due to thrombocytopenia, the lack of thrombocytes due to improved production, enhanced breakdown or enhanced use of thrombocytes. Thrombocytopenia leads to a prolonged bleeding time. In contrast: thrombocytosis is defined as a platelet count greater than 800.000 but it also characterized by insufficient bleeding. Insufficient clotting can cause thrombosis, the occurrence of a clot within blood vessel. This can occur following endothelial damage , blood stasis or enhanced coagulability.

An embolus: is a clot that breaks free of its attachment site and is carried within the circulation. Emboli are trapped by the breathing pattern characteristic of the precapillary side of the circulation. Venous emboli are trapped in the lungs, which have enhanced clot lysis abilities. Left ventricular emboli become trapped in the systemic circulation and block blood flow to the area distal to the occlusion. Emboli are often responsible for stroke and myocardial infraction. Blood vessels break and repaired continuously in the body. The multiple and complex interactions between clot formation, clot lysis and anticoagulation allow normal vessel repair without precipitation of a massive clot throughout the vascular system. Functional tests of coagulation include bleeding time, clot retraction and platelet aggregation.

WHITE BLOOD CELLS

The leukocytes (white blood cells) :are the mobile units of the body's protective system. They are formed partially in the bone marrow (granulocytes & monocytes) and partially in the lymph tissue (lymphocytes and plasma cells). After formation, they are transported in the blood to different parts of the body where they are needed.

Normal functions of the various WBCs:

Polymorphonuclear neutrophils, polymorphonuclear eosinophils, polymorphonuclear basophiles, monocytes and occasionally plasma cells. In addition, there are large numbers of platelets, which are fragments of another type of cell similar to the white blood cells found in the bone marrow , the megakaryocyte. The granulocytes and monocytes protect the body against invading organisms mainly by ingesting them by phagocytosis. The lymphocytes and plasma cells function mainly in connection with the immune system. The function of platelets is specifically to activate the blood clotting mechanism.

The role of diapedesis: Neutrophils and monocytes can squeeze through the pores of the blood capillaries by diapedesis. That is, even though a pore is much smaller than a cell, a small portion of the cell slide through the pore at a time, the portion sliding through is momentarily constricted to the size of the pore.

Tissue macrophages:It is mainly the neutrophils and tissue macrophages that attach and destroy invading bacteria, viruses and other injurious agents.The neutrophils are mature cells that can and destroy bacteria even in the circulating blood. Conversely, the tissue macrophages begin life as blood monocytes, which are immature cells, while still in the blood and have little ability to fight infectious agents at that time.

Chemotaxis:Many different chemical substances in the tissue cause both neutrophils and macrophages to move toward the source of the chemical. When the tissue become inflamed, at least a dozen different products are formed that can cause chemotaxis toward the inflamed area. **They include:**1. Some of the bacterial or viral toxins.2. Degenerative products of the inflamed tissue.3. Several reaction products of the ((complement complex)) activated in inflamed tissues areas as well as other substances Chemotaxis depends on the concentration gradient of chemotactic substance.The concentration is greater near the source, which directs the unidirectional movement of the white cells.Chemotaxis is effective up to 100 micrometers away from an inflamed tissue. Therefore, because almost no tissue area is more than 50 micrometers away from the capillary , the chemotatic signal can easily move hordes of white cells from the capillaries into the inflamed area.

Phagocytosis The most important function of the neutrophils and macrophages in phagocytosis, which means cellular ingestion of the offending agent. phagocytes must be selective of the material that is phagocytized; otherwise, normal cell and structures of the body might be ingested.Whether phagocytosis will occur depends specially on three selective procedures. First: most natural structures in the tissues have smooth surfaces, which resist phagocytosis.But if the surface is rough, the likelihood of phagocytosis is increased.Second: most natural substances of the body have protective protein coats that repel the



phagocytosis. Conversely, most dead tissues and foreign particles have no protective coats, which makes them subject to phagocytosis. Third: the immune system of the body develops antibodies against infectious agents such as bacteria. The antibodies then adhere to the bacterial membranes and thereby make the bacteria specially susceptible to phagocytosis. To do this, the antibody molecule also combines with the C3 product of the complement cascade, which attach to receptors on the phagocyte membrane, thus initiating phagocytosis. This selection and phagocytosis process is called opsonization.

Immunity

The human body has the ability to resist almost all types of organisms or toxins that tend to damage the tissues and organs. This capability is called immunity. Much of immunity is acquired immunity that does not develop until after the body is first attacked by a bacterium, virus, or toxin, often requiring weeks or months to develop the immunity.

Basic concept of innate immunity: An additional portion of immunity results from general processes directed at specific disease organisms. This is called innate immunity. It includes the following:

- 1- Phagocytosis** of bacteria and other invaders by which blood cells and cells of the tissue macrophage system.
- 2- Destruction** of swallowed organisms by the acid secretions of the stomach and the digestive enzymes.
- 3- Resistance** of the skin invasion by organisms.
- 4- Presence** in the blood of certain chemical compounds that attach to foreign organisms or toxins and destroy them.

Some of these compounds are:

- A- Lysozyme**, a mucolytic polysaccharide that attacks bacteria and causes them to dissolve.
- B- Basic polypeptides**, which react with and inactivate certain types of gram-positive bacteria.
- C- The complement complex**, a system of about 20 proteins that can be activated in various ways to destroy bacteria and
- D- Natural killer lymphocytes** that can recognize and destroy foreign cells, tumor cells and some infected cells.

Basic concept of acquired immunity : In addition to its generalized innate immunity, the human body has the ability to develop extremely powerful specific immunity against individual invading agents such as lethal bacteria, viruses, toxins and even foreign tissues from other animals. This is called acquired or adaptive immunity. Acquired immunity is caused by a special immune system that forms antibodies and activated lymphocytes that attack and destroy the specific invading organism and some of its associated reactions especially the allergies. Cell participating in cellular and humoral immunity. There are two basic but closely types of acquired immunity occur in the body:

- 1. The body develops circulating antibodies**, which are globulin molecules in the blood plasma that are capable of attacking the invading agent. This type of immunity is called humoral immunity or B-cell (because B lymphocytes produce the antibodies).
- 2. The second type of acquired immunity** is achieved through the formation of large numbers of activated T-lymphocytes that are specifically crafted in the lymph nodes to destroy the foreign agent. This type of immunity is called cell-mediated immunity or T-cell immunity (because the activated lymphocytes are T-lymphocytes). Both the antibodies and the activated lymphocytes are formed in the lymphoid tissue of the body.

Role of lymphocyte in acquired immunity: Acquired immunity is the product of the body's lymphocytes. The lymphocytes are essential to survival of the human beings. The lymphocytes are located most extensively in the lymph nodes, but they are also found in special lymphoid tissues such as spleen, submucosal areas of the gastrointestinal tract, thymus and bone marrow. The lymphoid tissue is distributed advantageously in the body to intercept invading organisms or toxins because they can spread too widely.

Functional classification of lymphocytes - The invading agent first enters the tissue fluids and then is carried by way of lymph vessels to the lymph node or other lymphoid tissue. The lymphoid tissue of the gastrointestinal walls is exposed immediately to antigens invading from the gut.

The lymphoid tissue of the throat and pharynx (the tonsils and the adenoids) is well located to intercept antigens that enter by way of the upper respiratory tract. The lymphoid tissue of the lymph nodes is exposed to antigens that invade the peripheral tissues of



the body. The lymphoid tissue of the spleen, thymus and bone marrow plays the specific role of intercepting antigenic that have succeeded in reaching the circulating blood.

Chapter V

Cardiovascular system

Introduction to the cardiovascular system

The different functional structure of the heart Cardiovascular system (CVS) is formed of central pump "the heart" and closed system of blood vessels. -The function of circulation :-Maintain a suitable environment in all tissue fluids of the body. -Transport of nutrients to the body tissues. -Transport of waste products away from the body tissues. -To conduct hormones from one part of the body to another.

The heart is formed of two separate pumps:

(1)A right heart (volume pump against low resistance) : pump the blood through the lungs .

2)A left heart(pressure pump against high resistance):pump the blood to the peripheral organ . -Each pump is composed of:-The atrium and The Ventricle.

I-The atrium: -Functions mainly as a blood reservoir . -It also pumps weakly to help move the blood into the ventricle.

II-The ventricle: -Is the main force that pushes the blood to either the pulmonary or systemic circulation .In mammals ,there are two circulatory systems:[A]Major(systemic)circulations : (B)Lesser(pulmonary) circulation:.

Functional parts of the circulation: The function of the Aorta & large Arteries(Elastic arteries) -Transport blood und high pressure to tissues The small arteries and arterioles-Act as control vessels through which blood is released into the capillaries .The function of the capillaries:--Exchange fluid , nutrients. The function of the venules & veins:-Collect blood from the capillaries from Larger veins the heart . Lymphatic system Represents an accessory route by which fluids can flow from the ISF spaces ins blood stream Capacitance vessels:-are the veins that are partially collapsed .

Vascular capacitance = Increase in volume/ Increase in pressure

Function of the valves:

Cardiac valves : *The Atrioventricular valves: (A-V) -The tricuspid (right) and mitral (left) valves . -Prevent backflow of blood from the ventricles to the atria during systole **The Semilunar valves:**-The aortic and pulmonary artery valves. prevent backflow of blood from the aorta and pulmonary arteries into the ventricles during diastole .

Function of the papillary muscle-They contract when the ventricular walls contract .They pull the cusps of the valves inward toward the ventricles .Aortic and pulmonary artery valves Different from A-V valves

CELLULAR EVENTS OF THE HEART

Cardiac muscle: The heart is composed of:--Cells full of contractile muscle protein such as ventricular muscle cells.-The cardiac muscle also contains titin & dystrophin.*Titin filaments{3rdfilament system}:1-Titin keeps myosin thick filaments centered in the sarcomere.2- Congenital anomalies in Titin abnormal dilated heart .

Dystrophin :-Provides structural support & strength to the muscle fibril .-Congenital defects in dystrophin muscular dystrophy . The cardiac muscles are consists of:-- **Pericardium.** **-Myocardium-**

En docarium

Cardio myocytes: -Act as functional syncytium because of their intercellular connection [Intercalated disks] Functions of the intercalated disks -Provide a strong union between fibers. Contain gap junction Gap junction -Low resistance intercellular junction .-Little distributed gap junctions in: -The atrioventricular(AV)node causing slow conduction (delay) .Large distributed gap junctions in:-Purkinje fibers & ventricular muscle fiber causing rapid conduction .

The cardiac muscle has three types of membrane ionchannels

(1)Fast sodium channels

(2)Slow sodium-calcium channels



(3)Potassium channels

Cardiac conduction system: Cardiac muscle contracts regularly in the absence of external innervation -This is due to the presence of pace-maker cells that discharge spontaneously.-The heart beat originates in cardiac conduction system & spreads to all parts of the myocardium

(1)The Sinusnode (sinoatrial)node(SA node):- -It is located in the superior posterolateral wall of the right atrium immediately below the opening of the superior vena cava .

(2)The inter nodal pathways:-That conduct the impulse from the sinus node to the atrioventricular(A-V) node .

3)A-V node:-In which the impulse from the atria is delayed before passing into the ventricles .

(4)The (A-V) bundles :-Which conducts the impulse from the atria into the ventricles .

(5)Left&right bundle branches of Purkinje fibers Which conduct the cardiac impulse to all parts of the ventricles.

Characteristic of the heart (1)Electrical properties (Excitability) (2)Rhythmicity properties (Automaticity (3)Conductivity . (4)Mechanical properties (Contraction).

Automatic electrical rhythmicity (automaticity) of the sinus fibers of self-excitation , a process that can cause automatic rhythmical discharge Some cardiac fibers have the capability and contraction .-This is true for the fibers of sinus node (S A node) to control the rate of heart beat .

(1)Electrical properties: Definition:-Contracts rhythmically in the absence of external innervations. Due to the presence of pace-maker (S-A node) cells that discharge spontaneously The resting membrane potential (RMP) of the cardiac cells -Is about -85mv. -K⁺ is the predominant cytoplasmic cation -At rest the membrane is permeable to K⁺ Inward current=Depolarization Na⁺ & Ca⁺⁺ move from ECF to inside the cell (influx) Outward current=RepolarizationK⁺ move from inside the cell to outside (efflux) , and \ or Cl⁻ move from outside to inside (influx). -Equilibrium potential for K⁺ is established at -98 mV .At this potential K⁺ influx & K⁺ efflux are balanced .-Na⁺=K⁺ pump transfers 3 Na⁺ ions out & 2 K⁺ ions into the cell creates -4 mV difference .-Equilibrium potential for Na⁺ is established at +64Mv The Action potential If the membrane depolarizes to a threshold voltage ,it shifts its permeability ,so that it is permeable to Na⁺ or Ca⁺⁺ So depolarization[inward of Na⁺] is followed by recovery (repolarization) [outward of K⁺].

The Ventricular Action potential:- -An excitatory stimulus or pace maker potential

Phase 0 (Rapid depolarization and overshoot) . Phase 1 (Rapid repolarization to +10mV) Phase 2 (Plateau). Phase 3 (Repolarization). Phase 4 (Resting membrane potential).

Aim of the Ventricular action potential Maintain entry of Ca⁺⁺ during long plateau forced contraction Proper ejection of the blood . Changes of excitability during the action potential

(1)Absolute refractory period: It is the interval of time during which normal cardiac impulse can't excite an already excited as of cardiac muscle .

(2)Relative refractory period : -During which the excitability(muscle contraction) of cardiac membrane is subnormal .-Cardiac muscle remain relative refractory until phase 4 (first half of diastole).

(3)Vulnerable or dangerous period:-A critical interval with the last half of diastole time .-In which the excitability is supernormal Autonomic control of Sinoatrial node(SA-nod) (1)Stimulation of parasympathetic (vagal fibers) Release of Ach at the nerve ending increase K⁺ Conductance of nodal tissue hyperpolarization. decrease rate of the heart . -This action is mediated by M2 muscarinic receptor

(2)Stimulation of the sympathetic cardiac nerves:-Release norepinephrine by the sympathetic nerve endings binds to β_1 receptors. Increase intracellular cAMP. Facilitates opening of L-type Ca⁺⁺ channels increasing the rapidity of the depolarization increase heart rate **N.B:** The temperature rises(fever) increase heart rate(HR). Digitalis (cardiac glycosides) decrease heart rate (HR).

THE HEART AS A PUMP



Excitation-contraction coupling: It is the process by which membrane depolarization (A.P) is translated into mechanical action .

The process occurs in 3 stages:-

(1) First ,Ca⁺⁺ is rapidly increased leading to a-Binding of Ca⁺⁺ to troponin .b-Allowing myosin to interact with actin . c-Contraction .

(2) Second ,Ca⁺⁺ is reduced to its resting level leading to:- a-Stop the actin-myosin interaction . b-Relaxation .

(3) Finally ,Calcium release process is recovered before next contraction . Excitation-contraction coupling in cardiac muscle -Is an example of Ca⁺⁺ induced Ca⁺⁺ release (CICR) -The Na⁺ current (AP) trigger Ca⁺⁺ influx. Ca⁺⁺ rises just under membrane surface. Ca⁺⁺ entering the cytoplasm from extracellular space. Bind to the channel on the surface of sarcoplasmic reticulum (SR) [called Ryanodine receptor RYR] Trigger Ca⁺⁺ release from SR. Contraction is initiated when enough Ca⁺⁺ is bound to troponin. L-type Ca⁺⁺ channel blockers (DHP) can reduce contraction (-ve inotropic effect). Three mechanisms lower (Ca⁺⁺) & produce relaxation :-

(a) Ca⁺⁺ is pumped back into the SR by an ATP-

B - dependent Ca⁺⁺ pump. (b) Ca⁺⁺ is transported out of the cell by Na⁺-Ca⁺⁺ exchanger.

(c) Ca⁺⁺ binds to Ca⁺⁺ intercellular puffing protein (calmodulin)

Relation between the action potential and the cardiac contractile response : The cardiac contractile response to. Begins just after the start of depolarization. Lasts about 1.5 the action potential. Cardiac contraction (systole) reaches its maximum by the end of plateau. Relaxation (diastole) begins with the rapid phase of repolarization. repolarization is completed by the end of the first half of diastole.

Conductivity: Definition:- Spread of cardiac excitation (A.P) -The heart tissue must maximize conduction of [A.P] from SAN through atrial & ventricular cells for pumping blood efficiently. The velocity of spread of A.P is determined by:- (A) Speed of upstroke of action potential: The ventricular (A.P) has a high speed of upstroke, [Na⁺ Entry] The SA nodal (A.P) has slower speed of upstroke, [Ca⁺⁺ Entry] (B) The intercellular resistance : **Intercellular gap junctions** :. Are distributed little in slowly conducting AV node.. Are distributed large in the rapidly conducting Purkinje system. Depolarization initiated in the SA node: inter nodal tracts through the atria Converges on the AV node. Atrial depolarization is completed in 0.1 second. ***AV nodal delay**: -Conduction in the AV node is slow (0.5 m/s) Delay of 0.1 s before excitation spreads to the ventricle. Allow sufficient time for atria to empty their blood into the ventricles (before ventricular systole occurs). -Sympathetic stimulation shortens the AV nodal delay. -Vagal (parasympathetic stimulation) and digitalis lengthen the AV nodal delay. **Purkinje fibers:** The wave of depolarization spreads very rapidly in the purkinje fibers (4m/s). To all parts of the ventricle [0.08-0.1] second. So, the ventricle contract as one unit. Correlation between muscle fiber length and tension:-

Starling's law of the heart:- Increasing sarcomere length associated with increased force of the muscle contraction within limits .(A) **Passive or resting length-tension curve** Progressive adding weights (preload) without stimulation leading to progressive increases in (B) **Active (contraction) length-tension curve**: .When a muscle strip is stretched by a load (preload) and stimulated The active length-tension curve can be obtained by: Plotting the peak tension for each contraction against the associated resting length. The passive & Active isometric-length-tension curve: *Also provides a frame-work for isotonic contractions because the tension developed by a muscle at the end of its shortening phase Two types of loads in the intact heart (1) **Preload in intact heart** -Is the degree to which the myocardium is stretched before it contracts. =End Diastolic Volume EDV. a .**The length of a resting muscle at (EDV).** b .**The tension developed** \propto the pressure developed inside the ventricles. (2) **Afterload in intact heart** The tension at which the load is lifted. -The muscle contracts & shortens isotonicly without further increase in tension. -Is the resistance against which blood is expelled =End systolic pressure (aortic pressure).

Factors affecting the performance of cardiac muscle : (1) Resting muscle length (preload) [End diastolic volume EDV]. (2) **The level of afterload** (aortic pressure). (3) **The inotropic state** (contractility). (4) **Frequency of contraction** . -The performance of cardiac muscle can be measured by : a-Extent of shortening (ΔL). b-Velocity of shortening (Δt) [(1) & (2)] preload & afterload [Mechanical determination]: -Two cardiac function curves are used to demonstrate the effect of preload & after load [1] Length-tension curve: Length shortening curve: .At the same level of after load Increasing preloads b) Load shortening curve: .At the same level of preload Increasing after loads 2] Load-velocity curve 2-At the same level of preload Increase after loads [3] The inotropic state {Contractility} Inherent capacity of the myocardium to contract independently of the changes in preload & after load Increase End diastolic Volume (EDV) increase the tension developed ((4) **Force-frequency Relation:** Stair case or treppe phenomenon: *As the heart rate represents the frequency of the contraction of the whole heart. *Heart rate affects the inotropic state through Variations in Ca⁺⁺ release and/ or reuptake. *Increases in heart rate:



CARDIC CYCLE

Cardiac cycle: The period from the beginning of one heart beat to the beginning of the next. -In propagation of cardiac impulse:-There is 0.1s delay between passages from the atria into the ventricles to Allows the atria to contract separate of the ventricle. -Pumping blood into the ventricles before ventricular contraction. The cardiac cycle consists of Diastole(relaxation)[heart fills with blood].-**Systole(contraction)**.In the vascular system:-Systolic pressure: is the peak(highest)pressure During systole. **Diastolic pressure: is the** lowest pressure during diastole.Length of systole & diastole :- **At heart rate 75 beats/min** ,the duration of cardiac cycle=0.80 s divided into systolic period=0.30 s & diastolic period=0.50 s. Variation in length of systole diastole with heart rate: during diastole: coronary blood flow to sub endocardial portions of the left ventricle occurs and most of the ventricular filling occurs in diastole -When the heart rate is increased: diastole is shortened greater than systole. -At heart rates up 180b|min sufficient venous return,& cardiac output per minute. -At very high HR>200b|min decrease filling & heart failure

Events of the cardiac cycle:The following parameters are recorded at the same time in different phases of the cardiac cycle:(1)Duration of each phase .(2)Closure & opening of each valve.(3)Ventricular volume.(4)Ventricular pressure.(5)Aortic pressure .(6)Atrial pressure .(7)Heart sounds.(8)Electrocardiogram (ECG). **A-In Late diastole** :(1) Atrial Systole(Booster phase) :. The mitral&tricuspid valves are open .The aortic &pulmonary valves are closed..Contraction of the atria pushes 30% of blood into the ventricles . **B-Ventricular Systole:**Isovolumetric(isometric)ventricular contraction: [0.05 s] At the start of ventricular systole:.The mitral& tricuspid(AV) valves closed (first sound) According to Laplace Law($T=P \times r$) the pressure increases ventricular ejection phases:Begins by opening of aortic & pulmonary valves.-At first: Ejection is rapid(maximum ejection.increase the left ventricular pressure to 120 mmHg.increase the right ventricle to 25mmHg .Then reduced ejections : as systole progresses . Late in systole: The aortic pressure > the ventricular pressure(but for a moment as to keep the blood moving forward) The AV valves:Are pulled down by the contractions Of the papillary muscle which lead to decrease the Atrial pressure .Stroke volume(SV):Is the amount of the blood ejected by each ventricle(at rest =70- 90 ml).The End-diastolic ventricular volum(EDV) = 130ml **Thus:The End-systolic ventricular volum(ESV) $ESV=EDV-SV=130-80=50$ ml** -It is the volume of blood remains in each ventricle at the end of systole Ejection fraction(EF): -% of the end-diastolic volume that is ejected with each stroke=60% -It is available index of ventricular function . In early diastole: Proto diastolic phase=0.04 s Once the ventricular muscle is fully contracted Leads to the ventricular pressure drops more rapidly (second sound) Isovolumetric ventricular relaxation After the aortic & pulmonary valves are closed decrease of intraventricular pressure without change in ventricular volume **Ventricular filling phases:** (7)At first rapid filling then slow . (8)Reduced ventricular filling in mid diastole .

Atrial pressure: -Continues to rise after the end of ventricular systole until the AV valves open,then drops and slowly rises again(another cycle) P wave precedes the atrial systole by 0.02 sec. QRS complex precedes the isovolumetric contraction phase by 0.02 sec. T wave: starts in maximum ejection phase .peaks in reduced ejection phase .ends by the end of isovolumetric relaxation phase .

Pressure-volume Graph of the left ventricle:--**Phase I:**Period of filling:-During Diastole:.The ventricle fill with blood passively **Phase II** : Period of isovolumic contraction -When the heart is activated: it moves from the diastolic curve to the systolic **Phase III:** Period of ejection: -As soon as the ventricular pressure > the aortic pressure The aortic valve opens and the ventricle eject blood into the aorta. **Phase IV** : Period of isovolumic relaxation :- -At the end of ejection ,end-systolic volume , the aortic valve closes and the heart relaxes isovolumetrically **Stroke volume(SV)=(EDV)- (ESV)=150 -75=75 ml** Aortic pressure curve-Systolic pressure caused by :- During ventricular ejection ,blood entry into the aorta after opening of the aortic- valve, then stretch the wall of the aorta & arteries increase the pressure to =120 mmHg -**Diastolic pressure:** Before the ventricle contracts again the aortic pressure falls to 80 mmHg

Arterial Pulse Definition :- -The blood forced into the aorta during systole Recording : The pulse is felt in the radial artery at the wrist. pulse pressure= systolic pressure – diastolic prThe atrial pressure changes are transmitted to the great veins:- producing 3 characteristic waves in the record of Jugular pressure. The "a" wave due to Atrial systole. The "c" wave due to: during isovolumetric ventricular contraction The "v" wave is due to: rise in atrial pressure before the AV valve open during diastole **Heart Sound Causes:**Closure of the valves and rapid movement of blood within the heart .Recording:-Heard by stethoscope at the chest wall.Types:Two sounds are normally heard during each cardiac cycle . sudden closure of mitral& tricuspid valves. Closure of aortic & pulmonary valves

The Electrical activity of the heart and the ECG

ECG records the rapid voltage changes(biphasic) of large tissue masses in the heart Because the body fluids are good conductors: So, the changes can be recorded extracellular on the surface of the skin .-A high-speed recording meter(electrocardiograph) on a moving strip of paper is used .

The Electrocardiograph Machine:It has two terminal electrodes : positive & negative electrode.-The voltage changes are detected in milli volt (mv).Cardiac Impulse and ECG Patterns:The ECG waves :-Shows the P , QRS complex ,&T waves .- The P wave Represent atrial depolarization.-The QRS waves: Represent ventricular depolarization.-ST segment& T wave: Represent ventricular repolarization .-The atrial repolarization is hidden by the QRS complex(ventricular depolarization) -P-R segment :-Caused by slows down conduction through the AV node .-An isoelectric segment .-From the end of P to the start of QRS complex-S T segment:Coincides with plateau phase of monophasic A. P Relationship of the Monophasic AP. Of cardiac muscle to the QRS&T



waves of ECG : The monophasic action potential of ventricular muscle recorded from a microelectrode inserted inside a single ventricular muscle fiber. -The simultaneous recording of the ECG from the same ventricle by placing two external electrodes on the skin shows: The QRS coincides with the rapid depolarization coincides with the last rapid repolarization. The ST segment: is part of repolarization coincides with plateau. -Relation of the cardiac contraction to the waves of ECG : Depolarization spreads through the muscle before its contraction. -The P waves occur before the beginning of contraction of the atria. -The QRS complex occurs immediately before the beginning of ventricular contraction. The ventricles remain contracted until after the end of the T waves.

Biphasic record : [Electrocardiogram Recording]: -Two important points are considered during the ECG record: **(1) The direction of the depolarizing current during the record.** **(2) The position of the positive electrode** of the ECG machine on the skin. If a mass of cardiac muscle is stimulated at its center : Before stimulation: outside is positive & inside is negative. When the central area becomes depolarized : Negative charge leak to the outside making the depolarized area negative (outside) & positive (inside). **In normal heart** : Current flow from the base to the apex during the cycle of depolarization [the skin area near the base of the heart will be negative & near the apex will be positive. **The depolarization** current flows from negative area to positive area **At repolarization** : The first part that depolarized is the first part that repolarized. [Is the rule]. -At the beginning of repolarization, the flow of current from positive to negative (The opposite of depolarization) -**At complete repolarization** The deflection returns back to the base line.

Calibration & measurements of the ECG : The horizontal lines are arranged : so, each 10 small divisions (upward or downward) represents 1 mV, with +ve in upward & -ve in downward direction. The vertical lines are time calibration lines. Each small square = 0.04s. Each 25 small squares = 1s. Each 1500 small squares = 1 min. [every 5 squares are involved in one big square]

Comment on normal ECG . **(1) Heart rate (HR):** HR = The no. of small squares in one min. (1500) / m. No. of small squares of one cardiac cycle. (between 2 following R waves). HR = 70 – 75 beats/ min & known as normal sinus rhythm (NSR). **(2) Rhythm** : Comparing the duration of the cardiac cycles, by counting the no. of small squares between 2 following R waves. Regular rhythm: the durations are nearly equal **(3) Voltage of ECG** : Normally, the voltage of the ECG from (1.5-3.5)mV [15-35 mm]. **(4) Axis of the heart** : from -30° to +90° is the main vector of QRS complexes at frontal plane (I, II, III). Physiological normal variations of axis of the heart : -Left axis deviation (such as -50°) pregnant woman -Short stunted adult -Right axis deviation (+130°) : Long slender individuals **5) P waves (+ve)** :-Represent atrial depolarization. -Amplitude 0.25 mV (2.5mm) -Duration 0.08s -0.1s (2.5mm) -Because depolarization of the right atrium occurs before the left atrium :-The first half of the P wave represents right atrial depolarization. -The second half of the P wave represents left atrial depolarization. **(6) The P-R segment & interval** :-PR segment: measured from the end of P wave to the beginning of QRS complex (0.08-0.1s) [2.5] Represents conduction through AV node. Duration 0.16 -0.2s [0.18s] Its abnormal variations shortening or lengthening : mean abnormal conduction from atria to ventricles **(7) QRS complex** : It represents ventricular depolarization. Duration 0.08s Amplitude (by normal summation): 1mV (10mm) in limb leads. 3-4mV (30-40) in chest leads. -The variations in voltage of QRS diagnosis of ventricular hypertrophy. **8) Q-T interval: From the beginning of QRS complex to the end of T wave.** 0.4s -Represents ventricular depolarization + ventricular repolarization. **(9) ST segment** : -It is an isoelectric line (Same level of T-P line) -It coincides with plateau phase of monophasic action potential Elevation of the ST segment indicates Myocardial infarction. **(10) T wave : represent ventricular repolarization** . Duration 0.16 s , 0.5 – 1.0 mV. ECG abnormalities

Disorders of Rhythm :- Normal sinus rhythm = (60 -100/ min.) **Simple sinus tachycardia** : HR (100 -150 b/min ECG is normal. [P, QRS & T]. Caused by: sympathetic stimulation lead to fever leads to increase in heart beats: 8 beats/minute in adult. 10-15 beats in child for each 0.5o C **Simple sinus bradycardia** : HR < 60 b/min ECG is normal [P, QRS & T]. Caused by: -Athletes at rest (high vagal stimulation). -Vagal stimulation leads to severe bradycardia in carotid sinus syndrome.

The control of the cardiac output

Stroke volume (SV) : It is the volume of the blood pumped by each ventricle/beat. -Stroke volume = End-diastolic volume (EDV) – End-systolic volume (ESV) = 70ml in a resting man

Cardiac output (COP): It is the volume of blood pumped by each ventricle / minute. -In a resting supine man: COP = SV × HR = 70ml × 72 beats/min. = 5 L/min .

Cardiac index (CI): Is the output per minute per square meter of body surface. Cardiac index = $5L \sqrt{1.7m^2} = 3.2 L/min/m^2$ There are 4 factors operate simultaneously to modulate the heart's performance to meet different physiologic conditions (e.g. changing posture, exercise): **(1) The pre load (EDV).** **(2) The after load (Aortic pressure).** **(3) The inotropic state (contractility).** **(4) The heart rate (HR).**

Regulation of the cardiac output : -The heart & the vascular system provide organs with a continuous blood flow to meet their metabolic demand. -Cardiac output is determined by: the interplay between the heart & the peripheral circulation (vascular system). COP primarily affected by: cardiac function So, in the steady state COP = VR.



Heterometric regulation: Regulation of COP due to changes in cardiac muscle fiber length (Preload) [EDV] Homometric regulation :[Independent of length] : Regulation of COP due to change in contractility (inotropic state of the heart)

Venous Return Curve: 3 factors affect venous return (VR): 1-Mean systemic filling pressure (MSFP). 2-Right Atrial Pressure (RAP). 3-Resistance to venous return (RVR). $VR = \frac{RAP - MSFP}{RVR}$. -Venous filling pressure: Is the pressure gradient between MSFP and RAP. -It is the primary determinant of venous return.-

Venous return is affected by :

(1)Mean systemic filling pressure (MSFP): Definition:It is the distending pressure of all vessels in the circulation at a particular blood volume.-Normally range = 6-8 mmHg. **2- Right atrial pressure (RAP):**-Decrease RAP Increase pressure gradient between peripheral veins & right atrium increase venous return (VR).-RAP is normally = 0-2 mmHg . **-3-Resistances to blood flow** between the peripheral vessels & right atrium:-At any RAP ,there is indirect relation between resistance to VR(RAR) & flow of blood In the normal human:.. $VR = 5 \text{ L /min. MSFP} = 7 \text{ mmHg} \text{ ..RAP} = 0 \text{ mmHg} \text{ . So ,RVR} = 1.4 \text{ mmHg / L of blood flow} \text{ . Cardiac output Curve Cardiac output curve utilizes the relation between COP \& Filling pressure (RAP).-COP curve can be influenced by: (1)Venous filling pressure. (2) After load : Aortic pressure. (3)Contractility "inotropic stat of the heart" . (4)Heart rate (HR). (5)Cardiac hypertrophy.Flow} = \frac{MSFP - RAP}{Resistance (RVR)}$

1)Venous filling pressure Factors that increases venous filling pressure, tone, increase EDV increase COP Factors that increases or decreases the length of ventricular muscle fibers(EDV). Increase Strong atrial contraction .-Increase total blood volume .-Increase sympathetic Decrease Standing .-Increase Intra pericardial pressure .-Decrease Ventricular compliance **Starling's law** : Increasing EDV tends to increase COP.-Increase COP is because of increase in SV. **2)After load : Aortic pressure** Is determined by : the left ventricular systolic pressure. = Aortic pressure. **(3)Contractility** : inotropic state of the heart .-Increase the force generation tension for muscle Length increase contractility increase the Stroke volume (SV) Factors that influence contractility (myocardial inotropic state): -Intrinsic factors.-Extrinsic factors.

(i) Intrinsic factors 1-Force frequency relation ship: Increase the frequency (HR) increase the force of 2-Insufficient blood supply (Ischemia): due to decrease O₂ & acidosis decrease the force of Contraction (decrease inotropic state). **3-Myocardial failure: decrease inotropic state . (ii)Extrinsic factors :*****Increase inotropics:** A-Sympathetic(adrenergic) stimulation:Causes release of norepinphrine in myocardium which acting on β_1 receptors Activation of c-AMP. Accelerating relaxation B-Xanthines (caffeine) inhibit the breakdown of c-AMP increase c-AMP C- Glucagon: increase the form.ation of c-AMP D-Digitalis :has inhibitory effect on the Na⁺-K⁺ ATP-ase in the myocardium: Increase strength of contraction . E-Increase extracellular Ca⁺⁺ -Increase the inotropic state of the cardiac muscle .Calcium rigior:at very high Ca⁺⁺ concen. **Decrease inotropic** : A-Parasympathetic (vaggous) [Acetylc choline] B-Calcium antagonists Dihydroopyridine(DHP) & Anti-arrhythmic drugs: decrease inotropic state . The effect of Heart Rate(HR) on COP : $COP = HR \times SV$. **Cardiac hypertrophy** : 1-Eccentric hypertrophy:(Volume Overload) During severe exercise 2-Concentric Hypertrophy(Pressure Overload):occurs during high blood pressure **Equilibrium between VR and COP** : -The heart represented by left ventricle using right atrial pressure(RAP)to provide heart's input . The only mechanism that equalizes VR with COP is Starling's Law where EDV=(Preload)when there is increase in RAP lead to decrease VR(preload) and when increase in preload(EDV) leads to increase in tension leads to increase COP. **Ejection Fraction (EF):** $EF = \frac{SV}{EDV}$.-It is the fraction of ventricular volume that is ejected with each beat Cardiac responses to exercise: **During exercise:** Increase COP (up to 8 fold[40L/min] in severe exercise in trained man **Venous return(VR) & cardiac output(COP) :** **A- In untrained normal subjects:** During initial , milder exercise: increase tension of abdominal & muscle increase resistance to VR (after load) **B-In trained** atheletes :As in long sistance runners (marathoner). The heart hypertrophy of the volume over load type (Eccentric hypertrophy) :increased EDV(Preload) increase COP up to 40 L /min Cardiac Work & Oxygen consumption: The heart is a constantly working organ(use high energy). The heart is only 0.3% of the body weight in man. Myocardial oxygen consumption[MVO₂] **The myocardial O₂ consumption is determined by:** -Systolic pressure. -Stroke volume. -Inotropic state (contractility) . -Heart rate . Because cardiac venous O₂tension is low : increase O₂ consumption require increases in Coronary blood flow . Work output of the heart : $Work = load \times distance = P \times L$. Stroke Volume =SV= [EDV- ESV]. Shortening of the muscle = L **The stroke work output of the heart** : Is the energy that the heart converts to work during each heart beat . The work output of the heart is in 2 forms : (1)Volume -pressure work or external work(98%) (2) The kinetic energy of blood flow (2%).

Cardiac arrhythmias

Disorder of Rhythm Normal sinus rhythm=60-100/min .

(1)Simple sinus tachycardia : Heart rate(HR)=100-150 b /min ECG is normal. -Caused by:Sympathetic stimulation.

(2)Simple sinus bradycardia : -HR = 60 b/min . ECG is normal. Caused by: Vagal stimulation

(3) Arrhythmias : -A- Atrial arrhythmias : [i] Atrial tachycardia:-Occurs in attacks [ii] Atrial flutter :discharges regularly and very rapidly(200)b/min [iii]Atrial fibrillation(AF): -Multiple ectopic foci discharge irregularly & Very rapidly(300-500 b/min).P waves absence **-B-Ventricular arrhythmias:-[i]Ventricular extrasystole (ventricular premature beat VPB)** Caused by: .Excessive smoking Lack of sleep. .Excessive coffee .Alcoholism [ii] Paroxysmal ventricular tachycardia:- -Appears as a series of VPBs without normal beats cardiac output is Decreased markedly .



II-Chamber Enlargement-(1)-Atrial enlargement: -a-Right atrial enlargement-As in chronic obstructive pulmonary disease (COPD) .-P waves narrow (b)Left atrial enlargement(LAE)"P-mitral" As in mitral valve disease P waves widened to 0.12 **(2)Ventricular enlargement:**[a]Left ventricular hypertrophy(LVH): -Left axis deviation.[b]Right ventricle hypertrophy(RVH):-There are reversal of precordial pattern with; Tall R over right Deep S over left

III :Disorders of conduction: (A)Incomplete heart block: 1-First degree heart block:-2-Second degree heart block:[B]Complete(third-degree)heart block [C]Bundle branch block :

IV Abnormalities due to organic lesion: Myocardial infarction :-Caused by: Interrupted blood supply to part of the myocardium Irreversible changes[death of the myocardium] Myocardial infarction

The E C G: (A)IN acute myocardial infarction:-There are 3 major abnormalities:(1)Abnormal rapid repolarization due to increase opening of K⁺ channel loss of intracellular K⁺ (2)The second change:Decline in the RMP of the infarcted area .(3)The third change:The infarcted fibers begin to depolarize more slowly.B)After some days or weeks-The ST segment abnormalities subside -The dead muscle and tissue become electrical silent .-The infarcted area is negative relative to the normal myocardium during systole the appearance of Q wave(not present) increase in the size of the normal Q wave

The autonomic nervous system and the cardiovascular system

Autonomic Nervous System: 1-The sympathetic nervous system. 2-The parasympathetic nervous system Sympathetic Innervation of the Blood Vessels. - In most tissues all the vessels except the capillaries, precapillary sphincters

Sympathetic Nerve Fibers to the Heart. -In addition to sympathetic nerve fibers supplying the blood vessels, sympathetic fibers also go directly to the heart.-Sympathetic stimulation markedly increases the activity of the heartControl of the Heart by the Sympathetic and Parasympathetic nerves:-The pumping effectiveness of the heart also is controlled by the sympathetic and parasympathetic(vagus) nerves, which abundantly supply the heart. -The amount of blood pumped each minute (cardiac output) often can be increased more than 100 per cent by sympathetic stimulation. - By contrast, the output can be decreased to as low as zero or almost zero by vagal (parasympathetic) stimulation.Mechanisms of Excitation of the Heart by the Sympathetic Nerves.- Strong sympathetic stimulation can increase the heart rate increase the maximum cardiac output as much as twofold to threefold Parasympathetic (Vagal) Stimulation of the Heart. - Strong stimulation of the parasympathetic nerve fibers in the vagus nerves to the heart can stop the heartbeat for a few seconds, but then the heart usually "escapes" and beats at a rate of 20 -40 beats/min Parasympathetic Control of Heart Function, Especially Heart Rate.-The parasympathetic nervous system plays only a minor role in regulation of the circulation **Emotional Fainting—Vasovagal Syncope.** vasodilatory reaction occurs in people who experience intense emotional disturbances that cause fainting. -The arterial pressure falls rapidly, which reduces blood flow to the brain and causes the person to lose consciousness. -This effect is called vasovagal syncope

Role of the Nervous System in Rapid Control of Arterial Pressure: - One of the most important functions of nervous control of the circulation is its capability to cause rapid increases in arterial pressure. **Baroreceptor Reflexes** - Basically, this reflex is initiated by stretch receptors, or pressoreceptors, located at specific points in the walls of several large systemic arteries. -A rise in arterial pressure ►stretches the baroreceptors and causes them to transmit signals into the central nervous system. -"Feedback" signals are then sent back through the autonomic nervous system to the circulation to reduce arterial pressure downward toward the normal level.**Function of the Baroreceptors During Changes in Body Posture.** - The ability of the baroreceptors to maintain relatively constant arterial pressure in the upper body is important when a person stands up after having been lying down. **Chemoreceptor reflex:** chemoreceptor reflex that operates in much the same way as the baroreceptor reflex except that chemoreceptors, instead of stretch receptors, initiate the response. The chemoreceptors are chemosensitive cells sensitive to oxygen lack, carbon dioxide excess, and hydrogen ion excess.**The Bainbridge Reflex:** An increase in atrial pressure also causes an increase in heart rate, sometimes increasing the heart rate as much as 75 %.An additional 40 to 60 per cent increase in rate is caused by a nervous reflex called the Bainbridge reflex. **The "Volume Reflex."**Stretch of the atria also causes significant reflex dilation of the afferent arterioles in the kidneys. And still other signals are transmitted simultaneously from the secretion of antidiuretic hormone.**Vasovagal syncope** Definition:Sever attacks of hypotension and fainting that occur in people with hypertensive carotid sinus. The sinus is sensitive to slight pressure e.g. during shaving or wearing a tight collar.**Treatment: By** 1-Anticholinergic drugs e. g. atropine. 2-Denervation of carotid sinus. **Clinical significance:-** This reflex could be used to terminate an attack

Interrelationships Among Pressure, Flow, and Resistance: Blood flow through a blood vessel is determined by two factors: (1) pressure difference of the blood between the two ends of the vessel, (2) The impediment to blood flow through the vessel, which is called vascular resistance. The flow through the vessel can be calculated by the following formula, which is called Ohm's law: $F = \Delta P/R$

Laminar Flow of Blood in Vessels When blood flows at a steady rate through a long, smooth blood vessel, it flows in streamlines, with each layer of blood remaining the same distance from the vessel wall. - Completely. In blood vessels if the blood pressure falls below critical closing pressure, then the vessels collapse. This happens during a measurement of blood pressure with a



sphygmomanometer. This occurs at the critical closing pressure, closing off blood supply to tissues which can lead to toxic shock. Turbulent Flow of Blood Under Some Conditions: .

Turbulent flow : - Means that the blood flows crosswise in the vessel as well as along the vessel, usually forming whorls in the blood called eddy currents. - When eddy currents are present, the blood flows with much greater resistance than when the flow is streamline because eddies add tremendously to the overall friction of flow in the vessel. The tendency for turbulent flow increases in direct proportion to the velocity of blood flow, the diameter of the blood vessel, and the density of the blood, and is inversely proportional to the viscosity of the blood, in accordance with the following equation: $Re = \frac{V \cdot D \cdot \rho}{\eta}$ where Re is Reynolds' number and is the measure of the tendency for turbulence to occur, n is the mean velocity of blood flow (in centimeters/second), d is the vessel diameter (in centimeters), ρ is density, and η is the viscosity (in poise). In the proximal portions of the aorta and pulmonary artery, Reynolds' number can rise to several thousand during the rapid phase of ejection by the ventricles; this causes considerable turbulence in the proximal aorta and pulmonary artery where many conditions are appropriate for turbulence: (1) high velocity of blood flow, (2) pulsatile nature of the flow, (3) sudden change in vessel diameter, and (4) large vessel diameter. However, in small vessels, Reynolds' number is almost never high enough to cause turbulence. Imagine blood flowing through a blood vessel which has a certain radius and a certain wall thickness. The blood vessel wall is stretched as a result of the difference between the blood pressure inside the vessel and the surrounding pressure outside the vessel. La Place's law describes the relationship between the transmural pressure difference and the tension, radius, and thickness of the vessel wall. Obviously, the higher the pressure difference the more tension there will be. On the other hand, the thicker the wall the less tension there is. Also, the larger the radius the more tension there is. These three rules culminate into one equation: $T = P \cdot R/M$ Where T is the tension in the walls, P is the pressure difference across the wall, R is the radius of the cylinder, and M is the thickness of the wall. An example of LaPlace Law is Dilated cardiomyopathy. In this condition heart becomes greatly distended and the radius (R) of ventricle increases. Therefore to create the same pressure (P) during ejection of the blood much larger wall tension (T) has been developed by the cardiac muscle. Thus dilated heart requires more energy to pump the same amount of blood as compared to the heart of normal size. The new surgical procedure, called ventricular remodeling, uses LaPlace principle to improve the function of dilated, failing hearts. Imagine yourself blowing a balloon. The harder you blow the higher the air pressure inside the balloon and the higher the pressure difference between the outside and inside of the balloon become. Since the pressure difference rises, the tension in the rubber walls of the balloon also rises, and this is what causes the balloon to stretch. Now imagine you are blowing a balloon which is made of much thicker rubber. Now you will notice that the balloon is harder to inflate because more pressure difference is required to raise the tension in the walls of the balloon. Inside the balloon at equilibrium. But examination immediately reveals that there are great differences in wall tension on different parts of the balloon. The variation is described by Laplace's Law. Once you have established the geometry of the balloon, then the tension, pressure and radius have a definite relationship and could be used to measure tension or pressure. In the interesting experiment of putting one end of a balloon into liquid nitrogen, you can collapse one end of it by cooling while the other end stays essentially at its previous radius.

Pressure and flow in systemic circulation

Arterial blood pressure (ABP) Arterial blood pressure: It is the lateral pressure exerted by the blood on the arterial wall. It normally oscillates during the cardiac cycle reaching a maximum during cardiac systole (S.B.P) & minimum at the end of diastole (D.B.P.). **Systole blood pressure (S.B.P):** It is the maximum pressure reached during systole. It equals 90- 140 mmHg (average 120 mmHg) in normal adults. **Diastole blood pressure (D.B.P.):** It is the minimum pressure reached during diastole. It equals 60- 90 mmHg (average 80 mmHg) in normal adults. **Pulse pressure (P.P.):** It is the difference between SBP & DBP. It equals $120 - 80 = 40$ mmHg (30- 50 mmHg). **Mean arterial blood pressure** It is the average pressure throughout the cardiac cycle. $= DBP + \frac{1}{3} PP = 80 + \frac{1}{3} \times 40 = 93$ mmHg (90-95 mmHg).

Physiologic factors affecting ABP:

- Age:** ABP varies with age: a- In newborns, it is about 80/40 mmHg. b- At the age of 20 years, it is about 120/180 mmHg. c- At the age of 60 years, it is about 150/90 mmHg. ABP is relatively low in infants because of: A- The lower pumping force of the heart. B- The greater width of the blood vessels. C- The greater elasticity of arterial walls. ABP increase with advanced age due to arteriosclerosis. $SBP = 100 + \text{age}$ (except than after 60 years) $DBP = \frac{1}{2} SBP + 20$. 2- **Sex:** i- In children, ABP is identical in both sexes. ii- In adult age, ABP is lower in female than in male by 5 mmHg. iii- At menopause, ABP is higher in female than in male by 5 mmHg due to: Hormonal changes as decreased estrogen. Emotional stress. 3- **Race:** Black races have higher arterial blood pressure than white races (due to genetic factors). Orientals have lower ABP than American & European due to: High cholesterol content of diet of European & Americans ► atherosclerosis. Stress of life in these industrial countries. The climate ► low temperature ► increased ABP. 4- **Body constitution (body built):** ABP is usually higher in obese persons than normal. 5- **Meals:** ABP increased slightly after meals (especially SBP) due to: Increased absorption from intestine. VD in splanchnic area. 6- **Emotions:** Emotions are accompanied with enhanced sympathetic activity ► increased cardiac output and V.C. tone ► increased ABP. 7- **Exercise:** SBP ► increased up to 180 mmHg (increased C.O. discharge). DBP ► due to VD of arterioles in active muscles. 8- **Sleep:** Quite and deep sleep ► ABP (due to decreased sympathetic activity). Stressful dreams & night mares ► increased ABP. 9- **Diurnal variation (circadian rhythm):** ABP is normally lowest in early morning & highest in the afternoon. 10- **Gravity:** On standing ► the force of gravity increased mean ABP and venous pressure below a reference point in the heart (in the right atrium near the tricuspid valves) and decreased them above that point by about 0.77 mmHg/cm in each case. So at the feet, ABP becomes 180- 200 mmHg & venous pressure 80- 90 mmHg. Mechanism of arterial blood pressure regulation: The endogenous regulation of arterial pressure is not completely understood. Currently, three mechanisms of regulating arterial pressure have been well-characterized:



Baroreceptor reflex: Baroreceptors in various organs can detect changes in arterial pressure, and adjust the mean arterial pressure by altering both the force and speed of the heart's contractions, as well as the total peripheral resistance. Renin-angiotensin system (RAS): This system is generally known for its long-term adjustment of arterial pressure. - This system allows the kidney to compensate for loss in blood volume or drops in arterial pressure by activating an endogenous vasoconstrictor known as angiotensin II. - Aldosterone release: - This steroid hormone is released from the adrenal cortex in response to angiotensin II or high serum potassium levels.- Aldosterone stimulates sodium retention and potassium excretion by the kidneys. - Since sodium is the main ion that determines the amount of fluid in the blood vessels by osmosis, aldosterone will increase fluid retention, and indirectly, arterial pressure. These different mechanisms are not necessarily independent of each other, as indicated by the link between the RAS and aldosterone release. Currently, the RAS system is targeted pharmacologically by ACE inhibitors and angiotensin II receptor antagonists. The aldosterone system is directly targeted by spironolactone, an aldosterone antagonist. The fluid retention may be targeted by diuretics; the antihypertensive effect of diuretics is due to its effect on blood volume. Generally, the baroreceptor reflex is not targeted in hypertension because if blocked, individuals may suffer from orthostatic hypotension and fainting

Effect of sudden standing up on ABP:SBP: Decreased due to decreased VR by the effect of gravity ►decreased SV.DBP:Increased due to:Decreased SBP ►decreased stimulation of baroreceptors in aortic arch and carotid sinus ►- Reflex VC ► increased PR& decreased blood velocity.b- increased Hr shorten diastolic period ►DBP doesn't go down to its normal value.- These effects on ABP can be prevented by standing up in water. The reference point for pressure measurement:This is the point in the heart at which changes in the body position has significant effect (1-2 mmHg) on hydrostatic pressure. This point is at the tricuspid valve level.It is almost in the midline above the lower end of the sternum & back to the anterior chest wall.**11- Respiratory movements:**ABP shows rhythmic fluctuations during the respiratory cycle called: respiratory pressure waves or traube- Hering waves.- **ABP increased during the late part of the inspiration** and early part of expiration, while it decreased during the remainder part of respiratory cycle **During inspiration:**a- **At the start of inspiration:**Increased -vety of IPP ►increased VR and RTV cardiac output and increased pulmonary circulatory capacity which accommodate most of the cardiac output of RTV ►decreased pulmonary VR ►decreased left ventricle cardiac output ►decreased ABP.**b) At late part of inspiration:**The active respiration center (RC) stimulate the VCC in MO ►VC ►increased ABP.**During expiration:**At the start of expiration: Pulmonary VR ►increased left ventricle cardiac output ►increased arterial blood pressure.**At the end of expiration:**The arterial blood pressure decrease ►decrease discharge to the VCC. **Factors maintaining normal arterial pressure:**Arterial blood pressure = cardiac output x P.R.Increased cardiac output or P.R. ► increased arterial blood pressure.Increased cardiac output (increased S.V.) ► increased systolic blood pressure.Increased P.R. ►increased diastolic blood pressure.**Cardiac output (C.O.):**Arterial blood pressure is directly proportional to the cardiac output.Cardiac output = SV x Heart Rate.**The Renin-Angiotensin System: Its Role in Pressure Control and in Hypertension** The kidneys have another powerful mechanism for controlling pressure. It is the renin angiotensin system. Renin is a protein enzyme released by the kidneys when the arterial pressure falls too low. In turn, it raises the arterial pressure in several ways, thus helping to correct the initial fall in **pressure Renin-angiotensin system** The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure and water (fluid) balance.When blood volume is low, the kidneys secrete renin. Renin stimulates the production of angiotensin. Angiotensin causes blood vessels to constrict, resulting in increased blood pressure.Angiotensin also stimulates the secretion of the hormone aldosterone from the adrenal cortex. Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water. This increases the volume of fluid in the body, which also increases blood pressure.If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high. There are many drugs that interrupt different steps in this system to lower blood pressure. These drugs are one of the main ways to control high blood pressure (hypertension), heart failure, kidney failure, and harmful effects of diabetes.It is believed that angiotensin I may have some minor activity, but angiotensin II is the major bio-active product. **Angiotensin II has a variety of effects on the body:**In the kidneys, it constricts glomerular arterioles, having a greater effect on efferent arterioles than afferent. As with most other capillary beds in the body, the constriction of afferent arterioles increases the arteriolar resistance, raising systemic arterial blood pressure and decreasing the blood flow.However, the kidneys must continue to filter enough blood despite this drop in blood flow, necessitating mechanisms to keep glomerular blood pressure up. To do this, angiotensin II constricts efferent arterioles, which forces blood to build up in the glomerulus, increasing glomerular pressure. The glomerular filtration rate (GFR) is thus maintained, and blood filtration can continue despite lowered overall kidney blood flowBecause the filtration fraction has increased, there is less plasma fluid in the downstream peritubular capillaries. This in turn leads to a decreased hydrostatic pressure and increased osmotic pressure (due to unfiltered plasma proteins) in the peritubular capillaries. The effect of decreased hydrostatic pressure and increased osmotic pressure in the peritubular capillaries will facilitate increased reabsorption of tubular fluid. Angiotensin II decreases medullary blood flow through the vasa recta. This decreases the washout of NaCl and urea in the kidney medullary space. Thus, higher concentrations of NaCl and urea in the medulla facilitate increased absorption of tubular fluid. Furthermore, increased reabsorption of fluid into the medulla will increase passive reabsorption of sodium along the thin ascending limb of the loop of Henle **Angiotensin II stimulates** Na⁺/H⁺ exchangers located on the apical membranes (faces the tubular lumen) of cells in the proximal tubule and thick ascending limb of the loop of Henle in addition to Na⁺ channels in the collecting ducts. This will ultimately lead to increased sodium reabsorption Angiotensin II stimulates the hypertrophy of renal tubule cells, leading to further sodium reabsorption. In the adrenal cortex, it acts to cause the release of aldosterone. Aldosterone acts on the tubules (e.g., the distal convoluted tubules and the cortical collecting ducts) in the kidneys, causing them to reabsorb more sodium and water from the urine. This increases blood volume and, therefore, increases blood pressure. In exchange for the reabsorbing of sodium to blood, potassium is secreted into the tubules, becomes part of urine and is excreted ADH also acts on the central nervous system to increase an individual's appetite for salt, and to stimulate the sensation of thirst. Release of anti-diuretic hormone (ADH), also called



vasopressin -- ADH is made in the hypothalamus and released from the posterior pituitary gland. As its name suggests, it also exhibits vaso-constrictive properties, but its main course of action is to stimulate reabsorption of water in the kidneys. These effects directly act in concert to increase blood pressure. predict how systemic vascular resistance (C.V.S.) will react in common situations: eating a meal, exercise and changes in posture

Cardiac reserve: Is the difference between the work performed by the heart under basal conditions (rest) and that performed during severe muscular exercise. Mechanism of cardiac reserve and its limits 1- Cardiac acceleration: Increased heart rate ►increased cardiac output specially when it is accompanied with the inotropic effect of sympathetic which occurs secondary to muscular exercise. Its limit: - Excessive acceleration above 200 beat/ min ►shortening of diastolic period ►decreased ventricle filling ►decreased cardiac output.

Mechanism of cardiac reserve and its limits : 1- Cardiac acceleration: 2- Increased Stroke Volume S.V. Homometric autoregulation of the heart: b) Heterometric autoregulation of the heart: 3) Cardiac hypertrophy:). a- Physiological hypertrophy b- Pathological hypertrophy:

Coronary vasodilatation reserve: A- Myocardial O₂ demand is the powerful control in coronary blood flow (reactive hyperemia).B- Adrenaline also produce marked increase in coronary flow.2- Increased Stroke Volume S.V.a) **Homometric autoregulation of the heart:**Musculars exercise ►increased sympathetic activity ►positive inotropic effect ►increased force of myocardial contraction ►increased SV.Its limit:The heart can not use its residual volume.(much decrease of SV ►cause injury of the endocardium).b) **Heterometric autoregulation of the heart:**Ms exercise ►increased VR ►increased EDV ►increased of ventricular contraction ►increased SV (Starling 's law).Its limit:Excessive dilatation of the ventricles ►reduction of strength of contraction ►decreased SV ►decreased cardiac output.

Cardiac hypertrophy: Increased size of myocardium occurs when the heart is exposed to repeated prolonged high work loading.a- Physiological hypertrophy:Occurs in athletes practicing continues sever exercise e.g. weight lifting or marathon runners (athletic heart b- Pathological hypertrophy: Occurs in patients with chronic hypertension or aortic stenosis. Coronary vasodilatation reserve:A- Myocardial O₂ demand is the powerful control in coronary blood flow (reactive hyperemia).B- Adrenaline also produce marked increase in coronary flow.

Effects of low cardiac reserve:1. Dyspnea and cyanosis:Resulting from low cardiac output ►stagnant hypoxia► sensation of air hunger.2- Tachycardia:Due to development of nervous reflexes to overcome the low cardiac output.3- Body fatigue:Resulting from muscle ischaemia.The compensatory mechanisms that maintain blood pressure on rising from the supine to the standing position:Body position accentuates the effect of gravity on venous return Orthostatic hypotension can occur when a person arise suddenly from a prone position or as blood pools in the legs of soldiers at parade attention for long period.The reduced venous return leads to the drop in blood pressure. Syncope causes the body to assume a prone position, which eliminates the gravity- induced circulatory problem.Prolonged bed rest causes a redistribution of circulating blood volume away from gravity dependent regions, such as the legs and toward the trunk ►increased venous arterial pressure and stretch of the cardiopulmonary receptors. Patients who stand after prolonged bed rest experience orthostatic hypotension. Acceleration can also induce venous pooling and syncope. This is prevented by augmenting the flow of blood from the legs toward the heart.

Cardiac metabolism compared to the skeletal muscle metabolism: Cardiac muscle is a type of involuntary striated muscle found in the walls of the heart, specifically the myocardium. Cardiac muscle cells are known as cardiac myocytes (or cardiomyocytes). Cardiac muscle is one of three major types of muscle, the others being skeletal and smooth muscle.Cardiac muscle shares similarities with skeletal muscle with regard to its striated appearance and contraction, with both differing significantly from smooth muscle cells.**Metabolism:** Cardiac muscle is adapted to be highly resistant to fatigue: it has a large number of mitochondria, enabling continuous aerobic respiration via oxidative phosphorylation, numerous myoglobins (oxygen-storing pigment) and a good blood supply, which provides nutrients and oxygen. The heart is so tuned to aerobic metabolism that it is unable to pump sufficiently in ischemic conditions.At basal metabolic rates, about 1% of energy is derived from anaerobic metabolism. This can increase to 10% under moderately hypoxic conditions, but, under more severe hypoxic conditions, not enough energy can be liberated by lactate production to sustain ventricular contractions. Under basal aerobic conditions, 60% of energy comes from fat (free fatty acids and triglycerides), 35% from carbohydrates, and 5% from amino acids and ketone bodies. However, these proportions vary widely according to nutritional state. For example, during starvation, lactate can be recycled by the heart. This is very energy efficient, because one NAD⁺ is reduced to NADH and H⁺ (equal to 2.5 or 3 ATP) when lactate is oxidized to pyruvate, which can then be burned aerobically in the TCA cycle, liberating much more energy (ca 14 ATP per cycle).

Circulatory changes that occur during exercise: A- General effects:I- Increased heart rate II- Increased venous return: III- Increased stroke volume IV- Increased cardiac output: V- Increased arterial blood pressure:VI- Increased CBF and cardiac metabolism B- Local effects in active muscles: A- Vasodilatation of muscle arterioles (increased muscle blood flow): B- Increased tissue fluid formation and lymph flow: C- Increased O₂ consumption:

Effect of acceleration on circulation: A-"Blacking out" phenomenon:B- "Redding out" phenomenon:Circulation changes after heavy meal:Circulatory changes that occur during exercise:A- General effects:I- Increased heart rate (up to 200 beats/min.) due to:1- Emotional influences: arising from cerebral cortex and hypothalamus ►inhibition of CIC & stimulation of CAC



increased heart rate may occur before the athlete starts his gain. 2- Stimulation of the respiratory center: By excess CO₂ & acid metabolites as lactic acid ► irradiation of inhibitory impulses to CIC and stimulatory impulses to CAC. 3- Stimulation of chemoreceptors: In aortic and carotid bodies by excess CO₂ increased H⁺ & O₂ lack ► stimulation of CAC (by hypernea). 4- Bainbridge reflex: Due to increased venous return pressure. 5- Increased blood temperature: ► Stimulation of hypothalamus, respiratory center, CAC and SA node. 6- Alam- Smirk reflex: Due to afferent impulses from skeletal muscle proprioceptors. 7- Secretion of adrenaline: By suprarenal medulla ► direct stimulation of SA node. II- **Increased venous return:** Due to 1- Contraction of the active muscle pumps blood in veins & capillaries towards the heart. They act as a peripheral hearts. 2- Contraction of respiratory muscles (respiratory pumps) ► increased negativity of intrapleural pressure during respiration. 3- Increased blood volume by contraction of the spleen & increased venous constrictor tone (increased venous activity). III- **Increased stroke volume:** 1- Increased coronary blood flow ► increased myocardial contraction. 2- Direct action of adrenaline on myocardium ► contractility (+ inotropic effect). 3- Starling's law due to greater filling of the ventricles due to increased venous return. IV- **Increased cardiac output:** (up to 35 liters/ min.): 1- Increased stroke volume. 2- Increased heart rate. Cardiac output= Stroke volume x heart rate. 3- Increased volume return. V- **Increased arterial blood pressure:** 1- The mean ABP increase ► increased cardiac output. 2- Systolic blood pressure increased ► increased SV. 3- Decreased diastolic blood pressure ► marked decrease in total PR by metabolic VD of skeletal muscle arterioles. 4- Increased pulse pressure. VI- **Increased CBF and cardiac metabolism: During rest,** about 200 ml of blood pass through the coronary flow and the cardiac metabolism. The rise in the effective perfusion pressure and the dilatation of the coronaries allow about 2 liters of blood to flow through the coronaries B- **Local effects** in active muscles: A- Vasodilatation of muscle arterioles (increased muscle blood flow): - This occurs before starting exercise, mainly through the sympathetic vasodilatation system, which consist of sympathetic cholinergic nerve fibers that supply the skeletal muscle vessels ► vasodilatation (with greatly increases the blood flow in active muscle). Once exercise has started, the following local mechanisms maintaining the vasodilatation and increased blood flow. 1- Accumulation of vasodilatation metabolites (particularly K⁺). 2- Fall of the O₂ tension and rise of CO₂ tension (i.e. local hypoxia and hypercapnia) as well as increased H⁺ due to lactic acid formation. 3- Rise of the temperature of active muscles. 4- Circulating epinephrine (adrenaline) released from the suprarenal medulla. 5- Loven 's reflex. 6- Mechanical vasodilatation by the increased arterial blood pressure. B- Increased tissue fluid formation and lymph flow: Vasodilatation of the muscle arterioles, metarterioles & precapillary sphincters increases the open capillaries 10- 100 times. These effects increase the capillary blood pressure more than the oncotic pressure of the plasma proteins throughout the whole length of the capillaries, which together with the accumulation of osmotically- active-metabolites in the tissue spaces ► a marked increase in the interstitial (tissue) fluid formation. - This results in a great increase in the lymph flow from the active muscles ► limits the accumulation of interstitial fluid & increase its turnover. C- **Increased O₂ consumption:** The O₂ consumption of skeletal muscles may increase 100 times during severe exercise. This is helped by: 1- The great increase in blood flow rate. 2- Shifting of the O₂ dissociation curve to the right, which decreases the O₂ affinity to Hb ► more O₂ is given up by the blood to the active muscles. 3- As a result, the coefficient of O₂ utilization in active muscles is increased & the arterio- venous O₂ difference rises up to 3 times **Effect of acceleration on circulation:** A constant speed acceleration whatever great has no effect on circulation. A change in speed of acceleration either linear or angular has great effect on circulation. No effect occurs when the force acts in the anteroposterior axis. Displacement of blood into the opposite direction leading to: A- "**Blacking out**" phenomenon: Occurs when blood shifts from head to lower limbs ► hypoxia of retinal receptors ► decreased VR ► decreased cardiac output ► loss of vision (Black out). This condition is temporary. B- "**Redding out**" phenomenon: - Due to shifting of blood from lower limbs to head ► excessive congestion of retinal vessels ► red vision as seeing everything red, hemorrhages may occur in eye, brain, face.....etc.

Circulation changes after heavy meal: 1- When we eat, hormones are activated to function in digestion and food absorption. These hormones increase blood pressure, speed heart beat, and contain substances, such as serotonin, that aid in the formation of clots. 2- After eating a heavy meal, blood pressure rises. Elevated blood pressure can cause plaque to rupture and form a clot. - High blood pressure also requires the heart to work harder to increase oxygen intake 3- A meal that is high in fat puts pressure on the walls of the arteries. This poses another risk factor for rupture of plaque and blockage of circulation by a blood clot. 4- Insulin rises more rapidly after a heavy meal and inhibits normal relaxation of the coronary artery. - This is yet another threat for plaque rupture and clot formation.

Special circulations

Coronary, pulmonary, Cerebral and Skeletal circulation

Systemic circulation:- Is the portion of the cardiovascular system which transports oxygenated blood away from the heart, to the rest of the body, and returns oxygen-depleted blood back to the heart.- Systemic circulation is, distance-wise, much longer than pulmonary circulation, transporting blood to every part of the body. In the systemic circulation, arteries bring oxygenated blood to the tissues. As blood circulates through the body, oxygen diffuses from the blood into cells surrounding the capillaries, and carbon dioxide diffuses into the blood from the capillary cells. Veins bring deoxygenated blood back to the heart Arteries Oxygenated blood enters the systemic circulation when leaving the left ventricle, through the aortic semilunar valve. The first part of the systemic circulation is the artery aorta, a massive and thick-walled artery. The aorta arches and gives off major arteries to the upper body before piercing the diaphragm in order to supply the lower parts of the body with its various branches. Capillaries Blood passes from arteries to arterioles and finally to capillaries, which are the thinnest and most numerous of the blood vessels. These capillaries help to join tissue with arterioles for transportation of nutrition to the cells, which absorb oxygen and nutrients in the blood. Peripheral tissues do not fully deoxygenate the blood, so venous blood does have oxygen, but in a lower concentration than in arterial blood. In addition, carbon dioxide and wastes are added. The capillaries can only fit one cell at a time. Venules The



deoxygenated blood is then collected by venules, from where it flows first into veins, and then into the inferior and superior vena cavae, which return it to the right heart, completing the systemic cycle. The blood is then re-oxygenated through the pulmonary circulation before returning again to the systemic circulation. Veins The relatively deoxygenated blood collects in the venous system which coalesces into two major veins: the superior vena cava (roughly speaking from areas above the heart) and the inferior vena cava (roughly speaking from areas below the heart). These two great vessels exit the systemic circulation by emptying into the right atrium of the heart. The coronary sinus empties the heart's veins themselves into the right atrium.

Pulmonary circulation: - Is the portion of the cardiovascular system which carries oxygen-depleted blood away from the heart, to the lungs, and returns oxygenated blood back to the heart. - The term is contrasted with systemic circulation. - A separate system known as the bronchial circulation supplies blood to the tissue of the larger airways of the lung. In the pulmonary circulation, deoxygenated blood leaves the right section of the heart through the pulmonary artery, enters the lungs and oxygenated blood comes through the pulmonary veins. - The blood then moves to the left atrium of the heart then to the left ventricle where the blood is pumped through the semilunar valve into the aorta. Right heart - Oxygen-depleted blood from the body leaves the systemic circulation when it enters the right heart, more specifically the right atrium through the superior (upper) vena cava and Inferior (lower) vena cava. - The blood is then pumped through the tricuspid valve (or right atrioventricular valve), into the right ventricle. - Blood is then pumped through the semilunar valve and into the pulmonary artery. Arteries - From the right ventricle, blood is pumped through the pulmonary semilunar valve into the left and right pulmonary arteries (one for each lung) and travels through the lungs. Lungs - The pulmonary arteries carry deoxygenated blood to the lungs, while the pulmonary veins carry oxygenated blood to the red blood cells where they release carbon dioxide and pick up oxygen during respiration. Veins - The oxygenated blood then leaves the lungs through pulmonary veins, which return it to the left heart, completing the pulmonary cycle. - This blood then enters the left atrium, which pumps it through the bicuspid valve, also called the mitral or left atrioventricular valve, into the left ventricle. - The blood is then distributed to the body through the systemic circulation before returning again to the pulmonary circulation.

Coronary circulation: The coronary circulatory system provides a blood supply to the heart. It provides oxygenated blood to the heart, it is part of the systemic circulatory system. The heart pumps oxygenated blood to the body and deoxygenated blood to the lungs. In the human heart there is one atrium and one ventricle for each circulation, and with both a systemic and a pulmonary circulation there are four chambers in total: left atrium, left ventricle, right atrium and right ventricle. The right atrium is the upper chamber of the right side of the heart. The blood that is returned to the right atrium is deoxygenated (poor in oxygen) and passed into the right ventricle to be pumped through the pulmonary artery to the lungs for re-oxygenation and removal of carbon dioxide. The left atrium receives newly oxygenated blood from the lungs as well as the pulmonary vein which is passed into the strong left ventricle to be pumped through the aorta to the different organs of the body.

Cerebral circulation: Inferior aspect of the human brain showing the arterial pattern Cerebral circulation The movement of blood through the network of blood vessels supplying the brain. The arteries deliver oxygenated blood, glucose and other nutrients to the brain and the veins carry deoxygenated blood back to the heart, removing carbon dioxide, lactic acid, and other metabolic products. Since the brain is very vulnerable to compromises in its blood supply, the cerebral circulatory system has many safeguards. Failure of these safeguards results in cerebrovascular accidents, commonly known as strokes. The amount of blood that the cerebral circulation carries is known as cerebral blood flow. The presence of gravitational fields or accelerations also determine variations in the movement and distribution of blood in the brain, such as when suspended upside-down. The following description is based on idealized human cerebral circulation. The pattern of circulation and its nomenclature vary between organisms. There are two main pairs of arteries that supply the cerebral hemispheres and the cerebellum: Internal carotid arteries: These large arteries are the left and right branches of the common carotid arteries in the neck which enter the skull, as opposed to the external carotid branches which supply the facial tissues. The internal carotid artery branches into the anterior cerebral artery and continues to form the middle cerebral artery. Vertebral arteries. These smaller arteries branch from the subclavian arteries which primarily supply the shoulders, lateral chest and arms. - Within the cranium the two vertebral arteries fuse into the basilar artery, which supplies the midbrain, cerebellum, and usually branches into the posterior cerebral artery. - Both internal carotid arteries, within and along the floor of the cerebral vault, are interconnected via the anterior communicating artery. - Additionally, both internal carotid arteries are interconnected with the basilar artery via bilateral posterior communicating arteries. The Circle of Willis, long considered to be an important anatomic vascular formation, provides backup circulation to the brain. In case one of the supply arteries is occluded, the Circle of Willis provides interconnections between the internal carotid arteries and basilar artery along the floor of the cerebral vault, providing blood to tissues that would otherwise become ischemic. Cerebral venous drainage The venous drainage of the cerebrum can be separated into two subdivisions: superficial and deep. - The superficial system is composed of dural venous sinuses, which have walls composed of dura mater as opposed to a traditional vein. The dural sinuses are, therefore, located on the surface of the cerebrum. The most prominent of these sinuses is the superior sagittal sinus which flows in the sagittal plane under the midline of the cerebral vault, posteriorly and inferiorly to the torcula, forming the confluence of sinuses, where the superficial drainage joins with the sinus that primarily drains the deep venous system. - From here, two transverse sinuses bifurcate and travel laterally and inferiorly in an S-shaped curve that form the sigmoid sinuses which go on to form the two jugular veins. In the neck, the jugular veins parallel the upward course of the carotid arteries and drain blood into the vena cava. - The deep venous drainage is primarily composed of traditional veins inside the deep structures of the brain, which join behind the midbrain to form the Vein of Galen. - This vein merges with the Inferior sagittal sinus to form the Straight sinus which then joins the superficial venous system mentioned above at the confluence of sinuses. The nerve supply of the skeletal blood vessels and the skeletal blood flow during muscular exercise: Previously mentioned in the last lecture. Tissue fluid formation and Edema **Frank-Starling law of the heart-** The Frank-



Starling law of the heart (also known as Starling's law or the Frank-Starling mechanism) states that the greater the volume of blood entering the heart during diastole (end-diastolic volume), the greater the volume of blood ejected during systolic contraction (stroke volume) and vice-versa. This allows the cardiac output to be synchronized with the venous return, arterial blood supply and humeral length without depending upon external regulation to make alterations Physiology As the heart fills with more blood than usual, the force of the muscular contractions will increase. This is a result of an increase in the load experienced by each muscle fiber due to the extraneous blood entering the heart. The stretching of the muscle fibers increases the affinity of troponin C for calcium, causing a greater number of cross-bridges to form within the muscle fibers; this increases the contractile force of the cardiac muscle. The force that any single muscle fiber generates is proportional to the initial sarcomere length (known as preload), and the stretch on the individual fibers is related to the end-diastolic volume of the ventricle. In the human heart, maximal force is generated with an initial sarcomere length of 2.2 micrometers, a length which is rarely exceeded in the normal heart. - Initial lengths larger or smaller than this optimal value will decrease the force the muscle can achieve. For larger sarcomere lengths, this is the result of less overlap of the thin and thick filaments; for smaller sarcomere lengths, the cause is the decreased sensitivity for calcium by the myofilaments. - Stroke Volume = End diastolic volume (preload volume) - End systolic volume (afterload volume) The role of the capillary pressure and the colloidal osmotic pressure of plasma protein in the formation of tissue fluid- Hydrostatic pressure is generated by the pumping force of the heart. - It pushes water out of the capillaries. - The water potential is created due to the ability of small solutes to pass through the walls of capillaries. - This buildup of solutes induces osmosis. - The water passes from a high concentration (of water) outside of the vessels to a low concentration inside of the vessels, in an attempt to reach an equilibrium. The osmotic pressure drives water back into the vessels. - Because the blood in the capillaries is constantly flowing, equilibrium is always reached. The balance between the two forces differs at different points on the capillaries. - At the arterial end of a vessel, the hydrostatic pressure is greater than the osmotic pressure, so the net movement favors water and other solutes being passed into the tissue fluid. - At the venous end, the osmotic pressure is greater, so the net movement favors substances being passed back into the capillary. - This difference is created by the direction of the flow of blood and the imbalance in solutes created by the net movement of water favoring the tissue fluid.

Physiological function: - Interstitial fluid bathes the cells of the tissues. - This provides a means of delivering materials to the cells, intercellular communication, as well as removal of metabolic waste. Composition- Interstitial fluid consists of a water solvent containing amino acids, sugars, fatty acids, coenzymes, hormones, neurotransmitters, salts, as well as waste products from the cells. The composition of tissue fluid depends upon the exchanges between the cells in the biological tissue and the blood. This means that tissue fluid has a different composition in different tissues and in different areas of the body. Not all of the contents of the blood passes into the tissue, which means that tissue fluid and blood are not the same. Red blood cells, platelets, and plasma proteins cannot pass through the walls of the capillaries. The resulting mixture that does pass through is, in essence, blood plasma without the plasma proteins. Tissue fluid also contains some types of white blood cell, which help combat infection. Lymph is considered a part of the interstitial fluid. The lymphatic system returns protein and excess interstitial fluid to the circulation. The ionic composition of the interstitial fluid and blood plasma vary due to the Gibbs-Donnan effect. This causes a slight difference in the concentration of cations and anions between the two fluid compartments

Edema : Is an abnormal accumulation of fluid beneath the skin or in one or more cavities of the body. Generally, the amount of interstitial fluid is determined by the balance of fluid homeostasis, and increased secretion of fluid into the interstitium or impaired removal of this fluid may cause edema. **Five factors can contribute to the formation of edema:** It may be facilitated by increased hydrostatic pressure or, Reduced oncotic pressure within blood vessels; by increased blood vessel wall permeability as in inflammation; 3. By obstruction of fluid clearance via the lymphatic; or, 4. By changes in the water retaining properties of the tissues themselves. 5. Raised hydrostatic pressure often reflects retention of water and sodium by the kidney. Mechanism Generation of interstitial fluid is regulated by the forces of the Starling equation. Hydrostatic pressure within blood vessels tends to cause water to filter out into the tissue. This leads to a difference in protein concentration between blood plasma and tissue. As a result the oncotic pressure of the higher level of protein in the plasma tends to suck water back into the blood vessels from the tissue Starling's equation states that the rate of leakage of fluid is determined by the difference between the two forces and also by the permeability of the vessel wall to water, which determines the rate of flow for a given force imbalance. Most water leakage occurs in capillaries or post capillary venules, which have a semi-permeable membrane wall that allows water to pass more freely than protein. If the gaps between the cells of the vessel wall open up then permeability to water is increased first, but as the gaps increase in size permeability to protein also increases with a fall in reflection coefficient. Changes in the variables in Starling's equation can contribute to the formation of edema either by an increase in hydrostatic pressure within the blood vessel, a decrease in the oncotic pressure within the blood vessel or an increase in vessel wall permeability. The latter has two effects. It allows water to flow more freely and it reduces the oncotic pressure difference by allowing protein to leave the vessel more easily. Edema types **1. Generalized edema :** A rise in hydrostatic pressure occurs in cardiac failure. A fall in oncotic pressure occurs in nephrotic syndrome and liver failure. It is commonly thought that these facts explain the occurrence of edema in these conditions. Causes of edema which are generalized to the whole body can cause edema in multiple organs and peripherally. For example, severe heart failure can cause pulmonary edema, pleural effusions, ascites and peripheral edema, the last of which effects can also derive from less serious causes. Although a low plasma oncotic pressure is widely cited for the edema of nephrotic syndrome, most physicians note that the edema may occur before there is any significant loss of protein in the urine or fall in plasma protein level. Fortunately there is another explanation available. Most forms of nephrotic syndrome are due to biochemical and structural changes in the basement membrane of capillaries in the kidney glomerulae, and these changes occur, if to a lesser degree, in the vessels of most other tissues of the body. Thus the resulting increase in permeability that leads to protein in the urine can explain the edema if all other vessels are more permeable as well. **2. Organ-specific edema:** Edema will occur in specific organs as part of inflammation, as in pharyngitis,



tendonitis or pancreatitis, for instance. Certain organs develop edema through tissue specific mechanisms. Examples of edema in specific organs: Cerebral edema is extracellular fluid accumulation in the brain. - It can occur in toxic or abnormal metabolic states and conditions such as systemic lupus. - It causes drowsiness or loss of consciousness. **2. Pulmonary edema** : Occurs when the pressure in blood vessels in the lung is raised because of obstruction to removal of blood via the pulmonary veins. This is usually due to failure of the left ventricle of the heart. It can also occur in altitude sickness or on inhalation of toxic chemicals. Pulmonary edema produces shortness of breath. 3. Pleural effusions may occur when fluid also accumulates in the pleural cavity. 4. Edema may also be found in the cornea of the eye with glaucoma, severe conjunctivitis or keratitis or after surgery. It may produce colored haloes around bright lights. Edema surrounding the eyes is called periorbital edema or eye puffiness. The periorbital tissues are most noticeably swollen immediately after waking, perhaps due to the gravitational redistribution of fluid in the horizontal position. 5. Common appearances of cutaneous edema are observed with mosquito bites, spider bites, bee stings (wheal and flare), and skin contact with certain plants such as poisonous (contact dermatitis). **6. Another cutaneous form of edema is myxedema**, which is caused by increased deposition of connective tissue. In myxedema (and a variety of other rarer conditions) edema is due to an increased tendency of the tissue to hold water within its extracellular space. In myxedema this is because of an increase in hydrophilic carbohydrate-rich molecules (perhaps mostly hyaluronan) deposited in the tissue matrix. Edema forms more easily in dependent areas in the elderly (sitting in chairs at home or on aeroplanes). Estrogens alter body weight in part through changes in tissue water content. There may be a variety of poorly understood situations in which transfer of water from tissue matrix to lymphatics is impaired because of changes in the hydrophilicity of the tissue or failure of the 'wicking' function of terminal lymphatic capillaries. In the case of human feet, the Starling forces are always a long way out of balance, because the variation in hydrostatic pressure in the vessels in the feet as compared to the face is about a metre of water. In severe heart failure the change in central venous pressure is tiny in comparison and cannot explain why edema of the feet develops simply through an effect on capillary leakage. Three other factors may be involved. If the central venous pressure rises to equal that of the thoracic lymph duct then clearance of fluid from the tissue will be impeded (see below). That is to say the edema may actually be caused by a change in output of fluid from the tissue, as much as input to the tissue. Secondly, severe heart failure is one of the most exhausting conditions there is. The sufferers tend to spend what little effort they can make trying to breathe with edematous lungs. They tend to sit up to make breathing easier and their feet hang immobile on the floor. Immobility is perhaps the commonest of all causes of edema, because clearance of fluid via the lymphatics needs muscle action. III. Thirdly, in severe heart failure endocrine and neural changes alter the way tissues are perfused in ways that are not fully understood. In lymphedema abnormal removal of interstitial fluid is caused by failure of the lymphatic system. This may be due to obstruction from, for example, pressure from a cancer or enlarged lymph nodes, destruction of lymph vessels by radiotherapy, or infiltration of the lymphatics by infection (such as elephantiasis). It is most commonly due to a failure of the pumping action of muscles due to immobility, most strikingly in conditions such as multiple sclerosis, or paraplegia. Lymphatic return of fluid is also dependent on a pumping action of structures known as lymph hearts. - It has been suggested that the edema that occurs in some people following use of aspirin-like cyclo-oxygenase inhibitors such as ibuprofen or indomethacin may be due to inhibition of lymph heart action.

CHAPTER VI

RESPIRATORY SYSTEM

Mechanics of breathing

Respiration includes 2 processes :

(1) External respiration: it is gas exchange between air in the lung and blood

(2) Internal respiration : Between the blood and the tissue Structure of the respiratory system

The respiratory system consists of 6 parts:

(1) Air passages. (2) Lungs. (3) Pleural sac. (4) Thoracic cages. (5) Muscles of breathing. (6) Centers in the brain stem

1-Conduction zone: from trachea to terminal bronchioles. Its function is conduction of air in and out of the lung.

2-Transition zone : respiratory bronchioles. Its function is air conduction, but respiration takes place due to presence of some alveoli.

3-Respiratory zone : Consists of alveolar ducts, alveolar sacs and alveoli. Its function is gas exchange.

Normal inspiration: (active process) - Initiated by: contraction of diaphragm & external-intercostal muscles. **(1) Diaphragm:** 75% - It is the most important inspiratory muscle. - When it contracts increasing the vertical diameter of the thorax. **(2) External intercostals muscles** - When it contracts the vertical dimension of the chest cavity is increased. In addition the lower ribs are moved out causing increase in the transverse diameter of the thorax.



During inspiration :There are 4 processes

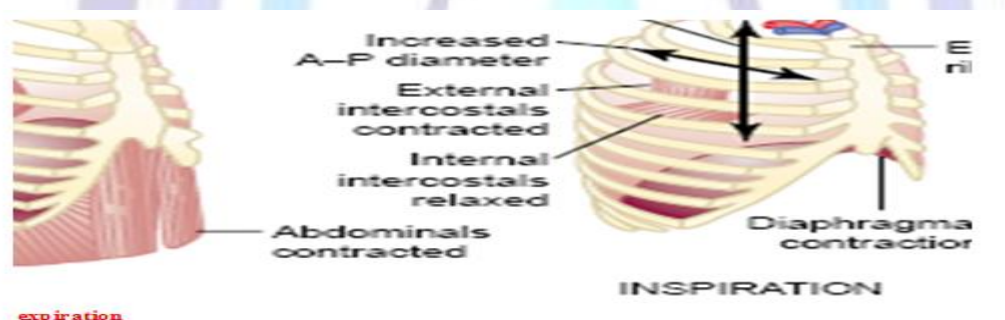
1-*Thoracic wall moves away from the lung surface increase the dimension of the chest wall 2-*Increase the force that expands the lung increase the sizes of alveoli . 3-*Decrease pressure within the alveoli(intra alveolar[pulmonary] pressure) to less than the atmospheric pressure(become -1). 4-*Air flows from the atmosphere into the alveoli .

The inward flow of air : Lead to increases the pressure in the alveoli back to the atmospheric pressure air flow stop

.During forced inspiration : In addition to contraction of the diaphragm and external intercostal muscles ,the contraction of other three accessory muscles of inspiration occur : **a-Scalene muscles:** which elevate the first two ribs **b-Sternomastoid muscles:** which raises the sternum. **c-Internal intercostal muscles.** -Breathing by diaphragmatic movement is called abdominal breathing . Breathing by movement of the chest wall is called thoracic breathing . -**During rest:** abdominal breathing accounts for 70% and thoracic 30% .

Normal expiration:(passive) -The lung and the chest wall are elastic and tend to return to their resting position after relaxation of the inspiratory muscles helped by: *Elastic properties of the lung. *Elevation of the diaphragm. -The diaphragm & external intercostal muscles relax . -The chest wall recoil inward to its original dimensions .

During expiration :the volume of the lung decreases, the pressure inside increases (the intra-alveolar pressure become +1 more than atmospheric pressure)and air comes out . The chest returns to the mid thoracic position . **During forced expiration** As during exercise or voluntary hyperventilation expiration becomes active .The most important muscles of expiration are **(1)The abdominal wall muscles**[as Rectus abdominus , internal & external oblique, transversus abdominus] when these muscles contract ,intra-abdominal pressure is raised and diaphragm is pushed upward decrease of vertical diameter decrease lung volume increase lung pressure pushing air out **(2)The internal intercostals muscles:** When they contract they pull the ribs downward and inward thus decreasing thoracic volume



Pressure changes during inspiration & expiration The lung is an elastic structure . It is hanged in the thoracic cavity and there is no attachment between it and the wall of the chest. -**The pleural sac :** It is a closed sac , of a thin sheet Called pleura surrounds each lung . there are **2 pleural sac** ,one surrounding each lung is completely separate from each other. -The layer which is attached to the outer surface of the lung is called visceral pleura . -The layer which is attached to the chest wall and diaphragm is called parietal pleura . In between there is a potential space(intra-pleural space) filled with pleural fluid .

Pleural fluid : It acts as lubricant which facilitates the gliding of two layers of pleura over each other preventing friction between lung and surrounding structures. Normally ,no gas exists in pleural space but rupture of the lung by a penetrating wound can cause gas , fluid ,blood or pus to enter If water is collected Hydrothorax. If pus is collected Pyothorax . If blood is collected Haemothorax. If air is collected Pneumothorax .

Pneumothorax: Presence of air in the intra-pleural space : -There are 2 types: [a]External or opened Pneumothorax: -If the pleural sac is broken ,by a knife or a gunshot wound to the chest loss the negative intrapleural pressure . [b]Internal or closed Pneumothorax: (spontaneous) -If a disease e.g. pneumonia damages the wall of the pleura Air from inside the lungs enters the intra-pleural space

Pulmonary pressures: Bulk flow :movement of fluids or gases from higher to lower pressure. $F = \Delta P / R$ pressure/resistance. -The Atmospheric Pressure(P atm) -**There are 3 types of pulmonary pressures (1)The Intra-Alveolar Pressure(P alv)** -It is the pressure of air in the alveoli . -At sea level, atmospheric pressure is normally 760 mmHg . -For simplicity :All pressures are expressed relative to P atm -For example: Intra alveolar pressure = 0 mmHg = atmospheric pressure

Changes in the Intra-Alveoli Pressure a]When intra-alveolar pressure is negative[-1] inspiration. b]When intra- alveolar pressure is positive[+1] expiration . c]At the ends of inspiration & expiration = 0mmHg. These changes are caused by changes in the volume of the lungs. **Boyle's law :** For any gas(such as air) in a container. -Increase volume of the container decrease pressure. Decrease volume of the container increase pressure .



(2)The Intra Pleural pressure(P i.p.) -It is the pressure inside the pleural space . -It is always negative under normal conditions. -At the end of normal expiration= -4 mmHg. -At the end of normal inspiration= -6mmHg to -8 mmHg -During forced inspiration(Muller's experiment)=-30 mmHg -40mmhg . -During forced expiration with the glottis closed (Valsalva) = +50 mmHg .

Functions of the Intra-pleural pressure : (1)It helps lung expansion . (2) It helps venous return & lymphatic return to the heart . Causes of negativity of the intrapleural pressure : Continuous tendency of lungs to recoil & the chest to expand *Both the lung & thoracic wall are elastic structures . *Relaxation volume: volume where it is neither stretched nor compressed . Volume of the lungs= 1 liter. Volume of the thoracic wall=5 liters. -At the end of expiration[muscles are relaxed] volume of lungs & thoracic = 2.3 liters. Causes of recoil tendency of the lungs (1)Elastic tissues :(collagen & elastic fibers)1/3 of recoil tendency . (2)Surface tension of the fluid lining the alveoli: 2/3 of recoil tendency .

Effect of Pneumothorax (1)The lungs recoil & Collapse while the chest wall recoils & expands . (2) Decreases venous return & lymph flow . Each lung is isolated in its own pleural cavity ,so that if one lung collapses ,the other can continue to function . (3)The Transpulmonary pressure(Palv - Pi.p.) : -The difference in pressure between the intra-alveolar & intra-pleural pressure. - Transpulmonary pressure = Palv - Pi.p. =0 - (-4)= 4mmHg . This trans- pulmonary pressure is the force acting to expand the lungs . -It is opposed by the elastic recoil of the expanded lungs

Pressure-Volume relationship in the respiratory tract Lungs 1)Type I pneumocytes: (Main type)[Rapid exchange : 2)Type II pneumocyte Surfactant Nature of surfactant : Function of surfactant(1)Decreasing the surface tension :(2)Stability of the pulmonary alveoli:[effect of surface tension on small & large alveoli] (3)Prevention of pulmonary Oedema:(4)It prevents collapse of the lung after their expansion at birth Factors affecting formation of surfactant **[1]Factors that stimulate its formation:** -Thyroid hormones. -Glucocorticoid hormones. -Certain proteins. **[2]Factors that decrease formation of surfactant:** - Smoking . -Insulin hormone. -Long term inhalation of pure O₂. Cessation of pulmonary circulation for long time.

The compliance

It measures the stretchability or expansibility of different organs

Lungs: The alveolar wall is made up of single layer of cells called Pneumocytes . -There are 2 types of Pneumocytes . (2)Type II pneumocyte: -a-Produce a detergent-like substance surfactant -b-Alveolar macrophages: engulf foreign particles. -Adjacent alveoli are connected by alveolar pores : which permit flow of air between them, and also allowing equilibration of pressure within the lungs

Surfactant : -It is the surface tension lowering agent which means that when it spreads over the surface of a fluid , it reduces the surface tension of the fluid. -It is secreted by type II alveolar epithelial cells. -Facilitating lung expansion during inspiration .

Nature of surfactant : Surfactant is formed of a complex lipoprotein mixture .The most important components are Phospholipid dipalmitoyl lecithin , apoproteins and calcium ions . -

Function of surfactant (1)Decreasing the surface tension (2)Stability of the pulmonary alveoli:[effect of surface tension on small & large alveoli] -. So surfactant maintains alveolar stability . (3)Prevention of pulmonary Oedema -Surface tension forces favour filtration of fluid from blood into alveoli . (4)It prevents collapse of the lung after their expansion at birth -The fetal lung is not collapsed but is inflated with liquid to about 40% of total lung capacity. After birth the infant makes several strong respiratory movement and the lung expand. Surfactant prevents it's further collapse. Factors affecting formation of surfactant **[1]Factors that stimulate its formation:** -Thyroid hormones. -Glucocorticoid hormones. -Certain proteins. **[2]Factors that decrease formation of surfactant:** -Smoking . -Insulin hormone. -Long term inhalation of pure O₂. -Cessation of pulmonary circulation for long time.

The compliance: It measures the stretchability or expansibility of different organs Distending pressure. -The difference between pressure inside & pressure outside. -Pressure inside > outside positive pressure expands . -Pressure inside < outside negative pressure collapse. Compliance(CL): -Change in volume per unit change in pressure $C = \Delta V(\text{change in lung volume}) / \Delta P(\text{inside} - P \text{ outside})$ [change in distending pressure

Compliance include: [A]Compliance of the lung (static lung c.) Definition: It is a volume change in the lungs per unite change in the alveolar pressure .[B]Compliance of the thoracic wall& lung together(Dynamic compliance It is much less because lung expansibility in the chest is limited by the rigid thoracic cage & the chest wall movement is limited by bony wall and respiratory muscle. -During quiet breathing : The resistance to air movement is relatively small. The intrapleural pressure changes appears before the lung volume changes producing a hysteresis loop rather than a straight line .

The work of breathing: During inspiration work is involved in Expanding the thoracic cavity . -Inflating the lungs . -Overcoming airway resistance . -**During quiet expiration** : passive process -No muscular work is performed ,due to elastic recoil of the lungs & chest wall **The work of breathing is divided into 3 fractions :** (1)Compliance work. (2)Tissue resistance work .



(3) Airway resistance work . 1) Compliance or elastic work: (Most of the work) work required to expand the lungs against lungs & chest wall elastic forces. (2) Tissue resistance work : (small percent) Work required to overcome the viscosity of the lungs and chest wall . (3) Airway resistance work : Work required to overcome airways resistance of air into the lungs . **Factors affecting the diameters of the airway passages: Factors causing bronchodilatation:** [1] Sympathetic stimulation nor-adrenaline β_2 receptors bronchodilatation (2) Lung expansion traction on the walls of the airways increase the diameter . **Factors causing bronchoconstriction** : 1-Vagal stimulation acetylcholine bronchoconstriction . 2-Decrease PCO₂ in alveolar air 3-Allergic reaction Histamine released from mast cells bronchoconstriction.

Neural Control of Breathing: Regulation of respiration involves : (1) Sensors =Afferent nerves : Detect and transmit information in the body. (2) Central controller =Respiratory center . -Receives sensory input. -Determines the response. - Sends efferent output to effector systems. (3) Effectors = respiratory muscles. (4) Negative Feedback: ex: Increase PCO₂ stimulate the chemoreceptor increase ventilation decrease PCO₂ 1) An involuntary neural control of breathing: This is the basic control mechanism and it is performed by respiratory centers. **-Respiratory centers include:** (a) The medullary respiratory centers (MRC). *The medullary inspiratory neurons (IN) *The medullary expiratory neurons (EN) (b) The Botzinger complex at nucleus ambiguus . (c) The pontine centers : apneustic & pneumotaxic centers 1) The involuntary neural control of respiration:-Respiratory center is composed of several group of neurons located bilaterally in the pons and medulla. I-Medullary respiratory centers (MRC) : T-They are dorsal respiratory group (DRG) and ventrolateral respiratory group (VRG). **A- Dorsal medullary inspiratory neurons** They are present in Medulla Oblongata . -They are inspiratory neuron causing inspiration. 1-Peripheral chemoreceptor. 2-Baro receptors . 3-Several types of receptors in the lungs . -All these sensory impulse help to control respiration . **B-Ventrolateral medullary expiratory neurons:** They are located in the ventral part of the Medulla lateral to the dorsal Medullary inspiratory neurons -They are found in the nucleus ambiguus and the nucleus retroambiguus. **-They cause deep expiration** .The Botzinger complex are inspiratory neurons located in Medulla (at nucleus ambiguus) .They inhibit inspiratory neurons and excite expiratory neurons .They play important roles in respiratory control as they are generator neurons for the rhythmic respiration

II-Pontine centers: They are group of neuron in the pons that modify the activity of medullary centers . -They are 2 groups : 1- Apneustic center (AP) . 2-Pneumotaxic center (PC) . -1- Apneustic center (AP): -It is located in the caudal part of the pons . produce deep and prolonged inspiration. The pneustic center is inhibited by : a-Impulses from the vagus nerve . b-Impulses from the pneumotaxic center . -2- Pneumotaxic center (PC) : -It located dorsally in the upper part of the pons in the nucleus parabrachialis . -Its function: is to limit inspiration i.e it controls the duration of inspiration It shortens inspiration and prevents over inflation of the lung . -A stronger PC signal increase in the rate of breathing. -where a weak PC signal may reduce the rate of breathing **2) Voluntary control mechanism:-**This can be performed for only a limited time, e.g. breathing can be voluntary inhibited but for short time. -Such voluntary control is produced by signals discharged from the cerebral cortex to the respiratory center. **There are 3 types of receptors** (1) Slowly adapting pulmonary stretch receptors: Located in the smooth muscles of the trachea , bronchi , bronchiole and alveolar ducts . **Function:** To prevent over inflation of the lung . (2) Rapidly adapting irritant receptors: Located in the epithelium of the air ways .They are free nerve endings . The response: -Signals from irritant receptors of the nose sneezing. -Signals from irritant receptors in trachea , larynx , bronchi And bronchioles coughing, bronchoconstriction and mucous secretion. 3) Juxt capillary-pulmonary receptors (J-receptor): Located near to the pulmonary blood vessels. They are terminal vagal fibers . The response: Vagus stimulation 1) rapid shallow breathing. 2) broncho-constriction . 3) Apnea . 4) Bradycardia . 5) Hypotension

Gas Diffusion & Blood flow to the lungs

Regional Differences

Diffusion: Is the exchange between the alveolar gas and the blood gases through the alveolar-capillary membrane

Diffusion through tissues is described by Fick's law which states that : the rate of diffusion of a substance through a membrane is proportional to the surface area of the membrane, the solubility of the substance in the membrane and pressure gradient and inversely proportional to the thickness of the membrane and square root of the molecular weight (MW of O₂ 32 - MW of CO₂ 44)

$$\text{Surface area} \times \text{Solubility} \times \text{Pressure gradient}$$

$$D_{\text{O}_2} = \frac{\text{Surface area} \times \text{Solubility} \times \text{Pressure gradient}}{\text{Thickness of membrane} \times \sqrt{\text{MW}}}$$

$$\text{Thickness of membrane} \times \sqrt{\text{MW}}$$

Factors that affect the rate of gas diffusion through the respiratory membrane: The rate of diffusion is directly proportion to: [1] **Pressure gradient** : -The pressure of O₂ in the alveoli (100 mmHg) is greater than in the blood entering the pulmonary capillaries (40 mm Hg) so , O₂ diffuse from alveoli to the blood . The pressure of CO₂ in the blood entering the pulmonary Capillaries (45 mm Hg) is greater than in the alveoli (40 mmHg) so, CO₂ diffuses from the blood into the alveoli. [2] **The diffusion coefficient** for transfer of each gas through respiratory membrane. -The solubility of CO₂ is very high than O₂ . CO₂ diffuses slower than O₂ by its high molecular weight. Diffusion coefficient for CO₂ through the tissue is faster than for O₂.



Diffusion capacity of the pulmonary membrane: It is the volume of gas that diffuses through membrane each minute with pressure difference of 1 mmHg . **Diffusion capacity for O₂** : -At rest 25 ml/ min/ mmHg -During exercise 65ml/min/ mmHg -It decreases in lung diseases as in fibrosis . **Diffusion capacity for CO₂**: -At rest 400 ml/ min /mmHg -During exercise 1200 ml/ min/mmHg . [3] **Surface area of the membrane:** The surface area of respiratory membrane is very large about 80 – 100 square meter in normal adult . [4]Temperature . [5]Thickness of the membrane(0.2 μ) Any factor increases the thickness of the membrane(pulmonary fibrosis – oedema) decreases diffusion . **Pulmonary circulation:** The blood supply of the lung is derived from: 1-Bronchial arteries: arising from the aorta . 2-Pulmonary artery: where mixed venous blood flows to the lung & visceral pleura. The alveoli get their O₂ from the atmosphere . Pressure in pulmonary circulationPulmonary circulation is a low pressure circulation -In pulmonary arteries: systolic pressure is 25 mmHg while diastolic pressure is 8 mmHg i.e : 25/8 mmHg

Regional pulmonary blood distribution: In the upright position: Lung blood flow decreases linearly from the bottom to the top reaching very low at the apex. In the supine position: The apical zone blood flow increases due to the distribution from the apex to base becomes equal . But the blood flow in the posterior region of the lung exceeds the flow in the anterior part In mild exercise: Both upper and lower zone blood flow increases and the difference becomes less . Causes of the regional distribution of the blood flow: (1)Hydrostatic pressure(at blood stream) It distends the vessels at the base of the lung and allows those at the apex to be narrow or even Collapsed. (2)The difference in pressures between arterial and venous ends of the lung capillaries drives blood through them, but the blood flows only when the hydrostatic pressure keeps the capillaries open. (3)Alveolar air pressure:Lung capillaries are separated from alveoli by a very thin layer of tissues, alveolar pressure=atmospheric pressure and affect blood flow through the capillaries. - **3 different perfusion zones. A-At the apex:** The pulmonary arterial pressure is sufficient to raise blood to the top of the lung i.e. maintain perfusion during systole but diastolic pressure is less than the alveolar so, blood flow is intermittent .If alveolar pressure is increased leads to collapse of some capillaries surrounding them so, no blood flow(no perfusion), no gas exchange takes place in affected alveoli .They become part of physiological dead space. This occurs only if: (1)Arterial pressure is reduced. (2) Alveolar pressure is raised. **B-At the middle zone:**The arterial pressure increases(due to hydrostatic effect) . It exceeds the alveolar pressure which exceeds the venous pressure . Therefore , the blood flow becomes better than at the apex . **C- At the base of the lung:**Arterial and venous pressures exceed alveolar pressure . Blood flow is continuous and the vessels are distended , more capillaries are opened with more blood flow and more perfusion **Ventilation/perfusion Relationship(V/Q):** It is the ratio of alveolar ventilation to pulmonary blood flow . Normal V/Q: Alveolar ventilation= 4.2 L/min. Cardiac output(perfusion) =5 L/min . If this amount of blood is distributed equally through the lung then:-

$$V/Q \text{ ratio} = \frac{\text{Alveolar ventilation}}{\text{Cardiac out put}} = \frac{4.2}{5} = 0.8$$

Both ventilation and perfusion increase from the apex to the base of the lung due to the effect of the gravity ,V/Q ratio varies from 0.6 at the base, to 3.3 at apex . At the apex of the lung: There is a decrease in both ventilation and perfusion but the decrease in perfusion is more than ventilation. V/Q=3.3 ; i.e. the apical alveoli are more ventilated than perfusion i.e. presence of dead space in this area of the lung . **At the base of the lung:** There is increase in both ventilation and perfusion but the increase in perfusion is more than ventilation. V/Q=0.6 -At the base small fraction of blood fails due to over perfusion than ventilation(represents physiological shunt **During exercise:** Blood flow to upper parts of the lungs increases markedly so that less physiological dead space exists and the effectiveness of gas exchange is the optimum. The transport of oxygen in the blood O₂ is transported in the blood in two forms: (1)Physical solution[dissolved]: -Arterial blood: 0.3ml /100ml blood . It causes a partial pressure of O₂= 100 mmHg. - Venous blood: 0.13ml /100ml blood . It causes a partial pressure of O₂= 40 mmHg . The amount of O₂in whole arterial blood which equal 5 liters(cardiac output)= 5000× = 15 ml for whole blood volume(5 liters) (2)O₂ in chemical combination(carried by haemoglobin): -About 19.5 ml of O₂/ 100ml arterial blood .It is essential for supplying tissues with O₂during rest and exercise . **Definitions:** O₂ content of blood: It is the volume of O₂ carried by blood combined with Hb /100 ml blood. -It depends on: *Amount of Hb present. *O₂ tension. *O₂ affinity of Hb . *Metabolic state of the organ. O₂ capacity of blood: It is the maximum volume of O₂ that can be carried by Hb ,when Hb is fully saturated with O₂ One gram of Hb combine with 1.34 ml ofO₂[fully Saturated]. -A healthy adults has approximately 15 gm of Hb/100ml blood. O₂ capacity=1.34 ml O₂/ gm Hb×15 gm Hb/100 ml of blood =20.1 ml O₂/ 100ml of blood. *The percentage of saturation of Hb with O₂(%HbO₂)

$$\%S = \frac{\text{o}_2 \text{ content}}{\text{o}_2 \text{ capacity}} \times 100$$

Hb% saturation does not vary with Hb content because: o₂ content & capacity are affected to the same extent O₂Pressure and content relation: -a-The relation between O₂pressure and O₂ in physical solution is a linear relationship i.e. any increase in O₂ in physical solution leads to increase in O₂ pressure. -The relation between O₂pressure and the % saturation of Hb with O₂ is not linear ,but S-shaped **Coefficient of O₂ utilization:** IS the % ratio of the volume of O₂ taken by the tissues from arterial blood to the total O₂ supplied by arterial blood to the tissues .

$$\text{Arterial O}_2 \text{ content} - \text{O}_2 \text{ utilized by the tissues}$$



Coefficient of O₂ utilization =-----

Arterial O₂ content

The coefficient of O₂ utilization is 25% at rest and reaches 75% in exercise. It depends on: (1) It is directly proportional to the metabolic tissue activity. (2) It is inversely proportional to the rate of blood flow. Oxyhemoglobin dissociation curve -The relationship between PaO₂ and % saturation of Hb with O₂ is not linear but S-shaped. -The S-shaped oxyhemoglobin dissociation curve indicates that: the volume of O₂ bound to Hb is relatively constant over a wide range: -At higher PaO₂ values (> 70 mmHg) [the flat part]. -At lower PaO₂ levels (steep part of the curve). -

Cause of the S shape :- This occurs because Hb is made up of 4 sub-units. -This is due to combination of O₂ with hem group of Hb molecule. Physiological analysis of the curve: (1) The flat upper part: represents zone of Hb saturation. It occurs when O₂ pressure is between 100 - 60 mmHg. This is called loading zone i.e. Hb at high pressure of O₂ has high affinity to combine with O₂. -It represents lung side. (2) The steep part: -It occurs when O₂ pressure decreases below < 60 mmHg, -The saturation of Hb decreases rapidly. -It is called unloading zone. -It represents tissue side

Physiological significance of the oxyhemoglobin dissociation curve:

[1] At the flat part of the curve Pressure % saturation of Hb & O₂: -At sea level 100 mmHg 97% -At high altitude 60 mmHg 90% -Alveolar PO₂ & PaO₂ can decrease with little change in % : **Saturation of Hb with O₂:** -As Hb have a very high affinity to O₂ at the lung. Even with low O₂ pressure. **[2] At the steep part of the curve:** -At rest 40 mmHg 70% So, tissues take about 27% of O₂ of arterial blood. During exercise 20 mmHg 30% **The curve enables the tissues to extract large amounts of O₂.** **Factors that shift the oxyhemoglobin dissociation curve to the right:** Bohr effect: during muscular exercise (1) Increase of temperature & PCO₂ (CO₂ pressure) & decrease of pH (increase H⁺): Shift to the right = less O₂ bound to Hb [More O₂ available to the muscle]. **The Causes for shift to right:** CO₂ and H⁺ combine with sites on hemoglobin and lead to changing its configuration. Facilitating the off loading of O₂ Provide more O₂ to the tissues. (2) Effect of 2,3 diphosphoglycerate (2,3-DPG): 2,3-DPG is an end product of the red blood cells metabolism. Facilitates the unloading of O₂ from hemoglobin. Increased in case of hypoxia [High altitude & exercise].

Factor that shift the oxyhemoglobin Dissociation curve to the left : (1) Decrease of temperature & PCO₂ (CO₂ pressure) & increase of pH [decrease H⁺]: Shift to the left = more O₂ bound to hemoglobin. [Less O₂ is available to the tissues]. (2) Effect of CO (Carbon monoxide): CO combines with hemoglobin to form carboxy-hemoglobin (CO Hb). Shift of the O₂ dissociation curve to the left. The affinity of CO for hemoglobin is more than 200 times greater than that of O₂. *The cause of this shift to the left: - Most of the O₂-binding sites are occupied by CO molecules -CO molecules do not respond to decrease in PaO₂ levels. O₂ molecules that remain are strongly bound to hemoglobin

O₂ Dissociation curve of myoglobin : One molecule of hemoglobin can combine with 4 molecules of O₂. Myoglobin has one Fe⁺⁺ atom which can combine with one O₂ molecule. The O₂ dissociation curve of myoglobin: Is a rectangular hyperbola. It remains horizontal, very low O₂ tension then suddenly descends vertically. -It does not give its O₂ easily except at very low O₂ tension ex. During severe muscular exercise. Myoglobin acts as an O₂ store to be used by muscles when O₂ tension becomes very low. - After exercise, myoglobin sucks O₂ from blood.

The transport of CO₂ in the blood

The transport of CO₂ in the blood There are 2 forms of CO₂ transport : **(1) Physical solution** : About 5% of CO₂ is dissolved in plasma and RBCs. It is called free CO₂: It is very important because: -It is responsible for CO₂ tension (Pco₂) in the arterial blood (40 mmHg) and the venous blood (46 mmHg) -PCO₂ controls the direction and the rate of flow of CO₂ **(2) Chemical form** : It represents 95% of CO₂ content. It is present in 3 forms 1- **As bicarbonate**: Most important form (90%). -It is present as bicarbonate KHCO₃ in the RBCs & NaHCO₃ in the plasma CO₂ + H₂O \xrightleftharpoons{CA} H₂CO₃ $\xrightleftharpoons{H^+}$ H⁺ + HCO₃⁻ -This reversible reaction in RBCs is several thousands (13,000) times faster than in plasma because of the presence of Carbonic anhydrase enzyme (CA) in RBCs and not in plasma, which accelerates the reaction in both directions. -Bicarbonates is present in plasma as Na HCO₃, and inside RBCs as K HCO₃ 2- **As carbamino-hemoglobin (CO₂-HHb)**: -In RBCs carbamino-hemoglobin (4%) more important because blood contains more Hb and Hb protein has greater affinity for CO₂ than plasma proteins -3- **As carbamino-protein (CO₂-R-NH₂)** -In plasma as carbamino protein (2%)

The tidal CO₂: This is the volume of CO₂ that is added to each 100 ml of the arterial blood during its flow through the tissues. At rest, it is about 4 ml/100 blood. i.e. 4 ml CO₂/100 ml blood released by the tissues as a result of metabolism. -Tidal CO₂ is buffered by: A-Tidal CO₂ is mainly carried in chemical combination as bicarbonate. B-Hb plays an important role in buffering the tidal CO₂. The buffering effect of Hb (H⁺ + Hb- HHb) so that, pH of blood does not markedly change. Transport of tidal CO₂ : In 3 forms: 1-In physical solution [0.4 ml]. 2-As bicarbonate [2.6 ml]. 3-As carbamino compounds (Hb and protein) [1 ml]. [1] At the tissues: -Because of the metabolic activity of the cells: *The CO₂ tension in the tissues is higher than that in arterial blood in capillaries. *Thus, CO₂ diffuses into the capillaries along pressure gradient. CO₂ + H₂O \xrightleftharpoons{CA} H₂CO₃ $\xrightleftharpoons{H^+}$ H⁺ + HCO₃⁻ **-The H⁺ is buffered by:** Deoxyhemoglobin in RBCs -Plasma proteins in plasma. HCO₃ ions diffuse out of the RBCs into plasma: *Prevent their accumulation in RBCs. -Since the K⁺ can not move in association with HCO₃ (because the red cell membrane is more permeable to anions than to cation). -Electrical balance can only be maintained by: Movement of Cl⁻ ions from plasma to Red blood cells which is known as Chloride Shift The net results at tissues: 1- The bicarbonate content increases in both RBCs and plasma (More in RBCs).



2-pH of both the red cells and the plasma undergo very little decrease (7.40 – 7.37). 3-Cl⁻ increases in red cells and decreases in the plasma . 4-The cation (Na⁺, K⁺) content of both red cells and plasma remains constant (Impermeability of the cell membrane to cations) . 5- The osmotic pressure of RBCs increases due to: *The increase of both HCO₃⁻ and Cl⁻ inside them *So, H₂O moves from plasma into the red cells to restore osmotic balance . - *Increase the red cells volume . - *Increase the haematocrite value in venous blood than in arterial blood . [ii] At the lung: The opposite effect occurs . ON exposure to a low tension of CO₂ HCO₃⁻ shifts from plasma to RBCs to be converted to CO₂ for exhalation. Cl⁻ returns from RBCs to plasma . **The CO₂ Dissociation curve:** Reduced Hb forms more carbamino compound than oxy-hemoglobin . Thus , 1 ml of tidal CO₂ is carried as carbamino compounds in venous blood [reduced Hb] . The CO₂ Dissociation curve: -Relates changes in the CO₂ content of whole blood to changes in the blood PCO₂ -Is not S-shaped like oxyhemoglobin dissociation curve -It is essentially linear in the physiologic PCO₂ range from 40-46 mmHg . -The total amount of CO₂ combined with the blood depends on the PCO₂ Arterial blood 40 mmHg 48 ml CO₂ Venous blood 46 mmHg 52 ml CO₂

CO₂ & O₂ are carried by haemoglobin at different sites: -O₂ with Fe⁺⁺ -CO₂ with NH₃[protein part] . -Yet the binding of one gas to haemoglobin interferes with the carriage of the other . **The Bohr effect:** Increases carbon dioxide in the blood at the tissues causes oxygen to be displaced from the hemoglobin . **The Haldene effect :** Increase oxygen at the lungs tends to displace carbon dioxide from the blood .

Chemical control of Breathing This is the basic mechanism for regulation of breathing . The goal of respiration is to maintain the proper concentration of O₂ ,CO₂ and H⁺ ion in the tissues . -The activity of the respiratory centers is highly responsive to changes in the O₂ , CO₂ and H⁺ content of the blood . **1-Co₂ content:** Any increase in CO₂ tension (Hypercapnia) of the arterial blood causing increase alveolar ventilation and vice versa. **2-H⁺ ions:** Increase H⁺ ions (acidosis) increase alveolar Ventilation . Decrease H⁺ (alkalosis) Decrease alveolar ventilation . **3-O₂ Lack :** Change in O₂ concentration have no direct effect on respiratory center itself but when O₂ decrease in the blood known as hypoxaemia ,it becomes chemical regulator and increase alveolar ventilation -This chemical effect is mediated through 2 types of Chemoreceptors: **(1)Central chemoreceptors:** Site: They are located on the ventral surface of the medulla oblongata ,near the respiratory centers but separated from them. Protected by: Blood brain barrier separates blood from the Cerebrospinal fluid (CSF). Blood –brain barrier is impermeable to H⁺, but CO₂ molecules can diffuse through it easily. -When the blood PCO₂ rises ,CO₂ diffuses into the CSF and reacts with H₂O forming H₂CO₃ which dissociates to HCO₃⁻ and H⁺ -Central chemoreceptors are highly sensitive to changes in CSF hydrogen ion concentration . If H⁺ increase stimulates the receptors increase ventilation . -Mild or moderate Hypoxia does not affected the central chemoreceptor . -Sever Hypoxia ,depresses CNS including respiratory centers .Blood –brain barrier is impermeable to H⁺, but CO₂ molecules can diffuse through it easily. -When the blood PCO₂ rises ,CO₂ diffuses into the CSF and reacts with H₂O forming H₂CO₃ which dissociates to HCO₃⁻ and H⁺ -Central chemoreceptors are highly sensitive to changes in CSF hydrogen ion concentration . If H⁺ increase stimulates the receptors increase ventilation . -Mild or moderate Hypoxia does not affected the central chemoreceptor . -Sever Hypoxia ,depresses CNS including respiratory centers .The Blood Brain Barrier & CSF-Barrier: It is the endothelium of blood vessels in the brain .-It separates the CSF from the blood .-It greatly restricts movements of ions ,but not of O₂ or CO₂ .-H⁺ does not cross this barrier :so most of H⁺ in metabolic acidosis & alkalosis are not reflected on brain , and increase PCO₂ in the blood , immediately increase PCO₂ in the CSF and brain. CSF: Protein(20 mg/ 100ml) – not highly buffered .-Small increase in PCO₂ change in CSF Ph Stimulatory effect on ventilation . **2)Peripheral Chemoreceptors:** Site: Outside the CNS .-There are 2 types: 1-Carotid bodies (small structures located bilaterally at the bifurcation of common carotid artery) They generate signals by glossopharyngeal nerve called carotid sinus nerve. -They are sensitive to hypoxia ,less sensitive to acidosis and least sensitive to hypercapnia (increase CO₂) .-Predominant in humans. 2-Aortic bodies (scattered over the aortic arch) . -They generate signals through vagus nerve Blood flow for peripheral chemoreceptors is very high , for this reason , the O₂ needed for cells is derived from the dissolved O₂ in the blood. -The response of these receptors very fast and responsible for increase of ventilation in response to arterial hypoxemia. -These receptors are not stimulated in anemia & CO poisoning .However , in cyanide poisoning they are stimulated because cyanide prevents O₂ utilization at the tissue level.**Importance of the peripheral chemoreceptor:** (1)They respond to increased H⁺ concentration in the blood which is caused by excess CO₂ (2)They respond to Co₂ excess more rapidly than the central Chemoreceptors . (3)The only mechanism in the body detect changes in O₂ tension in the body fluid ,rapidly increase their firing rate as the arterial O₂ tension falls below 55 mmHg i.e detect hypoxemia . **Effect of changes in PCO₂ on ventilation :** Increase PCO₂ (Hypercapnia) : Arterial PCO₂ is the major chemical regulator of respiration **(1)Acute increase PCO₂:** -Increase in arterial PCO₂ due to excessive inhalation or increased tissue metabolism. -When PCO₂ rises , the respiratory center is stimulated , then breathing increases in depth and rate increase Co₂ washout until PCO₂ returns to normal level. Most response of CO₂ by stimulation of central chemoreceptor and 30% of peripheral chemoreceptors , and the full stimulatory effect of hypercapnia on breathing is delayed for 5-10 minutes till the central chemoreceptors are fully activated .Severe increase in PCO₂ produces depression of respiratory center decrease respiratory rate coma (Co₂ narcosis). -The peripheral chemoreceptors are important in: 1-Hypoxia Metabolic acidosis & alkalosis. 3- Depression of central chemoreceptor. **2)Chronic increase in PCO₂ (as in lung disease):** -Excitation of respiratory center by excess CO₂ is greater at first then decrease after 2 days due to renal H⁺ ion concentration in circulating blood back to normal by increasing bicarbonate ,which bind to H⁺ in blood and CSF to reduce their concentration -Acute hypercapnia is a strong breathing stimulus but chronic hypercapnia is a weak stimulus provided that the kidney function is normal . Hypocapnia: (Decrease PCO₂): Results from hyperventilation . -It is a strong inhibitor of breathing & produce apnea. -When the arterial PCO₂ decreases ,H⁺ decreases **Causes :** -Respiratory alkalosis. -Central blood flow reduced 30% because of direct effect of hypocapnia on cerebral blood vessels headache. Alkalosis decreases Ca⁺⁺ level in blood causes tetany. -Decreases plasma HCO₃⁻ Ventilatory Response to O₂ Lack -In high altitudes: Po₂ 100-60mmHg no increase in ventilation. Po₂ 60-30 mmHg increase in ventilation . Severe hypoxia (Po₂< 20 mmHg) inhibit the respiratory center **Hypoxia stimulate peripheral chemoreceptor stimulate respiration .** Ventilatory response



to changes in Acid –Base Balance The normal pH of arterial blood is 7.4 Blood pH is regulated by respiratory system & kidneys
Acidosis (increase H⁺) result from: Increase CO₂ (respiratory acidosis) or decrease HCO₃⁻ (metabolic acidosis). **Alkalosis (decrease H⁺) results from:** Decrease CO₂ (respiratory alkalosis) or increase HCO₃⁻ (metabolic alkalosis). The lungs regulate CO₂ while the kidneys regulate HCO₃⁻.
Acid –Base Balance Occurs By [1] **Metabolic acidosis [++H⁺]** -caused by: Addition of acids (lactic acid in exercise) -Effects: These acids are rapidly buffered by the bicarbonate decrease Hco₃⁻ in blood Increase H⁺ concentration stimulate peripheral chemoreceptors increase Ventilation decrease PCO₂ Normal pH (compensated acidosis). [2] **Metabolic alkalosis [--H⁺ & ++Hco₃⁻]** Caused by: -Ingestion of bicarbonates (for treatment of peptic ulcers) . -Vomiting . Effects: Decrease H⁺ decrease ventilation increase CO₂ Normal pH (compensated alkalosis) [3] **respiratory acidosis [++H⁺]** Caused by: - Hypoventilation -Chronic lung diseases Effects: Increase Pco₂ & acidosis .Correct by the kidneys: Retain Hco₃⁻ adjusting pH towards normal (compensated acidosis) [4] **Respiratory alkalosis [--H⁺]** -Caused by: Hyperventilation e.g CNS disorders. Effects: Decrease Pco₂ & alkalosis Correct by the kidneys: increase excretion of Hco₃⁻ adjusting pH towards normal (compensated alkalosis) . Exercise and high altitude .

Physiological responses to Hypoxia , Hypercapnia Regulation of breathing during muscular exercise:
During muscular exercise, ventilation is markedly increased up to 120 L / minute in order to: 1- supply excess O₂ 2-Eliminate excess CO₂ 3-Allow more heat loss through the respiratory passage -Increase ventilation parallel to the rate of CO₂ production -The mechanism of stimulation of breathing differs according to the severity of the exercise : **A-Mild exercise or during few second of exercise** Pulmonary ventilation increases in depth due to signals from cerebral cortex ,limbic system and muscle proprioceptors to respiratory center . **B-Moderate exercise:** Ventilation increase in depth and rate: -Signals from chemoreceptors (increase PCO₂) **C-Severe exercise:** Excessive production of lactic acid which stimulates peripheral chemoreceptors which stimulate the respiratory center to increase rate and depth of ventilation **Other factors increase breathing and ventilation during exercise as:** 1-Increase body temperature . 2- Increase venous return 3-Excitation of lung irritation. Respiration under abnormal conditions Effects of decreased barometric pressure (high altitude): atmospheric pressure decreased and the partial pressure of O₂ also decreases
Hypercapnia (Increase PCO₂): (a) Acute increase PCO₂ Most of the ventilatory response of CO₂ is produced by stimulation of central chemoreceptors and only 30% of peripheral chemoreceptors (b) Chronic increase in PCO₂ (as in lung disease) Excitation of respiratory center by excess CO₂ is greater in the first few hours but then it gradually decrease by the action of kidney function.

HYPOXIA

HYPOXIA : It is oxygen deficiency at tissue level due to: -Decreased O₂ supply to tissues . -Decreased O₂ utilization by the tissues TYPES OF HYPOXIA: 1-Hypoxic Hypoxia . 2-Anemic Hypoxia . 3-Stagnant Hypoxia . 4-Histotoxic Hypoxia .

[1] Hypoxic Hypoxia A condition in which PO₂ is decreased in arterial blood i.e. Hb is not fully saturated Causes: (1) Decreased partial pressure of O₂ in inspired air at sea level or at high altitude . (2) Pulmonary disease

2- Anemic hypoxia -Deficiency of Hb capable of carrying O₂ (O₂ content decrease) , while the arterial PO₂ is normal . Causes: 1-Quantitative (insufficient Hb) : in all types of anemia . 2-Qualitative (abnormal forms of Hb) Ex :CO poisoning (carbon monoxide poison)

3-Stagnant Hypoxia Inadequate blood flow through the tissues or slow circulation (normal PO₂ and normal Hb).

4- Histotoxic Hypoxia A condition in which adequate amount of O₂ is delivered to tissues but the tissue becomes unable to utilize O₂ due to Cyanide poisoning: -cyanide blocks the action of cytochrome oxidase ,thus can not utilize O₂ .Oxygen Therapy in different types of Hypoxia O₂ therapy is highly beneficial in: -Hypoxic Hypoxia because it increases PO₂. - Carbon monoxide poisoning . O₂ Therapy is not beneficial in : Anemic hypoxia because the defect is in Hb . - Stagnant hypoxia because the problem is in the slow blood flow. - Histotoxic hypoxia because the tissues can not utilize it . O₂ Toxicity Cause: prolonged inhalation of pure O₂ produces toxic effects , due to O₂ free radicals .Effects: O₂ is converted to active forms (O₂ free radical) (1) Oxidizing cell membranes & enzymes and leading to: a-oxidative destruction of enzymes b- Damage of nervous tissue (2) Inhalation of 100% > 8 hours lead to irritation of upper respiratory passages . (3) Exposure for 24 -48 hrs which lead to damage to the lungs . (4) Hyperbaric O₂ : Administration of pure O₂ under pressure which lead to accelerates the toxicity and coma also treating some diseases

Cyanosis: It is the bluish coloration of skin and mucous membranes due to presence of increased amounts of reduced Hb in the blood (capillaries) -Cyanosis is visible in thin skin e.g. lips ,mucous membrane , nail & ear lobes . Types of cyanosis: (1) Central cyanosis . (2) Peripheral cyanosis

Relation between hypoxia and cyanosis :Cyanosis appears with: a-Hypoxic hypoxia: the amount of reduced Hb is increased because PO₂ is reduced .b- Stagnant hypoxia :the slow flow of blood provides more time for extraction of O₂ thus decreasing HbO₂ and increasing reduced Hb. Cyanosis not appears with : a- Anemic hypoxia: because the total amount of Hb is reduced . b-Histotoxic hypoxia: because there is no reduced Hb . c-CO poisoning: due to cherry red colour of CO-Hb
Acclimatization To High Altitudes Acclimatization is the physiologic adjustment of the body to chronic hypoxia . **Compensatory mechanisms in acclimatization:** [1] Hyperventilation: [2] Tachycardia and increased cardiac output: [3] Polycythemia Hypoxia lead to



stimulation of erythropoietin formation [4]Effects at cellular and tissue level : -increase oxidative enzyme. [5]Pulmonary hypertension:

Alveolar hypoxia. Problems associated with exposure to increased barometric pressure : **A- During Descent** : (Compression) Disorders of breathing compressed air: Nitrogen narcosis: breathing N₂ at high partial pressure: increase dissolved N₂ in the nervous fatty tissues decrease excitability anaesthetic effects . -To avoid N₂ narcosis: By breathing a mixture of helium and oxygen . **B- During Ascent : (Decompression)** The high alveolar pressure of gases in body are reduced So ,excess dissolved gases will diffuse from tissues to blood to lungs. If the decompression is too rapid ,the following will take place :- Decompression Sickness (Caiss on's diseases): The abnormalities of breathing: -Apnea: Temporary stoppage of breathing. Types: (1) Apnea following voluntary hyperventilation. (2)Apnea with periodic (Chyne-Stok's)breathing (3)Adrenaline apnea . (4)Voluntary apnea . (5)Swallowing apnea . (6)Sleep apnea :brief periods of apnea . **Periodic Breathing** It means alternate periods of apnea and breathing or waxing and waning . Causes: Physiological : 1-After voluntary hyperventilation 2-At high altitudes . 3-Children during sleep . Pathological:[Chyne-Stokes breathing] 1-Respiratory failure e.g brain damage or uremia 2-Circulatory failure due to slow circulation .

Asphyxia Definition: prevention of ventilation in alveoli . -Occlusion of air passage or breathing in a confined space . Causes: 1- Airway obstruction . 2-Drawning . 3-Paralysis of respiratory muscles . 4-Bilateral Pneumothorax . 5-Rebreathing in a closed system with limited volume of air .

Dyspnea Definition:It is a difficult breathing and sometimes described as air hunger . -Hyperventilation changes into dyspnea when : ventilation is doubled and subject becomes quiet conscious of his respiration

Dyspnic index: Normally dyspnic index is > 90% . Causes:When pulmonary ventilation is increased by: a-Chemical stimuli : by increased PCO₂ ,H⁺ or decreased PO₂ . b-Nervous stimuli: from rapidly adapting receptors in the lung .

[1]Respiratory dyspnea. (a)Ventilation dysfunction :e.g. bronchial asthma (b)Diffusion dysfunction: e.g. pulmonary edema (c)Perfusion defect: e.g. pulmonary embolism

[2]Cardiac dyspnea -Left side heart failure . -Decrease lung vital capacity. [3]Neurogenic dyspnea:emotional dyspnea [4]Acidosis :Diabetic acidosis or uremia . [5]Increased metabolism: Hyperthyroidism – Fevers

Artificial respiration:Artificial respiration can be life saving when natural respiration stops.Methods:(1)Mouth to mouth breathing:-In emergencies.-In temporary respiratory failure .The operator takes a deep inspiration and expires into the victim's mouth While closing his noseThe expired air contain CO₂ stimulates the victims respiratory center O₂ for oxygenation of hisblood .Extension of his head backwards and moving his mandible forwards .(2)Pressure breathing machines(Ventilators):In acute respiratory failure e.gCO poisoning .A mask fits over the face of the patient or use an endotracheal tube . The apparatus forces air through the mask into the lungs .(3)Tank respirator :In chronic respiratory failure e.g bulbar palsy .-The patient is put inside the tank of a respirator with the exception of his head .

CHAPTER VII

KIDNEY

Introduction to renal physiology

Different functions of the kidney

- 1- Excretion of metabolic waste products and foreign chemicals.
- 2- Regulation of water and electrolyte balances.
- 3- Regulation of body fluid osmolality and electrolyte concentrations.
- 4- Regulation of arterial pressure.
- 5- Regulation of acid- base balance.
- 6- Secretion, metabolism and excretion of hormones.
- 7- Gluconeogenesis.
- 8- Secretion of prostaglandins (PGE₂, PG₁₂) and bradykinin.

Role of the kidney in homeostasis:For homeostasis, excretion of water and electrolytes must match intake. If intake exceeds, the amount of that substance in the body will increase. If intake is less than excretion, the amount of that substance in the body will decrease Intake of water and many electrolytes is governed mainly by a person's eating and drinking habits, requiring



the kidney to adjust their excretion rates to match the intake of various substances. For example: Sudden 10- fold increase in sodium intake from a low level of 30 mEq/day to a high level of 300 mEq/day. Within 2-3 days after raising the sodium intake, renal excretion also increases to about 300 mEq/ day, so that the balance between intake and output is re- established. However, during 2-3 days of the renal adaptation to the high sodium intake, there is a modest accumulation of sodium that rises ECF volumes lightly and triggers hormonal changes and other compensatory responses that signal the kidneys to increase their sodium excretion.

The Different Parts of the Nephron Each nephron is composed of:

1- Glomerulus: It is formed of a tuft of capillaries (glomerular capillaries) contained within the dilated blind end of the renal tubule known as Bowman's capsule. The capillaries are supplied by an afferent arteriole and drained by a smaller efferent arteriole. The glomerulus is a high pressure capillary bed, the hydrostatic pressure in glomerular capillaries is 60 mmHg.

2-Renal tubule: It is a thin tube, which is subdivided into functionally and morphologically distinct segments:
a- Proximal convoluted tubule: It is about 15mm long that lies in the cortex. The wall of the proximal convoluted tubule is made up of a single layer of cells that are united by apical tight junction. Between the bases of the cells, there are extensions of the EC space called the lateral intracellular space. The Laminar edges of the cells have a brush border due to the presence of many microvilli. **b- Loop of Henle:** It is U- shaped extension of the proximal convoluted tubule that dips in the renal medulla. Each loop consist of: i- Descending limb (thin). ii- Ascending limb (thick). The walls of the descending limb and the lower half of the ascending limb are thin called the thin segment loop of Henle. After the ascending limb of the loop has returned part of its way back to the cortex, its wall becomes thick.

Descending limb and Ascending limb Thin segment - Thick segments Has an epithelium attenuated flat cells Lined by cuboidal cells with extensive invaginations of the basilar portion

The distal convoluted tubule: It lies in the cortex and is about 5mm long. Its epithelium is lower than that of the proximal tubule. There is no distinct brush border, but there are few microvilli.

Collecting ducts:- The tubules collected to form collecting ducts that are about 20mm long and pass through the renal cortex and medulla to empty into the pelvis of the kidney at the apexes of the medullary pyramids. The collecting duct is lined by two types of cells: 1- Principle cells (P- cells). 2- Interstitial cells (I- cells).

Physiologic significance of the juxtaglomerular apparatus; JGA is a combination of specialized tubular and vascular cells located at the vascular pole where the afferent and efferent arterioles enter and leave the glomerulus. - The juxtaglomerular apparatus plays an important role in autoregulation of the renal blood flow and GFR during changes in arterial pressure and is important for regulation of arterial blood pressure through renin- angiotensine aldosterone system.

Types of nephrone: There are two types of nephrone according to the location of the glomeruli in the cortex: 1- Cortical nephrons. 2- Juxtamedullary nephrons

The structure of the glomerular membrane: The membrane that separates the blood in the glomerular capillaries from the glomerular filtrate in Bowman's capsule is formed of three layers: 1- The capillary endothelium 2- Basement membrane

1- The capillary endothelium: It is perforated by small holes called fenestrated. This layer doesn't act as a major barrier for plasma proteins as the fenestrations are relatively large (70-90 nm) in diameter.

2- Basement membrane: - It consist of a meshwork of collagen & proteoglycan fibrillae that have large spaces The proteoglycan carry strong negative membrane prevents effectively filtration of plasma proteins, but filters large amounts of water and solutes.

3- Podocytes: These are epithelial cells that line the outer surface of the glomerulus. They have numerous pseudopodia that interdigitate to form slit pores (25nm wide) through which the glomerular filtrate moves. Mesangial cells: These are stellate cells located between the basement membrane and the endothelium at bifurcation of the capillaries. - These cells are contractile.

Renal Blood Supply; Blood flow to the two kidneys is normally about 22 per cent of the cardiac output, or 1100 ml/min. The renal artery enters the kidney through the hilum and then branches progressively to form the interlobar arteries, arcuate arteries, interlobular arteries (also called radial arteries) and afferent arterioles, which lead to the glomerular capillaries, where large amounts of fluid and solutes (except the plasma proteins) are filtered to begin urine formation. The distal ends of the capillaries of each glomerulus coalesce to form the leads to a second capillary network, the peritubular capillaries, that surrounds the renal tubules.- The renal circulation is unique in that it has two capillary beds, the glomerular and peritubular capillaries, which are arranged in series and separated by the efferent arterioles, which help regulate the hydrostatic pressure in both sets of capillaries causes rapid fluid filtration. whereas a glomerular filtration, tubular reabsorption, or both in response to body homeostatic demands.



The peritubular capillaries empty into the vessels of the venous system, which run parallel to the arteriolar vessels and progressively form the interlobular vein, arcuate vein, interlobar vein, and renal vein, which leaves the kidney beside the renal artery and ureter.

Renal blood flow and its control: Renal blood flow: In a resting adult, the kidney receive 1.2- 1.3 liter of blood per minute i.e.21% of the cardiac output. Renal vascular arrangement: The renal arteries are directed branches of the aorta. Each renal artery on entering hilum of the kidney divides to form the interlobar arteries. The afferent arterioles arise from the interlobular arteries. Each divides into glomerular capillaries in the glomerulus. The capillaries reunite to form the efferent arteriole, which in turn breaks up into the peritubular capillaries that supply the tubule. The capillaries draining the tubules of the cortical nephron from a peritubular network, whereas the efferent arterioles from the Juxtamedullary nephron drain not only into peritubular network, but also into the vasa recta which are hairpin capillary loops that lie side by side with the loops of Henle. -The peritubular capillaries reunite to veins ►interlobar veins ►renal veins. Therefore, there are two capillary beds associated with each nephron. **The glomerular capillary bed "High pressure bed"**It receives its blood from the afferent arteriole.The hydrostatic pressure in the glomerular capillaries is about 60 mmHg which cause rapid filtration of fluid.The pressure in the glomerular capillaries is higher than in other capillary beds due to:a- The renal arteries are direct branches of the abdominal aorta.b) The afferent arterioles are short, straight branches of the interlobular arteries.c) The efferent arterioles have high resistance than the afferent arteriole **The peritubular capillary bed "Low pressure bed"** The hydrostatic pressure is about 13mmHg. The peritubular capillaries behave like the venous ends of other capillaries. The low pressure in these capillaries permits fluid reabsorption from the interstitium into the blood.

Regional blood flow: The main function of the renal cortex is filtration of large volumes through the glomeruli, so it is no surprising that the renal cortex receives most of the renal blood flow (98%) as the renal medullary blood flow accounts for 2% of the total renal blood flow. This sluggish blood flow in the renal medulla allows the kidney to form concentrated urine

GFR is about 20% of the renal plasma flow: As in other capillaries, the GFR is determined by (1) The balance of hydrostatic and colloid osmotic forces acting across the capillary membrane and (2) The capillary filtration coefficient (Kf), the product of the permeability and filtering surface area of the capillaries. -The glomerular capillaries have a much higher rate of filtration than most other capillaries because of a high glomerular hydrostatic pressure and a large Kf. In the average adult human, the GFR is about 125 ml/min, or 180 L/day. The fraction of the renal plasma flow that is filtered (the filtration fraction) averages about 0.2; this means that about 20 per cent of the plasma flowing through the kidney is filtered through the glomerular capillaries. The filtration fraction is calculated as follows: **Filtration fraction = GFR/Renal plasma flow**

Filtration fraction: Is the fraction of renal plasma flow filtered across the glomerular capillaries , i.e. the ratio of GFR to the renal plasma flow.Normal value 0.16- 0.20. Thus, about 20% of the RPF is filtered. The remaining 80% leaves the glomerular capillaries by the efferent arterioles and became the peritubular capillary circulation

Autoregulation of the renal blood flow:When the kidney is perfused at a moderate pressure (90-220 mmHg) the renal blood flow is relatively kept constant by change of the renal vascular resistance. Renal autoregulation is present in denervated and isolated kidney, i.e. independent of nervous or hormones.

Mechanisms of autoregulation of renal blood flow:

1- Myogenic mechanism: a- With rise of pressure: (up to 220mmHg) Direct contractile response of the muscle of the afferent arteriole due to stretch. This contraction prevents excessive increase in renal blood flow. Stretch of the vascular wall increases calcium influx from the extracellular fluid into the muscle fibers causing them to contract ►increase the vascular resistance of different arterioles ►maintain renal blood flow . **b- At low pressure** Relaxation of the vascular smooth muscles of afferent arterioles ►decrease of vascular resistance ►maintain a constant blood flow.

2- Tubuloglomerular feedback: When renal arterial pressure increases both renal blood flow and GFR increase. The increase in GFR results in increase delivery of solutes and water to the macula densa The macula densa responds to increased delivered solute load by secreting the vasoactive substance; adenosine that produces vasoconstriction of afferent arterioles, reduces RBF, HP_{GC} and GFR return back to normal.) Conversely with drop of arterial blood pressure the HP_{GC} tends to drop. The GFR decreases Flow rate in the loop of Henle decreases, so that the reabsorption of sodium and chloride ions in the ascending loop of Henle increases. Sodium chloride reaching the macula densa decreases. **Macula densa send signal to:** Afferent arteriole : producing dilation which raises HP_{GC} and help to return GFR towards normal. Efferent arteriole: producing constriction. This occurs through increase of renin release from JGC. Renin released increases the formation of angiotensin I, which is covered to angiotensin II constricts the efferent arteriole, thereby increasing HP_{GC} and return GFR toward normal. A and b will increase HP_{GC} and return GFR towards normal. **Myogenic autoregulation:** This response is rapid and it is the first line of defense against rapid change in blood pressure. An increase in ABP results in stretching of the afferent arteriolar wall ►contraction of the smooth muscles and returns the diameter towards normal to minimize change in glomerular capillary pressure. Conversely a decrease in ABP results in relaxation of smooth muscle.iii) **Changes in Bowman's capsule hydrostatic pressure:**Increasing HP_{BC} reduces GFR. A stone in the ureter that obstructs the outflow of urine from the ureter will decrease GFR by raising HP_{BC} .iv) **Changes in the glomerular colloid osmotic pressure:Changes in the concentration of plasma proteins affect GFR as follows:** An increase in π_{GC} e.g. in dehydration will decrease GFR. A decrease in π_{GC} e.g. in case of hypoproteinemia will increase GFR v) **Renal vasodilators:** PGE_2 , PGE_1 and bradykinin produce



renal vaso- dilatation, and increase in RBF and GFR. administration of anti- inflammatory drug like aspirin that block PG synthesis may cause marked reduction in GFR. prostaglandin synthesis in the kidneys is increased by sympathetic nervous system stimulation and angiotensin II This may protect the renal vessels from severe vasoconstriction during high sympathetic activity and elevated angiotensin II in severe cardiovascular stress like hemorrhage. **VI) Effect of protein intake:** High protein intake increases RBF and GFR. **Mechanism:** High protein intake ►rise of amino acid into the blood ►filter in Bowman's capsule. Increased amino acids reabsorption stimulate sodium reabsorption in the proximal tubules. This decreases sodium delivery to the macula densa which in turn elicits tubuloglomerular feedback afferent arteriole vasoconstriction that rises HP_{oc} and GFR.

Sympathetic nervous system activation decreases GFR: Essentially all the blood vessels of the kidneys, including the afferent and the efferent arterioles, are richly innervated by sympathetic nerve fibers. Strong activation of the renal sympathetic nerves can constrict the renal arterioles and decrease renal blood flow and GFR. - Moderate or mild sympathetic stimulation has little influence on renal blood flow and GFR. - For example, reflex activation of the sympathetic nervous system resulting from moderate decreases in pressure at the carotid sinus baroreceptors or cardiopulmonary receptors has little influence on renal blood flow or GFR. The renal sympathetic nerves seem to be most important in reducing GFR during severe, acute disturbances lasting for a few minutes to a few hours, - such as those elicited by the defense reaction, brain ischemia, or severe hemorrhage. - In the healthy resting person, sympathetic tone appears to have little influence on renal blood flow.

Hormonal and autacoid control of renal circulation: - There are several hormones and autacoids that can influence GFR and renal blood flow. Norepinephrine, Epinephrine, and Endothelin Constrict Renal Blood Vessels and Decrease GFR. Hormones that constrict afferent and efferent arterioles, causing reductions in GFR and renal blood flow, include *norepinephrine* and *epinephrine* released from the adrenal medulla. - In general, blood levels of these hormones parallel the activity of the sympathetic nervous system; thus, norepinephrine and epinephrine have little influence on renal hemodynamics except under extreme conditions, such as severe hemorrhage. - Another vasoconstrictor, *endothelin*, is a peptide that can be released by damaged vascular endothelial cells of the kidneys as well as by other tissues. Endothelin may contribute to homeostasis (minimizing blood loss) when a blood vessel is severed, which damages the endothelium and releases this powerful vasoconstrictor. - Plasma endothelin levels also are increased in certain disease states associated with vascular injury, such and may contribute to renal vasoconstriction and decreased GFR in some of these pathophysiological conditions

Angiotensin II constricts efferent arterioles: - A powerful renal vasoconstrictor, angiotensin II, can be considered a circulating hormone as well as a locally produced autacoid because it is formed in the kidneys as well as in the systemic circulation. - Because angiotensin II preferentially constricts efferent arterioles, increased angiotensin II levels raise glomerular hydrostatic pressure while reducing renal blood flow. - It should be kept in mind that increased angiotensin II formation usually occurs in circumstances associated with decreased arterial pressure or volume depletion, which tend to decrease GFR. In these circumstances, the increased level of angiotensin II, by constricting efferent arterioles, helps prevent decreases in glomerular hydrostatic pressure and GFR; at the same time, though, the reduction in renal blood flow caused by efferent arteriolar constriction contributes to decreased flow through the peritubular capillaries, which in turn increases reabsorption of sodium and water. Thus, increased angiotensin II levels that occur with a low-sodium diet or volume depletion help preserve GFR and maintain normal excretion of metabolic waste products such as urea and creatinine that depend on glomerular filtration for their excretion. At the same time, the angiotensin II-induced constriction of efferent arterioles increases tubular reabsorption of sodium and water, which helps restore blood volume and blood pressure.

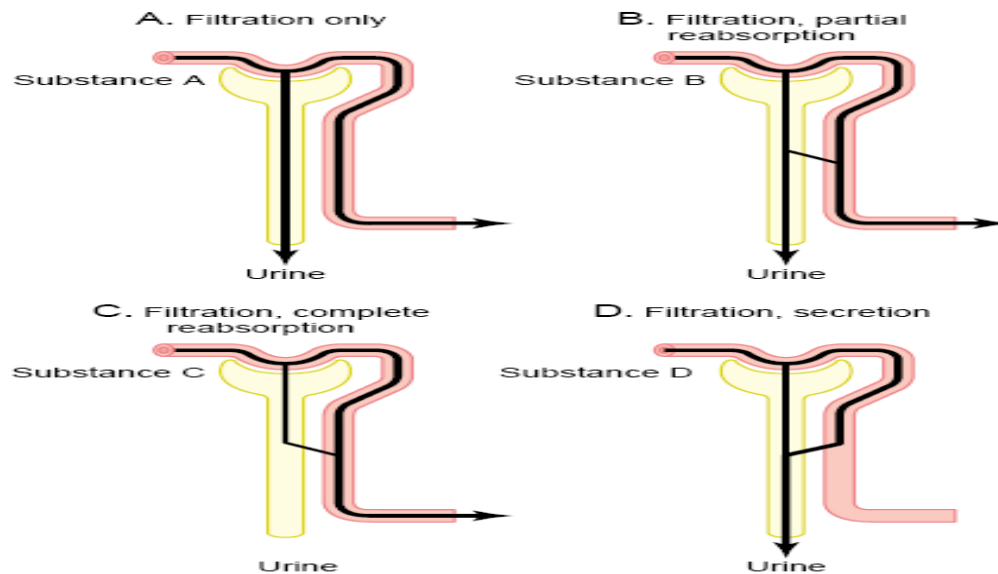
Renal function: Glomerular filtration and its control

1- Glomerular filtration Filtration from the glomerular capillaries into Bowman's capsule of fluid that is nearly free of protein.

2- Tubular Reabsorption Transported from the interstitial fluid into the peritubular capillaries.

3-Tubular Secretion Transport of substance from the blood in peritubular capillaries into the renal tubule.

Urine Formation The rates at which different substances are excreted in the urine represent the sum of three renal processes: (1) Glomerular filtration, (2) Reabsorption of substances from the renal tubules into the blood & (3) Secretion of substances Urinary excretion rate = Filtration rate - Reabsorption rate + Secretion rate Urine formation begins when a large amount of fluid that is free of protein is filtered from the glomerular capillaries into Bowman's capsule. Most substances in the plasma, except for proteins, are freely filtered, so that their concentration in the glomerular filtrate in Bowman's capsule is almost the same as in the plasma. As filtered fluid leaves Bowman's capsule and passes through the tubules, it is modified by reabsorption of water and specific solutes back into the blood or by secretion of other substances from the peritubular capillaries into the tubules. The substance shown in panel A is freely filtered by the glomerular capillaries but is neither reabsorbed nor secreted. Therefore, its excretion rate is equal to the rate at which it was filtered.



In panel B, the substance is freely filtered but is also partly reabsorbed from the tubules back into the blood. Therefore, the rate of urinary excretion is less than the rate of filtration at the glomerular capillaries. In this case, the excretion rate is calculated as the filtration rate minus the reabsorption rate. This is typical for many of the electrolytes of the body. In panel C, the substance is freely filtered at the glomerular capillaries but is not excreted into the urine because all the filtered substance is reabsorbed from the tubules back into the blood. This pattern occurs for amino acids and glucose, allowing them to be conserved in the body fluids. The substance in panel D is freely filtered at the glomerular capillaries and is not reabsorbed, but additional quantities of this substance are secreted from the peritubular capillary blood into the renal tubules. This pattern often occurs for organic acids and bases, permitting them to be rapidly cleared from the blood and excreted in large amounts in the urine. The excretion rate in this case is calculated as filtration rate plus tubular secretion rate.

Filtration, Reabsorption, and Secretion of Different Substances: Tubular reabsorption is more important than tubular secretion in the formation of urine, but secretion plays an important role in determining the amounts of potassium and hydrogen ions and a few other substances that are excreted in the urine. Most substances that must be cleared from the blood, especially the end products of metabolism such as urea, creatinine, uric acid, and urates, are poorly reabsorbed and are therefore excreted in large amounts in the urine. Certain foreign substances and drugs are also poorly reabsorbed but, in addition, are secreted from the blood into the tubules, so that their excretion rates are high. Conversely, electrolytes, such as sodium ions, chloride ions, and bicarbonate ions, are highly reabsorbed, so that only small amounts appear in the urine. Certain nutritional substances, such as amino acids and glucose, are completely reabsorbed from the tubules and do not appear in the urine even though large amounts are filtered by the glomerular capillaries. Each of the processes—glomerular filtration, tubular reabsorption, and tubular secretion—is regulated according to the needs of the body. For example, when there is excess sodium in the body, the rate at which sodium is filtered increases and a smaller fraction of the filtered sodium is reabsorbed, resulting in increased urinary excretion of sodium.

Glomerular Filtration Urine formation begins with filtration of large amounts of fluid through the glomerular capillaries into Bowman's capsule. Like most capillaries, the glomerular capillaries are relatively impermeable to proteins, so that the glomerular filtrate is essentially protein-free and devoid of cellular elements, including red blood cells. The concentrations of other constituents of the glomerular filtrate, including most salts and organic molecules, are similar to the concentrations in the plasma. Exceptions to this generalization include a few low-molecular-weight substances, such as calcium and fatty acids, that are not freely filtered because they are partially bound to the plasma proteins.

Determinants of the GFR: The GFR is determined by: (1) The sum of the hydrostatic and colloid osmotic forces across the glomerular membrane, which gives the net filtration pressure, and (2) The glomerular capillary filtration coefficient, K_f . Expressed mathematically, the GFR equals the product of K_f and the net filtration pressure: $GFR = K_f \times \text{Net filtration pressure}$. The net filtration pressure represents the sum of the hydrostatic and colloid osmotic forces that either favor or oppose filtration across the glomerular capillaries. These forces include: (1) Hydrostatic pressure inside the glomerular capillaries (glomerular hydrostatic pressure, P_G), which promotes filtration; (2) The hydrostatic pressure in Bowman's capsule (P_B) outside the capillaries, which opposes filtration; (3) The colloid osmotic pressure of the glomerular capillary plasma proteins (p_G), which opposes filtration. (4) The colloid osmotic pressure of the proteins in Bowman's capsule (p_B), which promotes filtration. (Under normal conditions, the concentration of protein in the glomerular filtrate is so low that the colloid osmotic pressure of the Bowman's capsule fluid is considered to be zero). The GFR can therefore be expressed as: $GFR = K_f \times (P_G - P_B - p_G + p_B)$.

Forces Favoring Filtration (mm Hg) Glomerular hydrostatic pressure 60 Bowman's capsule colloid osmotic pressure Forces Opposing Filtration (mm Hg) Bowman's capsule hydrostatic pressure 18 Glomerular capillary colloid osmotic pressure 32 Net filtration pressure = $60 - 18 - 32 = +10$ mm Hg



Increased Bowman's Capsule Hydrostatic Pressure Decreases GFR: Bowman's capsule pressure in humans is about 18 mm Hg under normal conditions. Increasing the hydrostatic pressure in Bowman's capsule reduces GFR, whereas decreasing this pressure raises GFR. However, changes in Bowman's capsule pressure normally do not serve as a primary means for regulating GFR.

Increased Glomerular Capillary Colloid Osmotic Pressure Decreases GFR: As blood passes from the afferent arteriole through the glomerular capillaries to the efferent arterioles, the plasma protein concentration increases about 20%. The reason for this is that about one fifth of the fluid in the capillaries filters into Bowman's capsule, thereby concentrating the glomerular plasma proteins that are not filtered. Assuming that the normal colloid osmotic pressure of plasma entering the glomerular capillaries is 28 mm Hg, this value usually rises to about 36 mmHg. Thus, two factors that influence the glomerular capillary colloid osmotic pressure are: The arterial plasma colloid osmotic pressure and The fraction of plasma filtered by the glomerular capillaries (filtration fraction). Increasing the arterial plasma colloid osmotic pressure raises the glomerular capillary colloid osmotic pressure, which in turn decreases GFR. Increasing the filtration fraction also concentrates the plasma proteins and raises the glomerular colloid osmotic pressure. Because the filtration fraction is defined as $GFR/\text{renal plasma flow}$, the filtration fraction can be increased either by raising GFR or by reducing renal plasma flow.

Increased Glomerular Capillary Hydrostatic Pressure Increases GFR: The glomerular capillary hydrostatic pressure has been estimated to be about 60 mm Hg under normal conditions. Changes in glomerular hydrostatic pressure serve as the primary means for physiologic regulation of GFR. Increases in glomerular hydrostatic pressure raise GFR, whereas decreases in glomerular hydrostatic pressure reduce GFR. Glomerular hydrostatic pressure is determined by three variables, each of which is under physiologic control: (1) Arterial pressure, (2) Afferent arteriolar resistance, and (3) Efferent arteriolar resistance. Increased arterial pressure tends to raise glomerular hydrostatic pressure and, therefore, to increase GFR. Increased resistance of afferent arterioles reduces glomerular hydrostatic pressure and decreases GFR. Conversely, dilation of the afferent arterioles increases both glomerular hydrostatic pressure and GFR. The primary cause of the eventual decrease in GFR is as follows: As efferent constriction becomes severe and as plasma protein concentration increases, there is a rapid, nonlinear increase in colloid osmotic pressure caused by the Donnan effect; the higher the protein concentration, the more rapidly the colloid osmotic pressure rises because of the interaction of ions bound to the plasma proteins, which also exert an osmotic effect.

Renal function: Tubular processing of the glomerular filtrate: tubular reabsorption and tubular secretion. Renal processes: Tubular reabsorption & tubular secretion. As the glomerular filtrate enters in the renal tubule (tubular fluid), it flows through the proximal tubule, the loop of Henle, the distal tubule, the collecting tubule and finally the collecting duct. As this tubular fluid passes down the tubules, its volume is reduced and its composition altered by the processes of tubular reabsorption and secretion, to form the urine that enters the renal pelvis. The rate at which different substances are excreted in urine represents the sum of three processes: glomerular filtration, tubular reabsorption and tubular secretion. $\text{Urinary excretion rate} = \text{filtration rate} - \text{absorption rate} + \text{secretion rate}$.

Tubular Reabsorption It involves: 1- Transport of the substance across the tubular epithelium into the renal interstitial fluid. 2- Transported from the interstitial fluid into the peritubular capillaries.

Tubular Secretion Transport of substance from the blood in peritubular capillaries into the renal tubule. Types of transport across the tubular epithelium: 1- Transcellular: Solutes are reabsorbed or secreted through cells. 2- Paracellular: Solutes are reabsorbed or secreted through the tight junction between the cells. **Mechanism of tubular transport** There are three basic principles by which solutes and water are transported across the tubular membrane: A- Active transport: 1- Primary active transport. 2- Secondary active transport. a- Co- transport. b- Countertransport. B- Passive transport C- Pinocytosis. A- Active transport Its against concentrations or electrical gradient. 1- Primary active transport: The energy for the primary active transport comes from hydrolysis of ATP by membrane bound ATPase. The ATPase is a component of a carrier that binds and moves solutes across the cell membrane. Sodium reabsorption across the proximal tubular epithelium is an example of the primary active transport. At the basolateral border of the tubular epithelium $\text{Na}^+ - \text{K}^+$ ATPase pump extrudes 3 Na^+ into the interstitium in exchange for 2 K^+ that are pumped into the cell. This ion pump results in: Creating a negative potential of about -70mV within the cell. Low intracellular sodium concentration. At the luminal border Na^+ diffuse across the luminal membrane from the tubular lumen into the cell due to the electrical and chemical gradient. Secondary active transport This type transport does not require energy directly from ATP or from the high- energy phosphate sources. It is of two types: Co- transport: The reabsorption of one substance is linked to passive reabsorption of another substance. The direct source of energy is that liberated by simultaneous diffusion of another transported substance down its electrochemical gradient. The two substances bind to a specific carrier molecule and are co- transported together across the membrane. One of the substances diffuse down its electrochemical gradient which the second substance is transported against its chemical gradient e.g. secondary active transport glucose. At the luminal border Glucose and Na^+ bind to a common carrier SGLT-2 in the luminal membrane. As Na^+ diffuses along its electrochemical gradient glucose is introduced into the cell. At the basolateral border The Na^+ is pumped out of the cell into the lateral intracellular spaces. Glucose is transported by another carrier GLUT-2 into the interstitial fluid by facilitated diffusion. **Counter transport:** The reabsorption of one substances e.g. secondary active secretion of H^+ into the tubule. As Na^+ is carried to the interior of the cell, hydrogen ions are forced outward in the opposite direction into the tubular lumen by sodium hydrogen counter transport protein in the brush border of the luminal membrane, of the proximal convoluted tubule. **B- Passive reabsorption** 1- Passive reabsorption of chloride: It occurs in through



Paracellular pathway following Na^+ reabsorption. The transport of positively charged Na^+ out of the lumen leaves the inside of the lumen negatively charged. This causes chloride ions to diffuse passively. **2- Osmosis of water:** When solutes are reabsorbed out of the tubule, their concentration decreases inside the tubule, while increasing in the interstitium. This creates a concentration gradient that causes osmosis of water from the tubular lumen into the renal interstitium mainly through Paracellular route **3- Passive reabsorption of urea:** As water is reabsorbed from the tubule, urea concentration in the tubular lumen increases. This creates a concentration gradient favoring reabsorption of urea. About 50% of the filtered urea is passively reabsorbed from the tubule and the remainder passes into the urine

C- Pinocytosis It is an active transport mechanism for reabsorption of proteins and peptides in the proximal convoluted tubule. proteins in the tubular fluid attach to the luminal membrane of the epithelial cells. This portion of the membrane invaginates to the interior of the cell until it's completely pinched off. A vesicle is formed containing the protein, which is digested into amino acids. the amino acids are reabsorbed through the basolateral membrane into the interstitial fluid.

Tubular Transport Maximum For many actively transported substance, there is a maximum rate at which each can be transported. The maximum rate that can be achieved is termed the transport maximum (T_m) for the substance expressed as mg/minute. Substances that are actively reabsorbed or secreted require a specific transport system i.e. specific carriers and enzymes in the tubular epithelial cells. Solutes that exhibit T_m - limited reabsorption Glucose, amino acids, phosphates and sulphates. the affinity of the transport system for many substances with T_m limited reabsorption is so high that the entire filtered load is reabsorbed from the tubular fluid so long as the transport system is unsaturated. for example, reabsorption of glucose and amino acids is completed if the filtered load doesn't saturates the transport system Substances that exhibit T_m - limited secretion The rate of secretion has a finite upper limit e.g. Para- aminohipuric acid PAH. Penicillin. The affinity of the transport system for secreted substances is so high that essentially all of the substance in the peritubular capillaries is secreted into the tubular fluid so long as the transport system is not saturated e.g. PAH. Threshold for substances that have a tubular maximum Substances that have a reabsorptive maximum have a threshold concentration in the plasma below which non of the substance appears in the urine and above which progressively large quantities appear

Gradient- time Transport All substances that are reabsorbed by diffusion do not exhibit a transport maximum. Instead, transport of this type is termed gradient- time transport as it is determined by: The Electro- chemical gradient for the substance across the membrane. The time that the fluid containing the substance remains within the tubule which in turn depends on the tubular flow rate Some actively transported substances also obey the gradient- time transport e.g. Na^+ reabsorption by the proximal tubules as it is determined by: The concentration of Na^+ in the proximal tubule: the greater the concentration of Na^+ in the proximal tubule, the greater the reabsorption rate. The rate of flow: the slower the flow rate of the tubular fluid, the greater the percentage of Na^+ that can be reabsorbed from the proximal tubule.

Absorption by peritubular capillaries Fluid and electrolytes are reabsorbed from the renal interstitium into the peritubular capillaries by bulk flow as the peritubular capillaries behave like venous end of capillary. The forces that act across the peritubular capillaries are

Forces that favour reabsorption: The colloidal osmotic pressure of the peritubular capillaries (about 32mmHg). The hydrostatic pressure in the renal interstitium (about 6mmHg). **Forces that oppose reabsorption** the hydrostatic pressure inside the peritubular capillaries (about 13 mmHg). the colloidal osmotic pressure of proteins in the renal interstitium (about 15 mmHg). Net reabsorptive force = $(32+6) - (13+15) = 38 - 28 = 10 \text{ mmHg}$ Through changes in the hydrostatic and colloidal osmotic pressure of the renal interstitium and the peritubular capillaries, the uptake of fluid and solutes by the peritubular capillaries is matched to the net absorption of water and solutes from the tubular lumen into the interstitium

The mode of reabsorption of different substances (e.g. Na^+ , K^+ , Cl^- , glucose, urea and water) Na^+ is filtered in large amounts through the glomeruli, but Na^+ is reabsorbed out of all proteins of the tubule except the thin descending segment of the loop of Henle. 96% to well over 99% of the filtered Na^+ is reabsorbed. 90% of the energy consumed by kidney is used for active transport of Na^+ . The reabsorption of Na^+ is coupled with: Reabsorption of most of the solutes in the filtrate by secondary active mechanism or by diffusion. Also, Na^+ reabsorption results in reabsorption of H_2O by osmosis. Again Na^+ reabsorption is coupled with secretion of H^+ and K^+ . Again Na^+ reabsorption is coupled with HCO_3^- reabsorption and H^+ secretion.

Na^+ reabsorption in the different segments of the renal tubule

Proximal tubule: 65% of the filtered load of Na^+ is reabsorbed by the proximal tubule. **a- First half of the proximal tubule:** Na^+ is reabsorbed by co- transport along with glucose, amino acids, sulphate, organic acids (lactate and citrate) and HCO_3^- . Within the proximal tubule cell: $\text{CO}_2 + \text{H}_2\text{O} \xrightarrow{\text{CA}} \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$ (CA carbonic anhydrase). H^+ is secreted into the tubular lumen where it combines with filtered HCO_3^- to form ultimately $\text{CO}_2 + \text{H}_2\text{O}$ under influence of carbonic anhydrase in the luminal membrane. **b- Late half of the proximal tubule:** Na^+ is reabsorbed with chloride ion (Cl^-). The late proximal tubule reabsorbed primarily NaCl . **Loop of Henle and early distal tubule** **Thin descending limb:** Reabsorb water, but has no capacity to reabsorb Na^+ as the Na^+ transport proteins or channels are absent from the luminal membrane. **Thin ascending limb:** Reabsorption of NaCl in the thin ascending limb in passive by the concentration gradient. The thin ascending limb of the loop of Henle is impermeable to water. As a result, tubular fluid Na^+ and tubular osmolarity decreases. These segment is called the diluting segment. **Thick ascending limb and early distal tubule:** 25% of the filtered load of Na^+ , K^+ and Cl^- are reabsorbed by co- transport



mechanism, that co- transport mechanism, that co- transports one Na^+ one K^+ and two Cl^- from the lumen into the cells. **Early distal tubule:** Is called the cortical diluting segment. Reabsorption of NaCl by Na^+ Cl^- co transport. It is impermeable to water, thus reabsorption of NaCl occurs without water which further dilutes the tubular fluid. **Late distal tubule and collecting duct:** Less than 10% of the filtered Na^+ is reabsorbed by the late distal tubule and collecting duct. The rate of reabsorption of Na^+ is controlled by aldosterone

Reabsorption of glucose At the plasma glucose concentration less than 200 mg/dl, all of the filtered glucose can be reabsorbed because Na^+ glucose transporter are plentiful. Thus the reabsorption equals filtration. At the plasma glucose concentration above 200mg/dl the reabsorption curve bends because some of the filtered glucose is not reabsorbed as there are limited number of Na^+ -glucose carrier. At the plasma glucose concentrations above 300 mg/dl, the carriers are completely saturated and the reabsorption reached its maximal value T_m . T_m is the point at which the carriers are saturated

K + Reabsorption K^+ is reabsorbed and secreted by the renal tubule 1. Proximal convoluted tubule: Reabsorption of 65% of the filtered K^+ . 2. Thick ascending limb of the loop of Henle: 25% of the filtered load of K^+ are actively co- transported with Na^+ and Cl^- . 3. Distal tubule and collecting tubule: Reabsorption of secreted K^+ depending on dietary intake. Reabsorption of K^+ : Involves H^+ - K^+ ATPase in the luminal membrane of intercalated cells 5% of the filtered load of K^+ is actively reabsorbed by intercalated cells by ATP dependent K^+ - H^+ antiporter in the luminal membrane and exist through K^+ channels in the basolateral membrane (occurs only in a low K^+ depletion).

Water reabsorption water reabsorption is passive process throughout the whole nephron. It is of two types: Obligatory water reabsorption: It comprises 87% of the filtered water which is reabsorbed independent of ADH in the following segments: Proximal convoluted tubule 65%. Loop of Henle 15%. Distal tubule 5%. Collecting ducts 2%. H_2O occurs by osmosis. **Facultative water reabsorption:** It comprises about 13% of the filtered water which is controlled by ADH in the following segments: Late distal convoluted tubule. Cortical collecting duct. Medullary collecting duct. This facultative water reabsorption can produce concentrated urine.

Regulation of tubular functions The nervous mechanism that regulate tubular function (renal sympathetic nerves) Activation of the sympathetic nervous system can decrease sodium and water excretion by constricting the renal arterioles, thereby reducing GFR. Sympathetic activation also increases sodium reabsorption in the proximal tubule, the thick ascending limb of the loop of Henle, and perhaps in more distal parts of the renal tubule. And finally, sympathetic nervous system stimulation increases renin release and angiotensin II formation, which adds to the overall effect to increase tubular reabsorption and decrease renal excretion of sodium.

Hormonal Control of Tubular Reabsorption Precise regulation of body fluid volumes and solute concentrations requires the kidneys to excrete different solutes and water at variable rates, sometimes independently of one another. For example, when potassium intake is increased, the kidneys must excrete more potassium while maintaining normal excretion of sodium and other electrolytes. When sodium intake is changed, the kidneys must appropriately adjust urinary sodium excretion without major changes in excretion of other electrolytes. Aldosterone Increases Sodium Reabsorption and Increases Potassium Secretion Aldosterone, secreted by the zona glomerulosa cells of the adrenal cortex, is an important regulator of sodium reabsorption and potassium secretion by the renal tubules. The primary site of aldosterone action is on the principal cells of the cortical collecting tubule. The mechanism by which aldosterone increases sodium reabsorption while at the same time increasing potassium secretion is by stimulating the sodium-potassium ATPase pump on the basolateral side of the cortical collecting tubule membrane. Aldosterone also increases the sodium permeability of the luminal side of the membrane. In the absence of aldosterone, as occurs with adrenal destruction or malfunction (Addison's disease), there is marked loss of sodium from the body and accumulation of potassium. Conversely, excess aldosterone secretion, as occurs in patients with adrenal tumors (Conn's syndrome) is associated with sodium retention and potassium depletion. Although day-to-day regulation of sodium balance can be maintained as long as minimal levels of aldosterone are present, the inability to appropriately adjust aldosterone secretion greatly impairs the regulation of renal potassium excretion and potassium concentration of the body fluids. Thus, aldosterone is even more important as a regulator of potassium concentration than it is for sodium concentration. **Angiotensin II Increases Sodium and Water Reabsorption** Angiotensin II is perhaps the body's most powerful sodium-retaining hormone. Angiotensin II formation increases in circumstances associated with low blood pressure or low extracellular fluid volume, such as during hemorrhage or loss of salt and water from the body fluids. The formation of angiotensin II helps to return blood pressure and extracellular volume toward normal by increasing sodium and water reabsorption from the renal tubules through three main effects: 1. Angiotensin II stimulates aldosterone secretion, which in turn increases sodium reabsorption. 2. Angiotensin II constricts the efferent arterioles, which has two effects on peritubular capillary dynamics that raise sodium and water reabsorption. **First:** Efferent arteriolar constriction reduces peritubular capillary hydrostatic pressure, which increases net tubular reabsorption, especially from the proximal tubules. **Second:** Efferent arteriolar constriction, by reducing renal blood flow, raises filtration fraction in the glomerulus and increases the concentration of proteins and the colloid osmotic pressure in the peritubular capillaries; this increases the reabsorptive force at the peritubular capillaries and raises tubular reabsorption of sodium and water. **3. Angiotensin II directly stimulates sodium reabsorption** in the proximal tubules, the loops of Henle, the distal tubules, and the collecting tubules. - One of the direct effects of angiotensin II is to stimulate the sodium-potassium ATPase pump on the tubular epithelial cell basolateral membrane. - A second effect is to stimulate sodium-hydrogen exchange in the luminal membrane, especially in the proximal tubule. Thus, angiotensin II stimulates sodium transport across both the luminal and the basolateral surfaces of the epithelial cell membrane in the tubules. These multiple actions of angiotensin II cause marked sodium retention by the kidneys when angiotensin II levels are increased. The anti diuretic hormone (ADH) Increases Water Reabsorption The most important renal action of ADH is to increase the water



permeability of the distal tubule, collecting tubule, and collecting duct epithelia. This effect helps the body to conserve water in circumstances such as dehydration. In the absence of ADH, the permeability of the distal tubules and collecting ducts to water is low, causing the kidneys to excrete large amounts of dilute urine. Thus, the actions of ADH play a key role in controlling the degree of dilution or concentration of the urine. ADH binds to tubules, collecting tubules, and collecting ducts, increasing the formation of cyclic AMP and activating protein kinases. This, in turn, stimulates the movement of an intracellular protein, called aquaporin-2 (AQP-2), to the luminal side of the cell membranes. The molecules of AQP-2 cluster together and fuse with the cell membrane by exocytosis to form water channels that permit rapid diffusion of water through the cells. There are other aquaporins, AQP-3 and AQP-4, in the basolateral side of the cell membrane that provide a path for water to rapidly exit the cells, although these are not believed to be regulated by ADH. Chronic increases in ADH levels also increase the formation of AQP-2 protein - in the renal tubular cells by stimulating AQP-2 gene transcription. When the concentration of ADH decreases, the molecules of AQP-2 are shuttled back to the cell cytoplasm, thereby removing the water channels from the luminal membrane and reducing water permeability.

Atrial Natriuretic Peptide Decreases Sodium and Water Reabsorption Specific cells of the cardiac atria, when distended because of plasma volume expansion, secrete a peptide called atrial natriuretic peptide. Increased levels of this peptide in turn inhibit the reabsorption of sodium and water by the renal tubules, especially in the collecting ducts. This decreased sodium and water reabsorption increases urinary excretion, which helps to return blood volume back toward normal.

Parathyroid Hormone Increases Calcium Reabsorption

Parathyroid hormone is one of the most important calcium-regulating hormones in the body.

Its principal action in the kidneys is to increase tubular reabsorption of calcium, especially in the distal tubules and perhaps also in the loops of Henle. Parathyroid hormone also has other actions, including inhibition of phosphate reabsorption by the proximal tubule and stimulation of magnesium reabsorption by the loop of Henle.

Plasma clearance (Renal Clearance of substance) Definition: It is the volume of plasma that is completely cleared of the amount of substance excreted in urine per minute. If the plasma passing through the kidneys contains 1 mg of substance in each ml and 1 mg of this is also excreted into the urine each minute, then 1 ml/ minute of the plasma is cleared of the substance. Thus, clearance refers to the volume of plasma necessary to apply the amount of substance excreted in urine per unit time. Calculation: The amount of substance (x) cleared from the plasma/ min. = $C_x \times V_x$ Where: C_x = volume of plasma cleared from substance x/ min. V_x = concentration of the substance per 1 ml plasma. The amount of substance (x) excreted in urine/ min. = $U_x \times V$ Where: U_x = concentration of the substance/ ml urine. V = volume of urine/min. $C_x \times V_x = U_x \times V$ This is the equation of clearance. **Importance of the determination of plasma clearance** 1- Study of the mode of tubular handling of the direct solute in the filtrate, i.e. either reabsorbed (glucose, urea, water, etc) or secreted e.g. creatinine and K^+ . 2- Measurement of GFR: By using inulin or creatinine clearance. A- Measurement of GFR by the use of inulin clearance: Quantity of inulin filtered per min = Quantity of inulin excreted in urine per minute. $C_{in} \times P_{in} = V \times U_{in}$ Where: P_{in} = concentration of inulin in plasma (same concentration as filtrate). U_{in} = concentration of inulin in urine. V = volume of urine / min. C_{in} = volume of filtrate/ min. i.e. GFR. $C_{in} = U_{in} \times V / P_{in}$ C_{in} is called the clearance of inulin which is the volume of plasma that is cleared from the quantity of inulin excreted in urine/ min. Creatinine clearance = C_{cr} Creatinine is an endogenous substance that is formed from creatine in muscle. It possesses the following criteria: Freely filtered. Not reabsorbed. Partially secreted by the renal tubule. However, GFR measured by creatinine clearance agree well with the GFR value measured with inulin because although the value for $U_{cr} \times V$ is high as a result of tubular secretion, the value for P_{cr} is also high as a result of nonspecific chromogens in plasma that are measured with creatinine and errors thus tend to cancel. Endogenous creatinine clearance is easy to measure and is worthwhile index of renal function.

3- Measurement of the renal plasma flow: The substance used is PAH (Para- Amino Hippuric acid) is freely filtered by the glomerulus. The amount of PAH in plasma of the renal artery = The amount of PAH excreted in urine. Renal plasma flow can be calculated from clearance of PAH. $CPAH = U_{PAH} \times V / P_{PAH}$ $CPAH$ provides the effective renal plasma flow (ERPF). $ERPF = U_{PAH} \times V / P_{PAH}$ Actual renal plasma flow (RPF) = $ERPF / \text{extraction ratio}$. Renal blood flow = $RPF / (1 - H_V)$ (H_V = hematocrite value).

4- Calculation of filtration fraction (F.F): Filtration fraction is the ratio of the GFR to the renal plasma flow. GFR is determined by the inulin clearance. Renal plasma flow is determined by PAH clearance. If $RPF = 700$ ml/ min $GFR = 125$ ml/ min $F.F = 125 / 700 = 0.19$ Normal value = 0.16- 0.20

5- Free water clearance: It tests the power of the kidney to concentrate or dilute urine. Free water is defined as distilled water that is free of solutes. **In the nephron:** Free water is generated in the diluting segments where the water solute is reabsorbed without water. Measurement of free water clearance CH_2O : It provides a method for assessing the ability the kidney to dilute or concentrate the urine. The principles underlying this measurement are as follows: When ADH levels are low; all of the free water generated in the thick ascending limb and early distal tubule is excreted, since it cannot be reabsorbed by collected ducts. The urine is hypo- osmotic and free water clearance is positive. 2. When ADH levels are high all of the free water generated in the thick ascending limb and the early distal tubule is reabsorbed by the late distal tubule and collecting duct. The urine is hyper- osmotic and free water clearance is negative. Calculation of CH_2O : $CH_2O = V - C_{OSM}$ Where: C_{OSM} = total osmolar clearance = $V \times U_{OSM} / P_{OSM}$ U_{OSM} and P_{OSM} = urine and plasma osmolarity respectively. V = urine flow rate (ml/min) - Free water clearance is important in qualifying the power of the kidney to concentrate or dilute urine.

Control of sodium and water balance: Regulation of plasma volume and osmolarity. Renal mechanisms for sodium regulation. Na^+ is the main cation in extracellular fluid. Sodium salt accounts for over 90% of the osmotically active solutes in the plasma and interstitial fluid. The amount of Na^+ excreted is adjusted to equal the amount ingested over a wide range of dietary intake. Thus, the urinary Na^+ output ranges from 1mEq/day on low- salt diet to 400mEq/day or more when the dietary Na^+ intake is high. Variations in sodium excretion are affected by: Amount filtered. Amount reabsorbed. Therefore, factors that GFR and tubular reabsorption will affect renal excretion of Na^+ .



Glomerular filtration rate (Glomerular Balance) Definition: An increase in GFR causes an increase in the reabsorption of solutes and consequently of water. Site: The main site is the proximal convoluted tubule. **Loop of Henle also shares.** The mechanism occurs independent of hormones and can occur in isolated kidney. This process is prominent for Na⁺ and it shows that the renal tubules reabsorb a constant percentage of the filtered Na⁺ (2/3 or 65%) rather than a constant amount. **Importance:** It helps to prevent overloading of the distal tubular segment when GFR increase. It prevents inappropriate losses of Na⁺ and water in the urine that can occur as a result of sudden increases in GFR. Thus increased GFR increases the amount of Na⁺ filtered and this increases the amount reabsorbed leading to a slight increase in Na⁺ excretion. It represents the ability of the proximal tubule to reabsorb a constant percentage of the filtered load of Na⁺ and water. **2. Rate of tubular flow:** Slow rate of flow will increase tubular reabsorption of Na⁺ as in cases of decreased GFR. 3. Effect of ABP on tubular reabsorption "Pressure Natriuresis" and "Pressure Diuresis"

Pressure Natriuresis: An increase in ABP cause marked increase in urinary excretion of Na⁺ and water. Mechanism: Decreased angiotensin II secretion with rise of ABP. Back leak of Na⁺ into the tubular lumen due to: Rise of hydrostatic pressure in peritubular capillaries with rise of ABP. Rise in the interstitial fluid hydrostatic pressure as a consequence of the rise in the peritubular capillaries. An increase in the renal interstitial fluid hydrostatic pressure enhance backleak of sodium into the tubular lumen, thereby reducing the net reabsorption of sodium and water and further increasing the rate of urine output when arterial pressure rises. This is primarily a compensatory mechanism for regulation of ABP independent of nervous or hormonal influence.

Hormonal control: Mineral corticoids: Aldosterone increases Na⁺ reabsorption in exchange with K⁺ or H⁺. It acts only on distal tubule and collecting duct. They act on P cells that contain Na⁺ channels in their apical membranes. **Glucocorticoids:** Cortisol has weak mineral corticoid activity. **Angiotensin II:** It is the most powerful sodium- retaining hormone, it increases Na⁺ reabsorption. **Sex hormones:** Estrogen increases Na⁺ reabsorption by renal tubule. **Atrial Natriuretic Peptide (ANP) :** ANP facilitates the excretion of NaCl and water under conditions of marked expansion of ECF. Increase GFR ► increase filtered Na⁺ ► ++ Na⁺ excretion. Inhibit renin secretion ► reduces the levels of angiotensin II and aldosterone. Inhibit Na⁺ reabsorption by collecting ducts. **PGE2: Increase Na⁺ excretion through:** Inhibit Na⁺ channel in the apical membrane. Inhibit Na⁺- K⁺ ATPase in the basolateral membrane. Endothelin Increases PGE2

Sympathetic stimulation: increases Na⁺ reabsorption and decreases Na⁺ excretion: Reduce GFR by constricting renal vessels. Increases renal secretion and angiotensin II formation ► increases Na⁺ reabsorption. Increases Na⁺ reabsorption by the proximal tubule and the thick ascending limb of the loop of Henle.

Regulation of renal water excretion The primary control of the renal water excretion is osmolality control. Since 2/3 of the body water normally is located within the cells, this is also an intracellular volume control. Following water deprivation even an increase in plasma osmolality of only one per cent stimulates both the hypothalamic osmoreceptors and similar (angiotensin-II-sensitive) thirst receptors. Thirst may increase the water intake of the individual and thus increase the ECV, with negative feedback to the thirst receptors Activation of the hypothalamic osmoreceptors and thirst receptors increases the hypothalamic neurosecretion to the neurohypophysis and releases antidiuretic hormone (ADH or vasopressin). Hyperosmolality elicits a linear increase in plasma ADH, which causes water retention until isosmolality is reached. ADH increases the reabsorption of water from the fluid in the renal cortical and medullary collecting ducts. ADH binds to receptors on the basolateral surface of the tubule cells, where they liberate and accumulate cAMP. This messenger passes through intermediary steps across the cell to the luminal membrane, where the number of water channels (aquaporin 2) are increased. The luminal cell membrane is thus rendered water-permeable, which increases the renal water retention. The increased water reabsorption leads to a small, concentrated urine volume (antidiuresis), and a net gain of water that returns ECF osmolality towards normal. Water overload decreases ECF osmolality and has the reverse effect, because the hypothalamic osmoreceptors suppress the ADH release, and the renal water excretion is increased already after 30 min. When a person rapidly drinks one litre of water, the intestine absorbs water. Ions diffuse into the intestinal lumen and the blood osmolality falls causing a block of the ADH secretion. Pure water is distributed evenly in all three body fluid compartments – just like intravenous infusion of one litre of 5% glucose in water. Intake of one l of isotonic saline implies ECV expansion, without dilution of body fluids. This expansion will not increase the urine volume much, so the increased ECV can be sustained for many hours. An intravenous infusion of one l of large dextran molecules (macrodex) stays mainly in the vascular space

Osmoreceptor An increase in osmotic pressure, e.g. after eating a salty meal activates osmoreceptors. There are osmoreceptors already in the central nervous system, more specifically in the hypothalamus, notably in two circumventricular organs that lack an effective blood-brain barrier, the organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ (SFO). However, although located in the same parts of the brain, these osmoreceptors that evoke thirst are distinct from the neighbouring osmoreceptors in the OVLT and SFO that evoke arginine vasopressin release to decrease fluid output

Thirst Is the craving for fluids, resulting in the basic instinct of animals to drink. It is an essential mechanism involved in fluid balance. It arises from a lack of fluids and/or an increase in the concentration of certain osmolites, such as salt. If the water volume of the body falls below a certain threshold or the osmolite concentration becomes too high, the brain signals thirst. Continuous dehydration can cause many problems, but is most often associated with neurological problems such as seizures and renal problems. Excessive thirst, known as polydipsia, along with excessive urination, known as polyuria, may be an indication of diabetes. There are receptors and other systems in the body that detect a decreased volume or an increased osmolite concentration. They signal to the



central nervous system, where central processing succeeds. Some sources therefore distinguish "extracellular thirst" from "intracellular thirst", where extracellular thirst is thirst generated by decreased volume and intracellular thirst is thirst generated by increased osmolyte concentration. Nevertheless, the craving itself is something generated from central processing in the brain, no matter how it is detected.

Role of the kidney in long term regulation of arterial blood pressure Currently, three mechanisms of regulating arterial pressure:

1- Baroreceptor reflex: Baroreceptors in various organs can detect changes in arterial pressure, and adjust the mean arterial pressure by altering both the force and speed of the heart's contractions, as well as the total peripheral resistance.

2- Renin-angiotensin system (RAS): This system is generally known for its long-term adjustment of arterial pressure - This system allows the kidney to compensate for loss in blood volume or drops in arterial pressure by activating an endogenous vasoconstrictor known as angiotensin II.

3- Aldosterone release: - This steroid hormone is released from the adrenal cortex in response to angiotensin II or high serum potassium levels. - Aldosterone stimulates sodium retention and potassium excretion by the kidneys. - Since sodium is the main ion that determines the amount of fluid in the blood vessels by osmosis, aldosterone will increase fluid retention, and indirectly, arterial pressure. The aldosterone system is directly targeted by spironolactone, an aldosterone antagonist. The fluid retention may be targeted by diuretics; the antihypertensive effect of diuretics is due to its effect on blood volume. Generally, the baroreceptor reflex is not targeted in hypertension because if blocked, individuals may suffer from orthostatic hypotension and fainting. Mechanism of formation of concentrated and diluted urine

Role of the kidney in the formation of diluted and concentrated urine The kidney can excrete either concentrated or diluted urine according to the water balance of the body. In dehydration: water is conserved in the body and concentrated urine having high osmolarity is excreted. In case of hydration, excess water is eliminated from the body and diluted urine is excreted.

Requirements for excreting concentrated urine The concentrating mechanism depends upon: High ADH levels, which increases the permeability of the late distal tubule, collecting tubule and medullary duct to water. **Hyperosmotic renal medulla:** The osmolarity of the interstitial fluid in the medulla of the kidney increases progressively from 300mOsm/L in the superficial layer of the medulla to about 1200 mOsm/L in the deep parts in the tips of the papillae. The high osmolarity of the renal medulla interstitium helps osmosis of water from the renal tubule into the renal interstitium where it is carried by the vasa recta. The mechanism that produce a hyperosmotic renal medullary interstitium include: The counter current multiplier system of the loop of Henle of the Juxtamedullary nephrons. **The counter current exchange system of the vasa recta.** Passive diffusion of large amounts of urea from the medullary collecting ducts into the medullary interstitium. Sluggish medullary blood flow accounting only for 1-2 % of the total renal blood flow. This helps to minimize solute loss from the medullary interstitium.

Counter current system Is a system in which the inflow runs parallel to counter to and in close proximity to the outflow for some distance. The loop of Henle of juxtamedullary nephron as a counter current multiplier. The loop of Henle of the juxtamedullary nephrons adds solutes to the interstitium. Thus, it creates the medullary hyperosmolarity. **Ascending limb Thick segment:** It is absolutely impermeable to water. Na⁺, K⁺ and Cl⁻ are co-transported at the luminal border dependent on sodium-potassium ATPase pump in the basolateral membranes. Considerable amounts of calcium, bicarbonate and magnesium are also absorbed in the thick segment. **Thin segment** Passive reabsorption of sodium chloride from the thin ascending segment into the medullary interstitium down their concentration gradient. The tubular fluid in the ascending limb becomes very dilute as it enters the distal tubule. **Descending limb** It is very permeable to water but much less permeable to sodium chloride and urea. Water diffuses from the descending limb into the medullary interstitium by osmosis. The ascending limb of the loop of Henle and the interstitial fluid reach osmotic equilibrium. Therefore, the tubular fluid osmolarity gradually rises from 300 mOsm/L to reach 1200 mOsm/L at the tip of the loop due to:

A - Osmosis of water out of the descending limb. B- Diffusion of sodium chloride from the medullary interstitium into the descending limb.

Vasa recta as a countercurrent exchange The osmotic gradient in the medullary interstitium would not last long if the solutes in the interstitium were removed by the circulation. These solutes remain in the medullary interstitium because the vasa recta act as a countercurrent exchanger, i.e. the U-shaped structure of the vasa recta minimizes loss of solutes.

The endothelium of the vasa recta is highly permeable to water and solutes thus: In the ascending limb of the vasa recta solutes diffuse from the medullary interstitium into the blood along concentration gradient; however, water diffuses from the blood to the interstitium. By the time, the blood reaches the tips of the vasa recta; it has a concentration of 1200 mOsm/L (the same as the medullary interstitium). In the ascending limb of the vasa recta solutes diffuse back out into the medullary interstitium along



concentration gradient. Meanwhile, water diffuses into the vasa recta. Thus, the vasa recta do not create the medullary hyperosmolarity but prevent it from being dissipated. The bulkflow of fluids and solutes into the blood through the usual colloid and hydrostatic pressure help reabsorption in these vessels. Contribution of urea to hyperosmotic renal medullary interstitium Urea contributes about 40% of the osmolarity (500 mOsm/L) of renal medullary interstitium; and thus plays an important role in production of concentrated urine in the collecting ducts. Urea moves passively out of the proximal tubule. The rest of the tubular epithelium is relatively impermeable to urea except for the medullary collecting duct. Consequently, urea is concentrated in the tubular fluid as water is removed in the loop and distal tubule. When the inner medullary portion of the collecting duct is reached, urea moves into the interstitium of the medulla adding to the hyperosmolarity. This movement is facilitated by ADH. Therefore, a high protein diet increases the ability of the kidney to concentrate the urine, while protein deficiency is accompanied by impairment of urine concentrating ability

Role of antidiuretic hormone (ADH) In presence of large amount of ADH: The epithelium of the late distal tubule, cortical collecting tubule become highly permeable to water by insertion of aquaporin- 2 water channels into the luminal membrane of the principal cells. Water diffuses from the tubule into the interstitium until osmotic equilibrium is reached with tubular fluid having about the same concentration as the renal medullary interstitium. Renal mechanism for excreting a dilute urine Glomerular filtrate has the same osmolarity as plasma 300, Osm/L. To excrete dilute urine, solutes are reabsorbed to a greater extent than water. This occurs in certain segments of the renal tubule. These segments include: The ascending limb of the loop of Henle:- Is impermeable to water. Reabsorption of Na⁺, K⁺, Cl⁻ takes place. Thus, tubular fluid becomes more dilute as it enters distal tubule (Osmolarity = 100 mOsm/L). 2- The distal tubule cortical collecting duct, medullary collecting ducts: Impermeable to water in absence of ADH. **Reabsorb NaCl.** The tubular fluid becomes more dilute with osmolarity of 50 mOsm/L

Physiology of Micturition

Micturition is the process by which the urinary bladder empties when it becomes filled. This involves two main steps: First: the bladder fills progressively until the tension in its walls rises above a threshold level; this elicits the second step, which is a nervous reflex called the micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate. Although the micturition reflex is an autonomic spinal cord reflex, it can also be inhibited or facilitated by centers in the cerebral cortex or brain stem. **Physiologic Anatomy and Nervous Connections of the Bladder** The urinary bladder, is a smooth muscle chamber composed of two main parts: The body, which is the major part of the bladder in which urine collects, and (2) The neck, which is a funnel-shaped extension of the body, passing inferiorly and anteriorly into the urogenital triangle and connecting with the urethra. The lower part of the bladder neck is also called the posterior urethra because of its relation to the urethra. The smooth muscle of the bladder is called the detrusor muscle. Its muscle fibers extend in all directions and, when contracted, can increase the pressure in the bladder to 40 to 60 mm Hg. Thus, contraction of the detrusor muscle is a major step in emptying the bladder. Smooth muscle cells of the detrusor muscle fuse with one another so that low-resistance. Therefore, an action potential can spread throughout the detrusor muscle, from one muscle cell to the next, to cause contraction of the entire bladder at once. On the posterior wall of the bladder, lying immediately above the bladder neck, is a small triangular area called the trigone. At the lowermost apex of the trigone, the bladder neck opens into the posterior urethra, and the two ureters enter the bladder at the uppermost angles of the trigone. Each ureter, as it enters the bladder, courses obliquely through the detrusor muscle and then passes another 1 to 2 centimeters beneath the bladder mucosa before emptying into the bladder. The bladder neck (posterior urethra) is 2 to 3 centimeters long, and its wall 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 normally keeps the bladder neck and posterior urethra empty of urine and, therefore, prevents emptying of the bladder 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 skeletal muscle, in contrast to the muscle of the bladder body and bladder neck, which is entirely smooth muscle. The external sphincter muscle is under voluntary control of the nervous system and can be used to consciously prevent urination even when involuntary controls are attempting to empty the bladder. **Innervation of the Bladder** The principal nerve supply of the bladder is by way of the pelvic nerves, which connect with the spinal cord through the sacral plexus, mainly connecting with cord segments S-2 and S-3. Coursing through the pelvic nerves are both sensory nerve fibers and motor nerve fibers. The sensory fibers detect the degree of stretch in the bladder wall. Stretch signals from the posterior urethra are especially strong and are mainly responsible for initiating the reflexes that cause bladder emptying. The motor nerves transmitted in the pelvic nerves are parasympathetic fibers. These terminate on ganglion cells located in the wall of the bladder. Short postganglionic nerves then innervate the detrusor muscle. In addition to the pelvic nerves, two other types of innervation are important in bladder function. Most important are the skeletal motor fibers transmitted through the pudendal nerve to the external bladder sphincter. These are somatic nerve fibers that innervate and control the voluntary skeletal muscle of the sphincter. Also, the bladder receives sympathetic innervation from the sympathetic chain through the hypogastric nerves, connecting mainly with the L-2 segment of the spinal cord. These sympathetic fibers stimulate mainly the blood vessels and have little to do with bladder contraction. Some sensory nerve fibers also pass by way of the sympathetic nerves and may be important in the sensation of fullness and, in some instances, pain. **The relation between intravesical pressure and volume of urine in the bladder** When there is no urine in the bladder, the intravesicular pressure is about 0, but by the time 30 to 50 milliliters of urine has collected, the pressure rises to 5 to 10 centimeters of water. Additional urine—200 to 300 milliliters— can collect with only a small additional rise in pressure; this constant level of pressure is caused by intrinsic tone of the bladder wall itself. Beyond 300 to 400 milliliters, collection of more urine in the bladder causes the pressure to rise rapidly. The tonic pressure changes during filling of the bladder are periodic acute increases in pressure that last from a few seconds to more than a minute. The pressure peaks may rise only a few centimeters of water or may rise to more than



100centimeters of water. These pressure peaks are called micturition waves in the cystometrogram and are caused by the micturition reflex.

Micturition Reflex As the bladder fills, many supposed micturition contractions begin to appear. They are the result of a stretch reflex initiated by sensory stretch receptors in the bladder wall, especially by the receptors in the posterior urethra when this area begins to fill with urine at the higher bladder pressures. Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexively back again to the bladder through the parasympathetic nerve fibers by way of these same nerves. Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexively back again to the bladder through the parasympathetic nerve fibers by way of these same nerves. When the bladder is only partially filled, these micturition contractions usually relax spontaneously after a fraction of a minute, the detrusor muscles stop contracting, and pressure falls back to the baseline. As the bladder continues to fill, the micturition reflexes become more frequent and cause greater contractions of the detrusor muscle. Once a micturition reflex begins, it is "self-regenerative." That is, initial contraction of the bladder activates the stretch receptors to cause a greater increase in sensory impulses to the bladder and posterior urethra, which causes a further increase in reflex contraction of the bladder; thus, the cycle is repeated again and again until the bladder has reached a strong degree of contraction. Then, after a few seconds to more than a minute, the self-regenerative reflex begins to fatigue and the regenerative cycle of the micturition reflex stop, permitting the bladder to relax. Thus, the micturition reflex is a single complete cycle of **(1) Progressive and rapid increase of pressure, (2) A period of sustained pressure, and (3) Return of the pressure to the basal tone of the bladder.** Once a micturition reflex has occurred but has not succeeded in emptying the bladder, the nervous elements of this reflex usually remain in an inhibited state for a few minutes to 1 hour or more before another micturition reflex occurs. As the bladder becomes more and more filled, micturition reflexes occur more and more often and more and more powerfully. Once the micturition reflex becomes powerful enough, it causes another reflex, which passes through the pudendal nerves to the external sphincter to inhibit it. If this inhibition is more potent in the brain than the voluntary constrictor signals to the external sphincter, urination will occur. If not, urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful.

Facilitation or Inhibition of Micturition by the Brain The micturition reflex is a completely autonomic spinal cord reflex, but it can be inhibited or facilitated by centers in the brain. **These centers include** strong facilitative and inhibitory centers in the brain stem, located mainly in the pons, and several centers located in the cerebral cortex that are mainly inhibitory but can become excitatory. The micturition reflex is the basic cause of micturition, but the higher centers normally exert final control of micturition as follows: 1. The higher centers keep the micturition reflex partially inhibited, except when micturition is desired. 2. The higher centers can prevent micturition, even if the micturition reflex occurs, by continual tonic contraction of the external bladder sphincter until a suitable time presents itself. 3. When it is time to urinate, the cortical centers can facilitate the sacral micturition centers to help initiate a micturition reflex and at the same time inhibit the external urinary sphincter so that urination can occur. **Voluntary urination is usually initiated in the following way: First: a person** voluntarily contracts his or her abdominal muscles, which increases the pressure in the bladder and allows extra urine to enter the bladder neck and posterior urethra under pressure, thus stretching their walls. This stimulates the stretch receptors, which excites the micturition reflex and simultaneously inhibits the external urethral sphincter. Ordinarily, all the urine will be emptied, with rarely more than 5 to 10 milliliters left in the bladder.

CHAPTER VIII

DIGESTIVE SYSTEM

THE PHYSIOLOGY OF THE UPPER GIT

Mouth and Esophagus In the mouth, food is mixed with saliva and propelled into esophagus then peristaltic waves move the food into stomach. **Mastication (Chewing):** Anterior teeth (incisors) provide a strong cutting action. Posterior teeth (molars) provide a grinding action. Most of the chewing muscles are innervated by the 5th cranial nerve. Much of the chewing process is caused by the chewing reflex **Chewing reflex:** Controlled by nuclei in the brain stem. The presence of bolus of food in the mouth causes reflex inhibition of the muscles of mastication, which allow the lower jaw to drop. Initiates a stretch reflex of the jaw muscles contraction. Automatically raises the jaw to cause closure of the teeth, but it also compresses the bolus again against the linings of the mouth; which inhibits the jaw muscles which allows the lower jaw to drop and so on.

Action: Breaks up large food particles. Mixes the food with the secretions of the salivary glands. Aids digestion. **Swallowing:** **Deglutition** -It is initiated voluntarily and completed involuntarily. *Center: Medulla and lower pons. *Stages: 3 stages [Buccal, pharyngeal and esophageal] **A-Voluntary (Buccal) stage:** Initiates the swallowing voluntarily. The food is "Voluntarily" Squeezed or rolled posteriorly into the pharynx. Mechanism: by pressure of tongue upward & backward against the palate. **B- Pharyngeal stage: [Involuntary (1-2 second)]** -The passage of food through the pharynx into the esophagus as: Stimulus: The bolus of food enters the pharynx. Receptor: around the opening of the pharynx. Center: deglutition center in medulla & lower pons. Response: automatic pharyngeal muscular contractions as follows: Nose is closed by elevation of the soft palate. Mouth is closed by elevation of tongue. **Larynx & trachea:** are closed by elevation of larynx to pulled upward & forwards to covered by epiglottis. -Successive contraction of superior, middle and inferior pharyngeal constrictor pushes the bolus to the esophagus. -The upper esophageal or pharyngo-esophageal sphincter relaxes allowing food to pass easily from pharynx into the upper esophageal. -Swallowing center inhibits the respiratory center of the medulla [stop respiration] **C-Esophageal stage of swallowing Involuntary** -The esophagus conducts food from pharynx to the stomach. -Esophagus is a muscular tube. 20cm long. a-Upper esophageal sphincter: (UES)



Prevents air from entering the stomach during inspiration. -It relaxes during the passage of food, then it contracts. Travelling along the esophagus: Fluid by gravity Bolus of food by peristalsis: 2 types **1)Primary peristalsis:** It is the continuation of peristalsis in the pharynx. Its duration is (8-10)seconds. However, food takes only(5-8) seconds to reach the stomach due to the effect of gravity **2)Secondary peristalsis:** It occurs if the primary peristalsis fails to move the food to the stomach. It is initiated by enteric nervous system in the esophagus & reflexly through vago - vagal reflex. **C-Lower esophageal sphincter(LES):** It is a physiologic sphincter. It prevent the reflux of gastric HCL to the esophagus during swallowing, LES relaxes to allow food passage. The tone of LES is controlled by Vagal fibers that release: A- Acetylcholine contraction of LES. B- NO(Nitric oxide) & VIP Relaxation of LES. -Tone of LES is decreased during pregnancy. -Between meals, the normal tonic activity of LES prevent reflux of stomach contents into the esophagus. **Salivary Secretion:** Secretion: by 3 pairs of glands: *The parotid. *The submandibular *The sublingual. In addition, many small buccal glands. Volume: 1500 ml/day. The pH: 7.0 Contains: Proteins (enzymes as ptyalin & mucin). Electrolytes (K⁺, HCO₃⁻, Na⁺ & Cl⁻) **Structure of salivary gland:** Is formed of acini secrete a primary secretion ducts oral cavity The acinus is formed of 2 types of secretory cells.

There are two types of salivary secretory cells: (1)Serous cells: (watery) secretion contain ptyalin.(2)Mucous cells: (viscous)secretion contain mucin.*The parotid glands acini are serous[25% of saliva]*The sublingual glands acini are mucous[5% of saliva].*The submandibular glands, acini are mixed.[70% of saliva].*The buccal glands secreted only mucous. Stages of salivary secretion **1st stage:**The acini secrete a primary secretion, contain ptyalin and or mucin in solution, which has the same ionic composition as plasma. **2nd Stage:** The ducts modify the primary salivary secretion. -Na⁺ is actively reabsorbed in exchange with K⁺, this exchange is stimulated by aldosterone. -Na⁺ reabsorption exceeds K⁺ secretion, this creates negativity -70mV in ducts. this causes Cl⁻ to be reabsorbed passively i.e. Cl⁻ ions follow Na⁺ ions. Bicarbonate [HCO₃⁻] ions are secreted into the ducts. -The ducts are impermeable to water, therefore, the saliva that reaches the mouth is Hypotonic[contain higher K⁺ & HCO₃⁻ contains lower Na⁺ & Cl⁻ (during normal condition). During Maximal salivation [parasympathetic stimulation] Rapid flow decrease ductal modification increase Na⁺, Cl⁻ & HCO₃⁻ & decrease K⁺. Aldosterone increase K⁺ & decrease Na⁺ & Cl⁻ in saliva (similar to its action on kidney).

Function of Saliva: [1] Protection of the oral mucosa:-Cooling hot food.-Acid buffering(keep oral pH at 7.0) -Maintaining healthy oral mucosa (lysosome & antibodies destroy oral pathogenic bacteria). 2] Protection of teeth: -Teeth do not lose calcium (saliva is saturated with Ca⁺⁺). -Keep the oral pH at 7.0 -Fluoride protects the teeth enamel. -Proline rich protein protect teeth enamel -In the absence of salivation Ulcer, infection & loss of Ca⁺⁺. [3]Lubrication & Wetting: -Swallowing: lubricates the food facilitating its swallowing -Speech: keeping mouth moist facilitates movements of lips & tongue. -Taste: saliva act as a solvent for the molecules stimulate taste receptors. [4]Digestion:Contains salivary amylase digests starch into disaccharid.. **Control of salivary secretion:** -Secretion is controlled by: autonomic nervous system reflexes. -Secretion occurs in response to: conditioned or unconditioned stimuli. Innervation of salivary glands:1)Parasympathetic efferent fibers. 2)Sympathetic efferent fibers. **(1)Parasympathetic efferent fibers:**a-Sublingual and submaxillary (submandibular) salivary glands. b- Parotid gland. Action: watery saliva rich in electrolytes.**(2)Sympathetic efferent fibers:** 1st & 2nd thoracic segments of the spinal cord. Action: Small amount of saliva rich in organic materials. Secretion of saliva occurs in response to: **A)Conditioned reflexes:**1- **Cerebral cortex:** CC Sight, smell and hearing the preparation of food stimulation of cerebral cortex stimulation of salivary nuclei salivation. 2- **Hypothalamus:**Appetite center in the hypothalamus receives signals from the taste and smell area in the cerebral cortex which stimulate the salivary nuclei. **Unconditioned reflexes:**Afferent impulses stimulate the salivary nuclei arise from:1-Taste receptors -Thermal & tactile receptors 3-Lower esophagus, stomach & upper small intestine How alimentary tract provides the body with water, electrolytes & nutrients (1)Movement of food through the alimentary tract. (2)Secretion of digestive juices and digestion of the food. (3)Absorption of the digestive products, water, and electrolytes. (4)Circulation of blood through GIT to carry away the absorbed substances. (5)Control of all these functions by the nervous and hormonal systems. Characteristics of the gastrointestinal wall: (1)The serosa. (2)A longitudinal muscle layer. (3)A circular muscle layer. (4)The submucosa. (5)The mucosa. *Gastrointestinal smooth muscle: Arranged in bundles connected by gap junction. -The bundles fuse with each other and act as syncytium. -The excitation wave travel up to the entire length of intestinal tract. Connection between longitudinal & circular muscle layer

Extrinsic Innervation from autonomic nervous system

1)Parasympathetic cholinergic fibers: The preganglionic fibers end on cholinergic nerve cell plexuses. They increase the motility & secretion of GIT. **(2)Sympathetic noradrenergic fibers:** The postganglionic fibers act in 2 ways: a-Directly on smooth muscles & glands (slight effect) b-Through the neurons of the enteric plexuses(major effect) They decrease the motility and secretion of GIT. However, sympathetic fibers causing the sphincters to contract **The Enteric Nervous System:** **1)The myenteric plexus(Auerbach's plexus):** between the outer longitudinal & inner circular muscle layers. **2] The submucous plexus(Meissner's plexus):** between the circular layer & the mucosa. -The plexuses are interconnected, and they contain: *Motor neurons innervate smooth muscle. *Secretory neurons regulate endocrine & exocrine secretion in the mucosa. *Sensory neurons respond to stretch, glucose, or amino acids. *Interneurons. The substances secreted by the neurons in the enteric nervous system: NO, acetylcholine, serotonin & a large number of polypeptides. Regulation of Gastrointestinal System **A:Nervous Regulation (1)Short reflex:[i.e. centers are enteric nervous system]**They are responsible for self-regulation of the GIT Stimulus:Stretch of the gut wall, digestive food product and change in the pH and osmolarity. Receptors: dendritic ending of the neurons of the local plexuses. Afferent: dendrites of the neurons of the local plexuses Centers: Myenteric and submucosal plexuses Efferent: axons of the neurons of the local plexuses 2)Long reflexes: [i.e. centers are brain and spinal cord] **Conditioned reflexes:** -Need training cerebral cortex. -Receptors: outside the gut [visual, auditory and smell receptors]. **-Center: Cerebral cortex.** b-Unconditioned reflexes(In born) -



Don't need training or cerebral cortex. -Receptors: in the wall of GIT[chemo or osmo receptor] -Center: reticular formation in the brain stem

Hormonal Regulation of GIT

Hormonal Regulation of GIT The GIT hormones are polypeptides, secreted by Special mucosal cells APUD cells: Amine Precursors Uptake & decarboxylation Circulation: Blood stream portal circulation venous circulation Heart arterial system GIT affect the smooth muscle or gland. According to structural and functional similarity many of the hormones fall into one of 2 families: (1)Gastrin family: Gastrin hormone & cholecystokinin (CCK) (2)Secretin family: Secretin, glucagon, glicentin(GLI), Gastrin inhibitory polypeptide(GIP) & vasoactive intestinal peptide(VIP) **Gastrin:** Site of release: gastrin-secreting cells in gastric ant rum & duodenum. **Mechanism of action:** 1-Distension of pyloric ant rum. 2-Soup extracts & peptones (phenylalanine & tryptophan). 3-Rise in pH above 2. -Vagal stimulation. *Inhibited by: Acid, Somatostatin, Secretin & GIP. feed back mechanism] **Physiological actions:** 1-Increase HCL secretion. 2-Stimulation of gastric motility Stimulation of insulin release after a protein meal. 4-Contraction of lower esophageal sphincter (LES). 5- Atrophic to gastrointestinal mucosa. Increase HCL Decrease Gastrin [-ve feed back mechanism] **Gastrin inhibitory peptide(GIP)** Site of release: Special cells in upper part of small intestine **Mechanism of secretion:** Decrease in the pH in the intestinal fluid. Physiological actions: 1-Decrease HCL secretion. 2-Increase insulin secretion. **Secretin:** Site of release: APUD cells in the upper part of small intestine. **Mechanism of secretion:** Decrease in the pH in the intestinal fluid below 4.5 **Physiological actions:** 1-Decrease HCL secretion. 2-Increase Pancreatic aqueous juice. 3-Inhibition of gastric acid secretion. Cholecystokinin (CCK): Site of release: APUD cells in the upper part of small intestine **Mechanism of secretion:** stimulated by amino acids, fat & bile salt. **Physiological action:** 1-Increase pancreatic enzymes secretion. 2-Contraction of the wall of the gallbladder. 3-Increase the action of secretin for stimulation of secretion of alkaline pancreatic juice 4-Enhance the motility of small intestine & colon. 5-stimulates insulin secretion. **Vasoactive intestinal peptide(VIP):** Site of release: special cells of upper part of small intestine Mechanism of secretion: stimulated by the presence of products of digestion in the lumen of small intestine. Action: 1- Regulate gastrointestinal motility. 2-Inhibition of HCL secretion. 3-Increase pancreatic bicarbonate secretion. 4-Relaxation of gastrointestinal smooth muscle. **Gastro intestinal Circulation** The blood flow to GIT, pancreas, and liver is arranged in a series of parallel circuits. The blood from intestines and pancreas draining through the portal vein to the liver. **GIT Motility** 1) Proximal motor unit: Funds and stomach Body. Thin wall. **Function: Storage of food (2)Distal motor unit:** Ant rum and pyloric sphincter Thick wall. **Function:** Mixing through peristalsis & partial digestion of food to form chyme. - Ant rum, pylorus & upper duodenum function as a unit i.e. contraction of the ant rum is followed by contraction of the pyloric region and contraction of the duodenum. -In ant rum, partial contraction prevents solid masses from entering the duodenum to the small intestine. Normally, regurgitation from the duodenum does not occur because contraction of the Pyloric segment tends to persist longer than that of duodenum. **Innervation: (1) Proximal motor unit:** A- Vagal purinergic inhibitory fibers which secrete ATP B- Sympathetic adrenergic inhibitory fibers from lower 6th segment. C- Enteric nervous system. (2)Distal motor unit: Vagal cholinergic excitatory fibers. Basic electrical rhythm(BER): Gastric slow waves: 3 -5 cycles/ minute. [They are not considered action potentials but slow changes in Resting Membrane Potential (RMP)which consists of gradual depolarization followed by gradual repolarization]. Some leads to spike burst and in turn perstalsis. At rest, spike burst 3/minute. Vagal stimulation and gastrin increase spike bursts to 5/minute. Peristalsis waves are stronger and faster in the pyloric ant rum. Solid contents lead to closure of pyloric orifice, so only small liquid part passes to duodenum ending in slow gradual gastric emptying. Receptive Relaxation Stimulus: gastric distension. Receptors: mechanoreceptors. Afferents: Vagus sympathetic. Centers: Vagal nucleus lower 6th segments. Efferents: Vagal purinergic fibers - Sympathetic adrenergic fibers. Response: Relaxation of stomach. Regulation of gastric evacuation (Emptying): (1) Gastric factors: Distension of the stomach leads to increased stomach emptying. Mechanism: Nervous reflexes and gastrin release leads to increase pyloric pumping force and slightly inhibit the pylorus. (2) **Intestinal factors (Nervous- Hormonal) A-Nervous:** [Enterogastric reflex] The presence of the following factors in the duodenum inhibit gastric emptying: 1- increased acidity 2-Irritation 3-distension 4- Hyper tonicity 5-fats & [protein. B- Hormonal: The presence of fats in the duodenum leads to the release of some GIT hormones called enterogastrone i.e. CCK and secretin which decrease the activity of pyloric pump and increase pyloric contraction. (3) Consistency of food: Fluids are evacuated more rapidly than solids. (4) Reflexes from outside the GIT: Pain produces reflex inhibition of gastric emptying. Emotion can either increase or decrease gastric motility. Hunger Contraction (Hunger pain) The feeding center in the hypothalamus is inhibited by satiety center. Hypoglycaemia decrease the activity of the satiety center leading to increased activity of the feeding center which sends impulses to a- Limbic cortex Hunger sensation. b- Vagal nucleus in the medulla Hunger contraction.

Vomiting:

Definition: Reflex evacuation of gastric content through the esophagus and mouth Center: Medulla oblongata, and is anatomically and functionally related to the respiratory centers. The center is affected by chemoreceptor. Vomiting is a protective mechanism, to protect the GIT against toxic or irritant substances. **Causes of vomiting:** (a) Reflex causes: 1- Mechanical stimulation of the posterior part of the tongue. 2- Irritation of gastric mucosa. 3- Intestinal irritation. 4- Visceral pain. **Central causes** Stimulate the chemoreceptor trigger zone in the medulla oblongata: 1- Drugs: Apomorphine and emetine. 2- Hypoxia. 3- Acidosis. **Mechanism of vomiting:** (1) Before vomiting: Nausea, salivation, sweating and tachycardia (increase heart rate). (2) During vomiting: **A- Protection of air passages:** Elevation of soft palate to close the nasal cavity. Closure of the glottis and apnea. **B- Stomach wall** is completely passive: Relaxation of the wall of the stomach. Relaxation of the lower esophageal sphincter. Contraction of pyloric ant rum. **C- Deep inspiration** is followed by strong contraction of diaphragm and abdominal muscle leading to increase intra-abdominal pressure.



which squeezed the contents of the stomach up through a relaxed lower esophageal sphincter (LES). **Effects of vomiting** : 1- Dehydration hypotension and tachycardia 2- Alkalosis due to loss of HCL hypoventilation and tetany. 3- Hypokalaemia .

GIT Secretion

GIT Secretion The gastric mucosa contains many deep glands: (1) In pyloric & cardiac regions, the glands secrete mucus. (2) In the body & fundus, the glands contain a- Parietal cells: secrete HCL and Intrinsic factor b- Chief cells: secrete pepsinogen. c- Cells in the neck of the glands: secrete soluble mucous in response to vagal stimulation. It lubricates the gastric chyme. d- Surface epithelium: secretes insoluble mucous protects against HCL. **Gastric juice**: Volume: 2.5 liters/day. pH: is highly acidic. Constituents: 1- Electrolytes: H⁺, Cl⁻, Na⁺ and K⁺ 2- Enzymes: pepsinogen, gelatinase & lipase 3- Mucous. 4- Intrinsic factor: important for absorption of vitamin B12 5- Water. **Function of HCL**: Maintains sterility of the stomach. Dissolves food particles changing them into chyme. Activation of pepsinogen to pepsin provides an optimum pH for pepsin. Helps in the process of iron absorption. Helps in the process of Calcium absorption. Stimulates the flow of bile. **Mechanism of Acid secretion**: (1) **Cl⁻ ion is transported** from cytoplasm to the lumen of the canal, and Na⁺ ions are transported out of the canal to the cytoplasm of the parietal cell and these two factors together create negative potential -40mv inside lumen. (2) **This lead to passive diffusion** of K⁺ and small amount of Na⁺ from cytoplasm to the lumen. (3) **H₂O dissociated** into H⁺ and OH⁻ in cytoplasm (4) **CO₂ which formed** during metabolism or entering by blood combines with H₂O forming carbonic acid. (5) **Carbonic acid dissociates** into HCO₃⁻ and H⁺ which combine with OH⁻ to form water. (6) **The HCO₃⁻** diffuses out of the cell in exchange for Cl⁻ then repeated and H₂O passes through the cell to the lumen by osmosis. Stimuli of acid [HCL] secretion: 1- Histamine: act through H₂ receptors increase intracellular cAMP. 2- Acetylcholine: act through M₃ receptors increase Ca⁺⁺ 3- Gastrin hormone: Direct on oxyntic cells increase intracellular Ca⁺⁺ Indirect Stimulating the secretion of Histamine from enterochromaffin like cells [ECI]. Mucosal Barrier: In normal individuals the gastric mucosa does not become digested because: The gastric juice also contains mucus forms a flexible gel that coats the mucosa The surface mucosa cells also secrete HCO₃⁻ so that pH ranges from 1 – 2 at the luminal side, 6 -7 at the surface of the epithelial cells. HCL cross this barrier in finger like channels Leaving the rest of the gel layer. The surface membranes of the mucosal cells, and the junctions between them are also parts of the mucosal barrier Protects the gastric epithelium from damage Substances that tend to disrupt the barrier include: Ethanol – Vinegar –bile salts –asprin –Corticosteroids. The three Phases of Gastric secretion: (1) Cephalic stimulatory phase (nervous) 1/3 (2) Gastric stimulatory phase (nervous & hormonal) 2/3 (3) Intestinal inhibitory phase (nervous & hormonal). I. Cephalic stimulatory phase: Both conditioned and unconditioned reflexes stimulate dorsal nucleus of the vagus lead to Increased HCL secretion, pepsinogen, mucous and gastrin. Vagal stimulation increases gastric secretion by releasing: (a) Acetylcholine that acts directly on the cells in the body & fundus. (b) Gastrin-releasing peptide that increases gastric secretion. [1] **Conditioned reflexes**: (a) **Cerebral cortex: sight**, smell & hearing the preparation of food stimulation of vagal nucleus (b) **Apetite center of hypothalamus**: Stimulate the dorsal nucleus of the vagus. 2] **Unconditioned reflexes**: Taste, thermal and tactile receptors in the mouth send impulses along VII, IX and V cranial nerves to stimulate the vagal nucleus II. **Gastric stimulatory Phase :2/3** Once the food enters the stomach, it increase gastric secretion by: 1- Long vagovagal reflexes. 2- Short local enteric reflexes: end on parietal cells increase the acid secretion. 3- **Gastrin hormone**. III. **The intestinal inhibitory phase**: Stimulus: Food in the duodenum. Response: Decrease gastric secretion by: a- Enterogastric reflex. b- Hormones: such as VIP, CCK and Secretin. **Small Intestine**: The length of small intestine in living human is 280cm. The first part is the duodenum, then jejunum (40%) and lastly ileum (60%). In the small intestine, digestion is completed in the lumen or in the mucosal cells. The absorptive surface of the small intestine is increased 600 folds by the valvulae conniventes, villi and microvilli (brush border) Out of 9L of fluid presented in the small intestine/day, only 2L pass into the colon. Paneth cells: are endocrine cells located in the depth of crypts of Lieberkuhn, and secrete defensins that are naturally occurring peptide antibodies.

Secretions of the small intestine (1) Intestinal mucus. (2) Intestinal alkaline fluid. (3) Enzymes. -I- Intestinal mucus: Composed of: Mucins and gel, forming blanket of mucus. **Functions**: 1- Covers, protects & lubricates the intestinal epithelium. 2- It binds some bacteria. 3- It holds immunoglobulins in place Mucus is secreted by: 1- Surface epithelial cells through the GIT. 2- Goblet cells of the small intestine. Brunner's glands in the duodenum which stimulated by: a- Chemical & physical irritation. b- Cholinergic fibers c- Gastrointestinal hormones especially **secretin**. 2- **Intestinal alkaline fluid**: -It is formed by the epithelial cells in the crypts of Lieberkuhn. Composed of isotonic fluid of sodium chloride and bicarbonate. Volume: 1800 ml / day - 3- Enzymes: They are not secreted but present at the brush border. So, they digest food substances while they are absorbed. Ex: (1) Peptidases for splitting small peptides into amino acids. (2) Sucrase, maltase, isomaltase & lactase for splitting disaccharides into monosaccharides. (3) small amounts of intestinal lipase for splitting neutral fats into glycerol & fatty acids.

Large Intestine (The Colon): The colon length is about 100 cm. The colon absorbs water, Na⁺ and other minerals. The colon absorbs 90% of the fluid (present in 1000 -2000ml chyme passing from the ileum daily to about 200 -250 ml of semisolid feces. The colonic glands secrete mucus. There are no villi on the mucosa.

Physiology of THE GALL BLADDER & PANCREAS

The Gallbladder The gallbladder wall contains fibrous tissue and smooth muscle. The mucous membrane contains glands and is folded to increase the surface area. Functions of the gallbladder: (1) Storage of bile: until needed in the duodenum (2) Concentration of bile: The maximum volume of the gallbladder is about 20 -60 ml, but it can store 450 ml bile (12 hours)



secretion).(3)Prevention of marked rise in the intrabiliary pressure (4)Acidification of bile: this is due to absorption of bicarbonate maintaining the normal properties of lecithin , cholesterol and bile salt . keeps them in solution inside the gallbladder. **Emptying of the gallbladder:** Occurs during digestion. *** Control of Gallbladder Emptying:(1) Cholecystokinin(CCK):Is the major stimulus for gallbladder contraction and relaxation of sphincter of Odd(2) Vagal stimulation:Causes a less strong gallbladder contraction and relaxation of sphincter of Odd .Occurs: directly during cephalic stage of digestionIndirectly during the gastric phase of digestion . Gallstones:In the USA & Europe:85% of gallstones are composed of cholesterol.15% are calcium bilirubinates stones .(1)Cholesterol stones [RadiolucentCholesterol & lecithin which are both insoluble in water kept in solution in bile through the formation of micelles .-When the proportion of lecithin cholesterol ,and bile salts are altered cholesterol crystallizes **Stone formation .** (2) Calcium Bilirubinates Stones [Radiopaque] Infection of the biliary tree: Bacterial deconjugation of conjugated bilirubine . Free bilirubine + calcium calcium bilirubinates [insoluble and precipitates] **Mechanism of secretion of aqueous(bicarbonate) secretion** In duct cells: $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3^-$ is secreted in the lumen by HCO_3^- ATP ase . H^+ ions are pumped out to the plasma in exchange with Na^+ ions which are pumped into the duct cells then Na^+ ions are passively transported into the lumen H_2O diffuses passively by osmotic forces to the lumenAcid tide: It is caused by H^+ ions, which are pumped to the blood . It neutralizes the alkaline tide of gastric venous blood .Alkaline Tide: increase pH of gastric venous blood duringHCL secretion. Explanation: for each HCl molecule formed in lumen , a molecule of $Na HCO_3$ is formed in blood**Function of aqueous secretion**1) It washes out the secreted enzymes .(2)It provides a neutral pH for enzymatic activity in the intestine .Hormonal Regulation of pancreatic secretion:It is the main mechanism. **1-secretin:** Site of release: APUD cells present in duodenum and upper part of small intestine[Amine Precursors Uptake & decarboxylation].**Mechanism of secretion:**Decrease in the pH in the intestinal fluid below4.5**Physiological action:**1- Decrease HCL secretion .2- Increase pancreatic aqueous juice ; large in volume , rich in $NaHCO_3$ and poor in enzymes 3- Inhibition of gastric acid secretion .**2-Cholecystokinin** Pancreozymin(CCK):Site of release: APUD cells in the upper part of small intestine **Mechanism of secretion:** Polypeptide , amino acids ,fat and bile salt **Physiological action:**1- Evacuation of gallbladder .2- Increase pancreatic juice ; small in volume , poor in $NaHCO_3$ and rich in enzymes .3- Inhibit the gastric emptying .4-Stimulation of insulin secretion.5-Enhance the motility of small intestine & colon

PHYSIOLOGY OF THE LARGE INTESTINE

Function of the Colon :(1) Absorption of water , Na^+ and other minerals .(2)Absorption of 90% of fluid in 1000 -2000 ml chyme passing from ileum daily Changed to about 200- 250 ml of semisolid feces .**Innervation of the colon****1- Sympathetic innervation** Through lesser splanchnic nerve.Sympathetic fibers are inhibitory to the wall of the colon but motor in the internal anal sphincter . **2- Parasympathetic innervation:**a- Vagus nerve: supplies the proximal half of the colon .b- Pelvic nerve: (sacral parasympathetic) supplies the distal half of the colon include the rectum.-Parasympathetic fibers are motor to the wall and inhibitory to the internal anal **sphincter****Motility of the Colon**Its diameter > diameter of the small intestine.Length = 100 cm in adults .Its external muscular layer is collected into: 3 longitudinal bands[teniae coli]These bands are shorter than the rest of the colon : So, the wall of the colon forms out pouchings (haustra) between the teniae Its movements are coordinated by: a slow wave of the colon.The frequency of this wave=2/min at ileocecal valve& 6/min at sigmoid.The colonic glands secrete mucus .Gastroileal reflex: When food leaves the stomach the cecum relaxesIncrease the passage of chyme through the ileocecal valve .**Mechanism of Defecation**It is mainly a spinal reflex.Center of defecation: Sacral segments of spinal cord. [Parasympathetic defecation reflex]Spinal parasympathetic reflex:This reflex occurs in new born babies and in some persons .Stimulus: rectal distension Receptors: mechanoreceptorsAfferent: pelvic nerve.Response: Contraction of rectal wall—Relaxation of internal anal sphincterVoluntary control of defecation(1)If the conditions are acceptable for defecation:a-The cerebral cortex sends excitatory impulses which activate the defecation center .b-External anal sphincter relaxes .c- Tacking deep breath plus contraction of the abdominal muscles which raises the intra- abdominal pressure to assist the emptying of the rectum .(2)If the conditions are not socially acceptable for defecation: a- The cerebral cortex sends inhibitory impulses which inhibit the defecation reflex .b- External anal sphincter contracts voluntarily which in turn ,inhibits the defecation reflex .

GIT Hormones

1)Gastrin :Site of release :- gastrin - secretory cells in the antrum & duodenum.Mechanism of release [stimuli]:Distension of pyloric antrum .Soup extracts& peptones(phenylalanine&tryptophane).Increase in pH above 2 .Vagal stimulation .Inhibited by: Acid , Somatostatin , Secretin ,& GIP inhibited gastrin secretion .Physiological actions 1-Increase HCL secretion 2-Stimulation of gastric motility 3-Stimulation of insulin release after a protein meal 4-Contraction of lower esophageal sphincter (LES). 5- Atrophic to gastrointestinal mucosa. Increase HCL lead to decrease Gastrin secretion [-ve feed back mechanism **Cholecystokinin Pancreozymin(CCK** Site of release: Certain APUD cells in the mucosa of the small intestine[Amine Precursors Uptake& Decarboxylation] .Actions :1-Increase pancreatic enzymes secretion .2-Contraction of the wall of the gallbladder.3-Increase the action of secretin for stimulation of secretion of alkaline pancreatic juice4-Enhance the motility of small intestine & colon.5-stimulates insulin secretion .**Secretin**Site of release : APUD cells present in duodenum & the upper part of small intestine.Mechanism of secretion: Decrease in the pH in the intestinal fluid below 4.5Physiological actions:1-Decrease HCL secretion.2-Increase Pancreatic aqueous juice.3-Inhibition of gastric acid secretion .Gastrin inhibitory peptide(GIP)Site of release: Special cells in upper part of small intestineMechanism of secretion:1-Decrease in the pH in the intestinal fluid .Physiological actions:1-Decrease HCL secretion .2-Increase insulin secretion.**Vasoactive intestinal peptide(VIP** Site of release: special cells of upper part of small intestineMechanism of secretion: stimulated by the presence of products of digestion in the lumen of small intestine.Action:1- Regulate gastrointestinal motility.2-Inhibition of HCL secretion .3-Increase pancreatic bicarbonate secretion .4-Relaxation of gastrointestinal smooth muscle**Zollinger – Ellison**



Syndrome Cause :Overgrowth of APUD cells in the islets of the pancreas :Leads to : increase Gastrin Hypergastrinemia which lead to increase Gastric Juice leads to duodenal ulcers .**Peptic Ulcer** :The gastric mucosal barrier protects the mucous membrane of the stomachThis barrier is :Impermeable to H⁺There is an active pump :H⁺ from mucosal cell into the gastric lumen.&Na⁺ from the cells into the interstitial fluid . **prostaglandins**:(1)Increase gastric mucosal barrier & blood flow.(2)Stimulate mucosal secretion & stimulate Na⁺ active transport(3)Inhibited acid secretion Causes of peptic ulcers :[A]Mucosal barrier can be broken by:1- Alcohol.2-A spirin.Both inhibit the production of prostaglandins anddecrease mucus&HCO₃⁻ secretion .3-Bacteria :which disrupt the mucosal barrier ,soH⁺ ions diffuse from lumen to the cell and Na⁺ ions diffuse from plasma to the cell increaseH⁺&Na⁺ intracellular concentration Destruction of cellular metabolic function Ulcer formation [B]Excess secretion of HCL:There is excess secretion of gastrin hormone by tumors in the pancreas . Gastrin prolonged secretion of acid severe UlcerGastric & duodenal ulcers can be given a chance to heal by :(1)Inhibition of acid secretion .(2) Stop use of aspirin & non-steroidal anti – inflammatory drugs . (3)Surgical removal of gastrin –secretion tumors .The Function of Enteric Nervous system & Basic Electrical RhythmThe Enteric Nervous System:1]The myenteric plexus (Auerbach’s plexus): between the outer longitudinal & inner circular muscle layers .2] The sub mucous plexus (Meissner’s plexus): between the circular layer & the mucosa.-The plexuses are interconnected ,and they contain:*Motor neurons innervate smooth muscle.*Secretary neurons regulate endocrine& exocrine secretion in the mucosa .*Sensory neurons respond to stretch , glucose ,or amino acids.*Interneurons.The substances secreted by the neurons in the enteric nervous system: NO ,acetylcholine ,serotonin & a large number of poly peptides .Regulation of Gastrointestinal SystemA:Nervous Regulation(1)Short reflex:[i.e. centers are enteric nervous system]They are responsible for self-regulation of the GITStimulus:Stretch of the gut wall, digestive food productand change in the pH and osmolarity.Receptors: dendritic ending of the neurons of the local plexuses.Afferent: dendrites of the neurons of the local plexusesCenters: Myenteric and submucosal plexusesEfferent: axons of the neurons of the local plexuse2)Long reflexes: [i.e . centers are brain and spinal cord]a-Conditioned reflexes:-Need training cerebral cortex.-Receptors : outside the gut [visual , auditory and smell receptors].-Center: Cerebral cortex .b-Unconditioned reflexes(In born)-Don’t need training or cerebral cortex.-Receptors: in the wall of GIT[chemo or osmo receptor]-Center: reticular formation in the brain stem **Electrical activity of gastro intestinal smooth muscle** :-It is continuous but slow activity and takes 2 types(1)Slow waves .(2) Spikes .Resting membrane potential unstable 56 m.v.Depolarization occurs by: 1- stretching of the muscle. 2- Parasympathetic nerves .Hyperpolarization occurs by sympathetic nerves1)The slow waves : Basic electrical rhythm (BER):They are not considered action potentials but slow changes in resting membrane potential which consists of gradual depolarization followed by gradual repolarization .Rate :3/min in stomach & 12/min in small intestine .Initiated by :The interstitial cells of GajalThey have muscle-like features.They send long multiple processes into the intestinal smooth muscle .Frequency : In stomach &small intestine , there is a descending gradient in pacemaker frequency.The pacemaker with highest frequency usually dominatesMechanism :The depolarization is due Ca⁺⁺ influx .The repolarization is due to K⁺ efflux .Function :The function of the basic electric rhythm (BER) is coordinate peristaltic& other motor activity . (2) The spike potentials:They are true action potentials and occur when the resting membrane potential RMP is depolarized from -50 or -60 to -40 m.vs-The higher the slow waves potentials (depolarization), the more the frequency of the spike potentials.Ca⁺⁺ ions and muscle contraction : Ca⁺⁺ ions move to the interior of the muscle fiber during the spike potential and act through calmoduline to activate myosin light chain kinase .

CHAPTER IX

Endocrinology

Endocrine glands These glands secrete hormones directly into the blood to affect their target tissues and organs all over the body. They include: Pituitary gland which is the master gland. Three endocrine glands under the control of pituitary gland: thyroid gland, suprarenal cortex and gonads (testis & ovaries). Three endocrine glands not under the control of pituitary gland: parathyroid glands, suprarenal medulla and pancreas.In addition, there are organs which possess endocrine function together with their non endocrine function: The heart secretes atrial natriuretic peptide (ANP). The kidney secretes erythropoietin and 1, 25 dihydroxychole- calciferol. The liver secretes somatomedines & dihydroxychole- calciferol. The pineal gland secretes melatonin. The skin secretes calciferol (vitamin D). The gastrointestinal gland secretes GIT hormones as gastrin, CCK, secretin and VIP.

Classification of hormones They are secreted directly into the blood in small amounts and carried by the circulatory system to cells throughout the body, where they bind with receptors and initiate many reactions. then they removed either by target cell uptake, or metabolic activation by liver or by excretion by kidney.Some endocrine hormones affect many different types of cells of the body; e.g. growth hormones (from the anterior pituitary gland) causes growth in most parts of the body, and thyroxin (from the thyroid gland) increases the rate of many chemical reactions in almost all the body 's cells. Other hormones affect only specific target tissues, because only these tissues have receptors for the hormone.Adrenocorticotropic hormone (ACTH) from the anterior pituitary gland specifically stimulates the adrenal cortex, causing it to secrete adrenocortical hormones, and the ovarian hormones have specific effects on the female sex organs as well as on the secondary sexual characteristics of the female body. The multiple hormone systems play a key role in regulating almost all body functions, including metabolism, growth and development , water and electrolyte balance, reproduction and behavior. Example: without insulin from the pancreas, the body 's cells could use little of the food carbohydrates for energy and without the sex hormones, sexual development and sexual functions would be absent.

Transport of hormones and plasma concentration Water soluble hormones (peptides and catecholamines): are dissolved in the plasma and transported from their sites of synthesis to target tissues. Steroid and thyroid



hormones: in contrast, circulate in the blood mainly bound to plasma proteins. Usually, less than 10% of steroid or thyroid hormones in the plasma exist free in solution. However, protein bound hormones cannot easily diffuse across the capillaries to their target cells and are therefore biologically inactive until they dissociate from plasma proteins. The relatively large amount of hormones bound to proteins serve as reservoirs, replenishing the concentration of free hormones when they are taken by target organs. Binding of hormones to plasma proteins greatly shows their clearance from the plasma. Concentrations of Hormones in the Circulating Blood, and Hormonal Secretion Rates The concentrations of hormones required to control most metabolic and endocrine functions are incredibly small. Their concentrations in the blood range from as little as 1 picogram (which is one millionth of one millionth of a gram) in each milliliter of blood up to at most a few micrograms (a few millionths of a gram) per milliliter of blood. Similarly, the rates of secretion of the various hormones are extremely small, usually measured in micrograms or milligrams per day.

Mechanism of hormone action Hormone receptors and their activation The first step of a hormone's action is to bind to specific receptors at the target cell. Cells that lack receptors for the hormones do not respond. Receptors for some hormones are located on the target cell membrane, whereas other hormone receptors are located in the cytoplasm or the nucleus. When the hormone combines with its receptor, this usually initiates a cascade of reactions in the cell with each stage, becoming more powerfully activated so that even small concentrations of the hormone can have a large effect. Hormonal receptors are large proteins highly specific for a single hormone; this determines the types of hormones that will act on a particular tissue. The locations for the different types of hormone receptors are generally the following: On the surface of the cell membrane: The membrane receptors are specific mostly for the protein, peptide and catecholamine hormones. **In the cell cytoplasm:** The primary receptors for the different steroid hormones are found mainly in the cytoplasm. **In the cell nucleus:** The receptors for the thyroid hormones are found in the nucleus and are located in direct association with one or more of the chromosomes.

Up regulation & down regulation of hormone receptors Characters of cell receptors: The number of receptors in a target cell does not remain constant. Increased hormone concentration and increased binding with its target cell receptors cause the number of receptors to decrease. This is known as down regulation. Down regulation of the receptors can occur as a result of: Inactivation of the receptor molecules, inactivation of some of the intracellular protein signalling molecules. Temporary sequestration of the receptor to the inside of the cell, away from the site of action of the hormones. Destruction of the receptors by lysosomes after they are internalized. Decreased production of the receptors. In each case, receptor down-regulation decreases the target tissue's responsiveness to the hormone. **Up-regulation of receptors:** It is an increase in the cell response secondary to prolonged exposure to the cells to decreased amounts of hormone. The target tissue becomes progressively more sensitive to the stimulating effects of the hormone either by increase in receptor expression or decrease in rate of internalization of receptors. Hormones That Act Mainly on the Genetic Machinery of the Cell Steroid Hormones Increase Protein Synthesis Another means by which hormones act—specifically, the steroid hormones secreted by the adrenal cortex, ovaries, and testes—is to cause synthesis of proteins in the target cells. These proteins then function as enzymes, transport proteins, or structural proteins, which in turn provide other functions of the cells. The sequence of events in steroid function is essentially the following: 1. The steroid hormone diffuses across the cell membrane and enters the cytoplasm of the cell, where it binds with a specific receptor protein. 2. The combined receptor protein-hormone then diffuses into or is transported into the nucleus. 3. The combination binds at specific points on the DNA strands in the chromosomes, which activates the transcription process of specific genes to form mRNA. 4. The mRNA diffuses into the cytoplasm, where it promotes the translation process at the ribosomes to form new proteins. To give an example, aldosterone, one of the hormones secreted by the adrenal cortex, enters the cytoplasm of renal tubular cells, which contain a specific aldosterone receptor protein. After about 45 minutes, proteins begin to appear in the renal tubular cells and promote sodium reabsorption from the tubules and potassium secretion into the tubules. Thus, the full action of the steroid hormone is characteristically delayed for at least 45 minutes—up to several hours or even days. This is in marked contrast to the almost action of some of the peptide and amino acid-derived hormones, such as vasopressin and norepinephrine. **G Protein-Linked Hormone Receptors** Many hormones activate receptors that indirectly regulate the activity of target proteins (e.g., enzymes or ion channels) by coupling with groups of cell membrane proteins called heterotrimeric GTP-binding proteins (G proteins). There are more than 1000 known G protein-coupled receptors, all of which have seven transmembrane segments that loop in and out of the cell membrane. Some parts of the receptor that protrude into the cell cytoplasm (especially the cytoplasmic tail of the receptor) are coupled to G proteins that include three (i.e., trimeric) parts—the α , β , and γ subunits. When the ligand (hormone) binds to the extracellular part of the receptor, a conformational change occurs in the receptor that activates the G proteins and induces intracellular signals that either: (1) Open or close cell membrane ion channels or (2) change the activity of an enzyme in the cytoplasm of the cell. The trimeric G proteins are named for their ability to bind guanosine nucleotides. In their inactive state, the α , β , and γ subunits of G proteins form a complex that binds guanosine diphosphate (GDP) on the α subunit. When the receptor is activated, it undergoes a conformational change that causes the GDP-bound trimeric G protein to associate with the cytoplasmic part of the receptor and to exchange GDP for guanosine triphosphate (GTP). Displacement of GDP by GTP causes the α subunit to dissociate from the trimeric complex and to associate with other intracellular signaling proteins; these proteins, in turn, alter the activity of ion channels or intracellular enzymes such as adenylyl cyclase or phospholipase C, which alters cell function. The signaling event is rapidly terminated when the hormone is removed and the α subunit inactivates itself by converting its bound GTP to GDP; then the α subunit once again combines with the β and γ subunits to form an inactive, membrane-bound trimeric G protein. Some hormones are coupled to inhibitory G proteins (denoted G_i proteins), whereas others are coupled to stimulatory G proteins (denoted G_s proteins). Thus, depending on the coupling of a hormone receptor to an inhibitory or stimulatory G protein, a hormone can either increase or decrease the activity of intracellular enzymes. This complex system of cell



membrane G proteins provides a vast array of potential cell responses to different hormones in the various target tissues of the body.

Hypothalamic Hormones

Pituitary Gland and Its Relation to the Hypothalamus Pituitary Gland: Two Distinct

Parts—The Anterior and Posterior Lobes. The pituitary gland also called the hypophysis, is a small gland—about 1 centimeter in diameter and 0.5 to 1 gram in weight— that lies in a bony cavity at the base of the brain, and is connected to the hypothalamus by the pituitary (or hypophysial) stalk Physiologically, the pituitary gland is divisible into two distinct portions: The anterior pituitary, also known as the adenohypophysis, and The posterior pituitary, also known as the neurohypophysis. - Between these is a small, relatively avascular zone called the pars intermedia, which is almost absent in the human being but is much larger and much more functional in some lower animals.

Six important peptide hormones plus several less important ones are secreted by the anterior pituitary, and two important peptide hormones are secreted **by the posterior pituitary**. The hormones of the anterior pituitary play major roles in the control of metabolic functions throughout the body. • Growth hormone promotes growth of the entire body by affecting protein formation, cell multiplication, and cell differentiation. • Adrenocorticotropin (corticotropin) controls the secretion of some of the adrenocortical hormones, which affect the metabolism of glucose, proteins, and fats. Thyroid-stimulating hormone (thyrotropin) controls the rate of secretion of thyroxine and triiodothyronine by the thyroid gland, and these hormones control the rates of most intracellular chemical reactions in the body. • Prolactin promotes mammary gland development and milk production. • Two separate gonadotropic hormones, follicle-stimulating hormone and luteinizing hormone, control growth of the ovaries and testes, as well as their hormonal and reproductive activities. The two hormones secreted by the posterior pituitary play other roles. • Antidiuretic hormone (also called vasopressin) controls the rate of water excretion into the urine, thus helping to control the concentration of water in the body fluids. **Oxytocin helps** express milk from the glands of the breast to the nipples during suckling and possibly helps in the delivery of the baby at the end of gestation.

Synthesis of anterior pituitary hormones There is one cell type for each major hormone formed in the anterior pituitary gland. At least five cell types can be differentiated: Somatotropes- for human growth hormone (hGH). Corticotropes- for adrenocorticotropin (ACTH). Thyrotropes- for thyroid stimulating hormone (TSH) Gonadotropes- for gonadotropic hormones, which include both luteinizing hormone (LH) and follicle-stimulating hormone (FSH). 5. Lactotropes- for prolactin (PRL). about 30- 40% of the anterior pituitary cells are somatotropes acidophils that secrete growth hormone and about 20% are corticotropes that secrete ACTH. Each of the other cell types accounts for only 3- 5% of the total.

Synthesis of posterior pituitary hormones The body's of the cells that secrete the posterior pituitary hormones are not located in the pituitary gland itself but are large neurons, called magnocellular neurons, located in the supraoptic and paraventricular nuclei of the hypothalamus. The hormones are then transported in the axoplasm of the nerve fibers passing from the hypothalamus to the posterior pituitary gland.

Control of secretion of the anterior pituitary Hypothalamic control: Almost all secretion by the pituitary is controlled by either hormonal or nervous signal from the hypothalamus. The hypothalamus secretes many substances which affect the secretion of anterior pituitary by secreting releasing or inhibiting hormones

Releasing or inhibiting hormones Characters: 1- They are small polypeptides. 2- Non specific in function. 3. Work through CAMP system. Site of release: Median eminence which is the collection of many hypothalamic which secrete releasing and inhibiting hormones. Mode of delivery: hypothalamo- hypophyseal portal circulation (which is a connection between 2 organs or 2 sets of capillaries not involving the heart but if the heart is involved it is called (systemic circulation)).

Types of releasing and inhibiting hormones: GHRH (growth hormone releasing hormone present more in children). GHIH (growth hormone inhibiting hormone present more in adults) also called "somatostatin hormone". PIH (prolactin inhibiting hormone) which inhibits of prolactin secretion. TSH- RH ("TRH- thyrotropin releasing hormone"). ACTH- RH (CRH "corticotropin releasing hormone"). 6. FSH- RH & LH- RH: both of them are called "gonadotropin releasing hormone" (GRH).

Feed back control: 1. Long loop feed back control (negative feed back) done by the hormones of the target endocrine glands either on the pituitary or hypothalamus. It is always inhibitor except: Estrogen stimulates luteinizing hormone (LH) secretion from anterior pituitary which in turn increases estrogen secretion from ovaries and so on (positive feed back). . Positive feed back control done by pituitary hormones on the hypothalamus. It is always inhibitory. 3. Ultra short feed back control(short- short) done by releasing hormones on themselves (autocrines). The aim of the feed back control is to maintain constant level of hormones throughout the day

Hypothalamic hormones The main regulatory system are the nervous and the endocrine systems which are intercommunicating. The nervous system can affect the endocrine system: Hypothalamo hypophyseal portal circulation Exist between the hypothalamus and the anterior pituitary gland. The hypothalamus (nervous system) can affect the secretion of the anterior pituitary gland, either by releasing or inhibiting hormones released from ventromedial, arcuate, preoptic and paraventricular nuclei of



hypothalamus. They are carried by the portal circulation to alter the secretion of the anterior pituitary which then can affect other endocrine glands as thyroid gland by thyroid stimulating hormone (TSH), suprarenal cortex by adrenocorticotrophic hormone (ACTH) and gonads by follicle stimulating hormone (FSH) & Luteinizing hormone (LH).

Hypothalamo- hypophyseal tract Exist between the hypothalamus and posterior pituitary: The ADH and oxytocin hormones are formed in the supraoptic and paravertebral nuclei of hypothalamus but released and secreted by their nerve endings present in the posterior pituitary. Direct connection between hypothalamus and suprarenal medulla Which affect secretion of epinephrine & norepinephrine. The nervous and endocrine systems are complementary to each other. On the other hand the endocrine system can also affect the nervous system; parathyroid glands control Ca^{++} level in blood that affects the excitability of the nervous system. Also, thyroid hormones can affect the excitability of the nervous system.

Feedback control of hormone secretion Negative feedback prevents overactivity of hormone systems. It ensures a proper level of hormone activity at the target tissue. The hormone (or one of its product) has a negative feedback effect to prevent oversecretion of the hormone. Feedback regulation of hormones can occur at all levels, including gene transcription and translation steps involved in the synthesis of hormones and steps involved in processing hormones or releasing stored hormones. Surges of hormones can occur with positive feedback. In rare conditions, positive feedback occurs when the biological action of the hormone causes additional secretion of hormone. For example: the surge of luteinizing hormone (LH) that occurs as a result of the stimulatory effect of estrogen on the anterior pituitary before ovulation. The secreted LH then acts on the ovaries to stimulate additional secretion of estrogen, which in turn causes more secretion of LH. Finally, LH reaches an appropriate concentration & negative feedback control of hormone secretion is then occurred. Cyclic variations occur in hormone release. Superimposed on the negative and positive feedback control of hormone secretion are periodic variations in hormone release that are influenced by seasonal changes, various stages of development and aging, the diurnal (daily) cycle and sleep. Pituitary Function & Control of Pituitary Hormones

Anterior pituitary hormones Six important peptide hormones are secreted by the anterior pituitary which play major roles in the control of metabolic functions throughout the body. Growth hormone (GH): promotes growth of the entire body by affecting protein formation, cell multiplication and cell differentiation. Adrenocorticotrophic hormone (corticotrophin) ACTH: controls the secretion of some of the adrenocortical hormones, which affect the metabolism of glucose, proteins and fats. 3. Thyroid stimulating hormone (thyrotropin) TSH: controls the rate of secretion of thyroxin and tri-iodothyronin by the thyroid gland, and these hormones control the rates of most intracellular chemical reactions in the body. 4. Prolactin: promotes mammary gland development and milk production. Two gonadotropic hormones: control growth of the ovaries and testes, as well as their hormonal and reproductive activities. 5. Follicle stimulating hormone (FSH). 6. Luteinizing hormone (LH).

Growth hormone (somatotropin): Nature of growth hormone: it is protein hormone, 22,005 molecular weight (22K) hGH and having 191 amino acids. Other forms may exist as variant hGH (20K) and desamino forms which are less active than normal hGH. It is secreted by special type of cells called "somatotrophic acidophilic cells" or "somatotropin acidophilic cells". **Mechanism of action of growth hormone** One growth hormone molecule bind to 2 GH receptors forming hormodimer which activates JAK2 (Janus family of cytoplasmic tyrosine kinase enzymes). These tyrosine kinases phosphorylate tyrosine in themselves (autophosphorylation) as well as other substances resulting in the following: Activation of the membrane kinase C (PKC) & phospholipase C (PLC). Stimulating the phosphorylation of insulin receptor substrate IRS which is intermediary product in many cellular metabolic pathways induced by insulin. Production of nuclear responses through phosphorylation of signal transducer and activator of transcription (STAT) proteins, which activates transcription by target genes to initiate protein synthesis. **Physiological functions of growth hormones** Growth hormone, in contrast to other anterior pituitary hormones, does not function through a target gland but exerts its effects directly on or almost all tissues of the body. It has two main actions: I. **Metabolic action:** it affects all aspects of proteins, carbohydrate and lipid metabolism. II. **Growth:** It promotes growth of many body tissues. **Metabolic effects:** a. **Effect on protein metabolism** by increasing protein synthesis all over the body so there is increase in size and number of the cells. Mechanism: Enhancement of amino acid uptake and transport through cell membrane into the cell. Enhancement of RNA translation to cause protein synthesis by the ribosomes by turning on the ribosomal machinery. It increase the formation of messenger RNA and it stimulates transcription of DNA. **Protein sparing effect.** Growth hormone is a "protein spare", it causes the fatty acid for production of energy so decreasing protein catabolism. it consider to be an anabolic hormone. b. **Effect on carbohydrate metabolism:** Growth hormone decreases carbohydrate utilization. It is diabetogenic hormone so it increases blood glucose level by: It decreases glucose uptake into the cells by inhibiting hexokinase or glucokinase in the skeletal muscle and fat cells. It increases glucose production by the liver. It decreases glucose utilization by the cell (by decreasing glycolysis and oxidation of glucose). it promotes glycogen deposition due to polymerization of glucose into glycogen (glycogenesis). It increases insulin secretion. **Effect on fat metabolism:** It is a lipolytic ketogenic hormone. Growth hormone enhances fat utilization for energy production. It increases lipolysis leading to hyperlipidemia. It increases uptake of fatty acids by the liver and increases keton body formation & acetyl CoA. Excessive amounts of growth hormone causes large quantities of acetoacetic acid to be formed by the liver and released into the body fluids, thus causes ketosis. This excessive mobilization of fat from adipose tissue also frequently causes a fatty liver. So, growth hormone is a diabetogenic, anabolic, lipolytic ketogenic hormone. **Effect on growth:** Growth hormone has short duration of action while somatomedin C has prolonged action. Growth hormone attaches only weekly to the plasma proteins in the blood. Therefore, it is released from the blood into the tissues, having a half-time in the blood of less than 20 minutes. **Control of growth hormone secretion:** Normal level of growth hormone 2-4 ng/ml in adults but this level is 5- 8 ng/ml in children. The growth hormone secretion is under 2 main controlling systems: Hypothalamic control (hypothalamo-hypophyseal portal circulation) The median



eminence secretes two types of hormones releasing and inhibiting hormones, GHIH, GHRH which are released from the ventromedial nuclei of the hypothalamus to affect the anterior pituitary. 2. Feed back control Long loop feed back control: IGF-1 secreted from the liver under the effect of hGH stimulates the hypothalamus to secrete somatostatin that inhibits GH secretion and also directly inhibits anterior pituitary secretion of GH. Short loop feed back: (which is always negative) The growth hormone inhibits the GHRH and GHIH. c. Ultra short (short- short) negative feedback: GHRH on itself.

Disturbances of GH function These disturbances may be hypofunction or hyperfunction. According to the site of disturbance, it may be: Primary: if it is pituitary in origin. Secondary: if it is hypothalamic in origin

Effects of hypofunction Pituitary dwarfism: -This case of short stature may be due to: GHRH (growth hormone releasing hormone) deficiency. GH deficiency. Deficient local secretion of IGF-1 by condrocytes. In one type of dwarfism (Levi- Lorain dwarf), the rate of growth hormone secretion is normal or high, but there is a hereditary inability to form somatomedin C. GH insensitivity: mutation of GH receptor gene leading to defective GH receptor (Laron- dwarfism). In these cases the child growth is arrested, there is a decrease in the size of the trunk and all extremities, and they are well proportioned i.e. span= height and vertex to symphysis= symphysis to heel. The dwarf is normal mentally and sexually. Some of them are intelligent but they may be unstable psychologically. b. Pituitary infantilism: is pituitary dwarfism, associated with hypogonadism. There is deficiency in of gonadotropic hormone in addition to GH. **Differential diagnosis: Achondroplastic dwarf:** It is the most common clinical form of dwarfism. It is an autosomal dominant mutation of the gene for fibroblast growth factor receptor- 3. The trunk is normal: head, neck, chest and pelvis; while the limbs are short (there is disproportion between limbs and trunk). Thyroid dwarf (cretin): He is a dwarf due to deficiency of thyroid hormones during infancy. Physically (dwarf) he is retarded in growth, he is disproportionate in visceral size (big tongue, liver, abdomen) in relation to skeletal size. He is mentally and sexually retarded. Treatment with human growth hormone: Human growth hormone synthesized by Escherichia coli bacteria by recombinant DNA technology. **Effect of hyperfunction** Depending on the age, increase in growth hormone secretion leads to gigantism (before adolescence) and acromegaly (after adolescence).

A- Gigantism (Giantism): Causes: due to increase in growth hormone before adolescence (per adult life) and before the union of epiphysis with the shaft as a result of acidophilic adenoma. Characters: 1. Symmetrical over growth of all bones, so that the patient becomes taller than normal (height 200- 210 cm) with normal proportions (span= height and vertex to symphysis= symphysis to heel). 2. Symmetrical over growth of all soft tissues, splancomegaly and muscles at first strong while later on very weak due to over stretch. There is increased secretion of 4- hydroxy proline in urine which is indicator excessive soft tissues growth. 3. Hyperglycemia, glucosuria and in about 10% diabetes mellitus eventually develops. 4. Hypogonadism due to pressure on basophiles secreting gonadotropins. 5- Ends by panhypopituitarism leading to death (due to destruction of all cells of the pituitary). Treatment: microsurgical removal of the tumor or by irradiation of the pituitary gland.

B- Acromegaly: It occurs when hyperfunction develops after the ossification and union of the epiphyses of long bones (after puberty). There is no linear growth of long bones. All bones of the body (flat & long) increase in thickness, which is clearer in the terminal portions of the skeleton: the limbs (acro= periphery). The hands, feet, finger and digits becomes large and broad (megaly= enlarged). growth of the skull flat bones produces a characteristic acromegalic facies: it is box shaped with prominent cheeks, nasal bones, super ciliary ridges and protruded lower jaw (prognathism) with widely separated teeth (because the teeth do not overgrow). The skin and soft tissues (nose and lips) of the face also overgrow producing wrinkling of the scalp & forehead (bulldog facies). The thyroid gland is enlarged (goiter) and there is increased production of T3 more than T4. Bending of the spine: kyphosis, due to overweight of the spine & upper limbs, the patient may require an ape like posture. It may produce osteoarthritic changes in the spine. Pituitary enlargement may press on the optic chiasma, producing visual field loss bitemporal hemianopia: a tubular field. Overgrowth of muscles and viscera renders the patient very strong for few years . Later on he becomes weak due to inadequate muscular development relative to bony and visceral enlargement. Hyperglycemia, glucosuria & secondary diabetes due to exhaustion of beta cells occurs late in the disease. So the patient becomes weak. A structural chemical similarity between GH and prolactin molecule produces in males: breast enlargement: gyncomastia & milk production Acromegaly may occur on top of gigantism: acromegalic giant (if the cause of increased GH secretion is not treated).

ADH: Vasopressin It is a non peptide (9AA) that circulates in the blood and reaches its target organs to bind to its receptors. It is also known as arginine vasopressin. It is secreted from: 1. Supraoptic nucleus: mainly when it is released from the posterior pituitary into the systemic circulation. 2. Paraventricular nuclei: to a less degree; where it is released into: The brain third ventricle. The median eminence (co- secreted with CRH), and then carried by the adenohipophyseal portal vessels to reach the anterior pituitary corticotropes. ADH receptors: Vasopressin (V) receptors: are renal and external. Types and mechanism of action of ADH: V1: V1A: acts through G coupled protein by the inositol phosphate pathway & the increase in intracellular Ca²⁺. V2: acts through G coupled protein of the adenyl cyclase pathway that increases the intracellular cAMP. V3: V1B: acts through G coupled protein on the phospholipase to produce prostaglandin from the membrane phospholipids.

Function of ADH I. Renal effects: a. In the tubular system: its main effects are: 1. On the V2 of the late distal tubule (principal cells), the cortical collecting tubule & medullary duct. The second messenger cAMP induces a translocation of water channels (aquaporin 2) from endosomes to the cell membrane. This allows the passage of water from the renal tubule lumen to the inside of the cell and then to the renal interstitium according to the osmotic gradient producing decreased urine volume (antidiuresis). 2- In the cortical collecting tubule, H₂O under ADH effect leads to an increase in urinary K concentration, which will



antagonize K secretion. ADH stimulates K secretion, to balance this effect. 3- in the medullary collecting tubule, ADH induces the insertion of urea transporters (UT1), to increase the flow of urea into the medullary interstitium. The increased amounts of solutes in the renal interstitium, helps more water reabsorption. B. In the renal vascular system: the V3 receptors in the glomerular mesangium induce a local production of a dilator prostaglandin (prostaglandin E2). This ADH- prostaglandin relation is a local negative feedback , which antagonize the ADH renal vasoconstrictor effect & maintains renal perfusion **II- External effects:** In the vascular system: activation of the V1 receptors increases intracellular Ca²⁺, which induces intensive vasoconstriction that raises the dropped arterial blood pressure in case of hemorrhage (vasopressor effect). This effect is minor, since renin- angiotensin & sympathetic nervous system are the primary regulators of BP. 2. In cases of stress: as pain & trauma ADH & CRH are co- secrete from the paraventricular nuclei. CRH stimulates the corticotropes. Also, ADH stimulates the V3 receptors of the corticotropes. The stimulated corticotropes secrete ACTH that in its turn causes cortisol secretion to antagonize the effects of these stressful conditions. **Control of ADH secretion** The supraoptic nuclei are affected by many stimuli: Stimuli that increases ADH secretion Increased plasma osmolarity: a 1% increase in osmolarity increases ADH secretion to retain water through the kidneys & to readjust the plasma osmolarity. Hyperosmolarity causes outflow of water from the osmoreceptors through water channels and reduces the cell size. The shrunken cells activate the stretch inactivated cation channels, which leads to depolarization & ADH secretion & then synthesis. Hypovolemia: a decrease of about 10% of blood volume affects the systemic arterial BP , which in turn increases ADH secretion producing systemic vasoconstriction and rise of ABP. **Mechanism:** a. Afferents from the carotid sinus baroreceptors affect the medullary vasomotor center and subsequently ADH secretion from paraventricular nuclei. b. The low pressure receptors in the atria & big veins through the vagi stimulate ADH secretion (this response is weak in humans). Stress: through the CRH- ADH system. After surgery the ADH rise persist for few days. Drugs: morphine, some tranquilizers & anesthetics. **Stimuli that inhibit ADH secretion:** Decreased pl. osmolarity, Hypovolemia, Alpha- adrenogenic agonists and Ethyl alcohol.

Physiology of Thyroid Hormones

Thyroid gland The thyroid is a butterfly shaped gland; composed of two lobes connected by an isthmus. It is present in front and on either side of the upper part of the trachea. It possesses one of the highest rate of blood flow in the body (about 5ml/ gm/ min). It is composed of follicles: each follicle surrounds a cavity full of colloid material (thyroglobulin). Parafollicular cells, lie in between the follicles.

Hormones of the thyroid gland Thyroid hormones: thyroxine: T₄ and tri- iodothyronine: T₃, by the thyroid follicle cells: it affects the iodine & the general body metabolism. Thyrocalcitonin: TCT: from the parafollicular cells. TCT together with PTH and 1,25 dihydroxycholecalciferol (extrathyroidal hormones) maintain a normal plasma Ca²⁺ and affects the body Ca metabolism. Amounts of the thyroid hormones; 500 µg of iodides are to be ingested/ day. Iodine ingested is absorbed & carried in blood in the form of iodide (I⁻). About four fifth of ingested iodides are rapidly excreted by the kidney. About one fifth is trapped by the thyroid for T₃ and T₄ synthesis. Iodine content of the thyroid hormones, after its metabolization is excreted in urine and stools

Effects of thyroid hormones- **Effect on metabolism:** a. Effect on mitochondria: they increase in size and number (in most cells), which leads to an increase in size & number (in most cells), which leads to an increase in the rate of ATP formation. Excessive increase in thyroid hormones produces mitochondrial swelling and increased uncoupling results in a smaller increases ATP & a greater loss of heat. **b. Effect on cell membrane** ions transport: there is increased activity of Na/ K ATPase enzyme, which leads to increased transport of Na & K through the cell membrane of all body cells and increased energy consumption. **2. Effects on carbohydrate metabolism:** the increase in cell metabolic activity stimulates insulin secretion, glucose absorption by the GIT glucose uptake by the cell, glycolysis & gluconeogenesis. **3. Effect on fat metabolism:** a. All aspects of fat metabolism are stimulated and cause mobilization of lipid from fatty tissue, increased free fatty acid oxidation and depletion of fat stores. b. Effect on plasma lipids: thyroid hormone, decrease plasma cholesterol. This is due to increased secretion of cholesterol in bile and stools and increased number of low- density lipoproteins receptors from plasma and increased secretion of lipoprotein cholesterol by liver cells. **4. Effects on protein metabolism:** anabolic hormone, it increases protein synthesis all over the body. **5- Effects on vitamin metabolism:** the general increase in enzyme activity leads to a general increase in the body needs for vitamins: the coenzymes. **6- Effect on basal metabolic rate (BMR):** BEE: basal energy expenditure) and body weight: the different amount of thyroid hormones is responsible for a normal BEE of about 40 calories/ hr/ m² surface area in a normal adult male & a normal body weight due to a normal appetite with a normal food intake & normal energy consumption. **Effect on growth:** Growth and development of the brain: It is important during fetal & first few years of postnatal life for normal mental development especially of the nervous system. It induces neuronal, axonal and nervous ending formation. **b. Skeletal growth: bones & epiphysis grow and fuse normally.** **Effects on body systems:** a. Primary effect: the majority of the body systems are stimulated by direct hormonal action. b. Secondary effect: the various body systems are stimulated by the increased metabolism of the tissues: calorigenic action. This action causes an increase in O₂ consumption in most tissues e.g. CVS, respiratory, GIT, muscular and endocrine systems. In some tissues O₂ consumption is not increased e.g. adult brain, lymph nodes, spleen, testes & uterus. In the anterior pituitary O₂ consumption is decreased. **Carriage of thyroid hormones** Thyroid hormones are carried in blood on the following plasma proteins: albumin, thyroxine binding prealbumin (TBPA), thyroxine binding globulin (TBG) between alpha1 and alpha2. The thyroid hormones are essential for: Normal development: physical , mental and sexual in young. Normal functions: physical, mental and sexual in adults. Characters of plasma protein binding to thyroid hormones More than 99% of thyroid hormone is bound. Less than 1% is free. Affinity of globulin is higher than albumin or prealbumin to thyroid hormones. Globulin carry 2/3 of T₄ and 1/2 of T₃. Bind of thyroid hormones to thyroid receptors The thyroid hormones in blood T₄, T₃ and rT₃ reach the thyroid receptors in tissue cells to exert their effects. T₃ is more active than T₄ because it is: More free (less bounds to plasma proteins). More affine to the thyroid receptors (10-



15 fold greater affinity than T4). Sites of thyroid receptors in the cell There are at least four types: α_1 , α_2 , β_1 and β . As regards binding of the hormones to the receptors: T3 binds to: α_1 , β_1 and β . T4 binds to all: α_1 , α_2 , β_1 and β . The thyroid hormones diffuse inside the cells to bind to their receptors. Extranuclear receptors: are found at the plasma membrane, the cytoskeleton, in the cytoplasm and in the mitochondria. These receptors responsible for many of the non genomic actions, e.g. adenylate cyclase, sugar transport, pyruvate kinase, type II deiodinase and actin polymerization. Nuclear receptors: are present in close proximity or bound to DNA.

Regulation of thyroid gland function The hypothalamus neurosecretory cells: secrete into the first capillary set of the hypothalamo- hypophyseal portal circulation the Thyrotropin Releasing Hormone: TRH: which is then carried by blood to the anterior pituitary cells: the thyrotropes. TRH binds to TRH receptors of the thyrotropes producing activation of the membrane bound G proteins that activate the phospholipase enzyme. The resulting Ca^{2+} & diacyl glycerol, produce finally TSH release from the thyrotropes, into the second capillary set of the hypothalamo- hypophyseal portal vessels. **2. TSH: thyroid stimulating hormone: thyrotropin:** Binds to TSH serpentine receptors on the basal membrane of the thyroid gland cells leading to activation of the membrane bound G proteins, the activation of adenyl cyclase enzyme, increasing cAMP, which in turn activates the protein kinas, producing multiple phoshorylations in the thyroid cells. Activation of the thyroid cells produce: a. Within 30 min.: Increased proteolysis of the thyroglobulin, increasing T3 & T4 in blood. b. Within hours, days, and weeks: Activation of iodide pump which makes intracellular to extracellular iodide about 8:1. Increased iodination of tyrosine & increased formation of thyroid hormones. Increased size, secretory activity and number of thyroid cells. 3. Feedback effect of thyroid hormones: the increased thyroid hormones produce: A direct effect of T3 and T4 on the pituitary causing decreased production of TSH secretion. T4 that reaches the anterior pituitary is converted to T3 to exert its feedback effect. Secondary weak effect of the hypothalamus causing a decrease in TRH secretion.

Physiology of goiter Goiter: is enlargement of the thyroid gland. It is used clinically to indicate that an enlarged thyroid is associated with either: normal, decreased or increased thyroid activity. Its types are: a. Physiological: during puberty in females. The thyroid cells and follicles enlarge, to secrete more thyroid hormones, to supply the body with the generalized increased needs in body metabolism. b. Hypothyroidism: the thyroid follicles are full of TG. It occurs in: Iodine deficiency (thyroid hormones are not formed). Inability to secrete the formed and stored thyroid hormones due to the effect of antibodies (TSH-R[block] Ab, TG, TPO Ab) c. Hyperthyroidism: the thyroid cells increase in size and number.

Thyroid tumor (adenoma). Autoimmune (TSH- R[stim] AB) abnormal stimulation. Secondary stimulation in response to a pituitary tumor. d. Nodular goiter: in the form of multiple enlarged nodules. The thyroid nodules may be hot (active) or cold (inactive).

The Physiology of the Adrenals gland

Action of glucocorticoids Cortisol is essential for life. Human being cannot survive when both adrenal glands are removed without glucocorticoid replacement. Action of cortisol are affected mainly by its plasma level, its types of action are: Permissive action: i.e. in small amounts it allows certain processes to occur, although glucocorticoids by themselves do not initiate these reactions. **Physiological action** Due to the effects of the normally present hormone levels in plasma. Permissive actions cortisol augments and stimulates glycogenolysis produced by glucagon. cortisol is necessary for catecholamines and growth hormone to exert their lipolytic effect. Allows normal response for the arterioles to the vasoconstrictor effect of catecholamines and angiotensin II.

Physiology action of cortisol

Effect on metabolism Cortisol acts to facilitate the mobilization of fuels. **A- on carbohydrate metabolism:** Stimulation of gluconeogenesis by the liver: Promotes protein catabolism in extrahepatic tissues as in muscle and lymphoid tissues by releasing amino acids (AA) in blood. Stimulates the enzymes required for hepatic uptake of amino acids into glucose and its conversion. This leads to: Increased intrahepatic glycogen storage. Increased release of glucose of in blood. iii. Increased glucogenesis leads to build up of sufficient glycogen stores (glycogenesis) in the liver cells, on which other hormones can act. **2- Decrease the utilization of glucose by muscle and adipose tissue and lowers their sensitivity to insulin: Anti- insulin action.** Decrease the affinity of insulin receptors to insulin. ii. Decrease the mobility of glucose transporters from inside the cell to the cell membrane, thus reducing glucose uptake. iii. Inhibition of phosphorylation. The brain and the heart are spared from the anti- insulin action, so the increase in plasma glucose provides extra glucose to these vital organs. **B- On protein metabolism:** 1. Cortisol reduces protein stores in all body cells except liver cells through: Decreased protein synthesis. Increased catabolism of proteins already in cells. 2- cortisol inhibits amino acid transport into extrahepatic cells (mainly muscle and adipose tissue), and thus, AA plasma level increases. 3- Stimulates amino acid transport into liver cells. **C- On fat metabolism:** Cortisol has a lipolytic action.- Sensitive lipase in adipose tissue that breakdown stored triglycerides into glycerol and fatty acids, which are released into the circulation to be used as a source of energy during stress. 2. In cases of insulin lack e.g. diabetics, it increases keton body formation (ketogenic). **II. Effect on appetite** Cortisol increases appetite and calori intake by inducing neuropeptide Y (orexiogenic) synthesis in the hypothalamus and suppressing CRH (anorixigenic). Cortisol induces leptin synthesis in adipocytes. Leptin in turn exerts a negative feed back effect on appetite center in hypothalamus and reduces the gain in fat mass. Thus its normal effect is equivocal **III. Effect on skeletal muscle** It increases acetylcholine synthesis and so helps neuromuscular transmission and maintains contractility. **IV. Effect on C.V.S.** Cortisol is required for the maintenance of



normal arterial blood pressure: It possess an inotropic action on cardiac muscle and increases both Na^+ - K^+ ATPase and β - adrenergic receptors. Decreases the production of vasodilator prostaglandins. 3. Helps to maintain blood volume by decreasing the permeability of the vascular endothelium. **V. Effect on kidney** 1. Cortisol increases glomerular plasma flow and so increases GFR. 2. Cortisol is essential for rapid excretion of a water load by facilitating excretion of free water. 3. Cortisol is required for formation of ammonium ion from glutamate in response to acid loads. 4. Cortisol decreases PO_4 absorption in proximal tubules and so increases urinary PO_4 excretion. **VI. Effect on central nervous system** Cortisol modulate excitability, behavior and mood of individuals. Cortisol decreases REM sleep, but increases slow rate sleep and time spent awake. **VII. Effect of cortisol on blood cells** 1. Decreases the number of eosinophils by stimulating their apoptosis and also by increasing their sequestration in the spleen and lungs. 2. Increases number of neutrophils, platelets and red blood cells. Cortisol stimulate the release of neutrophils from bone marrow and increases their number, but depress their function. 3. Decreases the number of T lymphocytes by inhibiting lymphocytes mitosis. **VIII. Functions of cortisol in stress** Physical or mental stress including: trauma, pain infection, intense heat or cold, surgery, anxiety, shock etc. Stressful stimuli increases ACTH secretion and consequently elevate cortisol level in blood. Most of the stressful stimuli also activate the sympathetic nervous system. Cortisol is required for catecholamines to exert their pressor and lipolytic actions (permissive action). 4. Both glucocorticoids and catecholamines increases FFAs as an energy source, and raise blood glucose level to ensure glucose supply to vital organs. 5. Increased plasma amino acids by cortisol to be used for gluconeogenesis and for formation of new proteins by damaged tissues. **IX. Other effects** Cortisol has a very slight mineral corticoid activity. During fetal life, cortisol accelerates the maturation of surfactant in the lungs. **Control of glucocorticoid secretion. ACTH:** ACTH maintains the normal secretory activity of zona fasciculata and reticularis ACTH, increases the size and number of cells in these two zones. Chronic stimulation by ACTH increases their mass and absence of ACTH leads to their atrophy. ACTH binds to its receptor on the membrane of cortisol secreting cells. This activate adenylyl cyclase via G8 with cyclic AMP that activates protein kinase A. Protein kinase A phosphorylates cholesteryl ester hydrolase enzyme increasing its activity and stimulates conversion of cholesteryl esters to free cholesterol. ACTH is not an important regulator of aldosterone production, although it is required for optimal secretion. ACTH has a marked melanocyte stimulating hormone (MSH) activity since its molecule contains a number of amino acid similar to that present in MSH. **II. Free cortisol negative feedback to:** Hypothalamus to inhibit CRH secretion. Corticotropes in the anterior pituitary to inhibit ACTH secretion. The degree of ACTH inhibition is proportionate to cortisol level in blood. In chronic adrenal insufficiency there is marked increase in ACTH secretion. **III. Circadian Rhythm:** The level of CRH, ACTH and cortisol in plasma are not constant but show a diurnal fluctuation. The high rate of secretion occurs in the early morning and is lowest in the evening. This effect results from a 24 cyclic alteration in signals from hypothalamus that causes cortisol secretion. **IV. Stress:** Act on the hypothalamus by raising its setting point and so increases the secretion of CRH that stimulates ACTH secretion that is in turn increases cortisol secretion. Plasma cortisol levels are increased by the various type of stress of surgery, burns, infection, fever, psychosis, acute anxiety, prolonged and strenuous exercises and also hypoglycemia. **IV. Large doses of vasopressin, serotonin and VIP** act directly on the adrenal cortex to stimulate cortisol secretion.

Actions of Aldosterone Aldosterone maintains ECFV by conserving body sodium. Aldosterone increases the reabsorption of Na^+ from the urine, sweat, saliva, gastric juice and colon. In the kidney, aldosterone causes increased exchange transport of Na^+ and K^+ i.e. reabsorption of Na^+ and simultaneous active secretion of Na^+ by tubular epithelial cells of distal tubules and collecting duct. Therefore aldosterone causes more Na^+ to be conserved in ECF and more K^+ to be excreted into urine (K^+ diuresis). Because H_2O is passively reabsorbed with Na^+ . There is a little increase in plasma Na^+ concentration. Hence ECF expands in an isotonic manner. Aldosterone causes H^+ to be secreted by renal tubules in exchange with sodium. Thus, excess aldosterone causes mild alkalosis and an increase in urine acidity. **Regulation of aldosterone secretion & role of Angiotensin II** **1- Activation of the renin- angiotensin system:** Aldosterone secretion is not regulated by the renin- angiotensin system in a feedback manner. The juxtaglomerular cells of the kidney secrete the enzyme renin into circulation. Renin acts on angiotensin (α_2 globulin in the hepatic origin to form angiotensin I (inactive). Angiotensin I is changed into Angiotensin II by Angiotensin converting enzyme (ACE) present in lungs. Angiotensin II binds to specific receptors on zona glomerulosa cells and stimulate aldosterone synthesis and secretion. Angiotensin II has an early action, to convert cholesterol to pregnenolone and at late action, to convert corticosterone to aldosterone. Increased stimulation of the zona glomerulosa with All produces hypertrophy of these cells. **Arterial naturetic peptide (ANP):** inhibits renin secretion and also inhibits aldosterone synthesis by decreasing the responsiveness of zona glomerulosa to All. **g. Renin secretion is mainly increased by all stimuli that are related to a decrease in ECF plasma volume, renal blood flow and pressure. Depletion of body Na^+ by dietary restriction or acute diuresis (macula densa senses the decrease in tubular fluid Na^+). Hemorrhage. – Assuming an upright posture for several hours. - Increased sympathetic activity induced by hypovolemia: catecholamines act on β_1 adrenergic receptors in JG cells. 2- Plasma K^+ level: increased K^+ level by only 1 mEq/L as occurs after a meal rich in K^+ stimulates aldosterone secretion, its mechanism is through: It stimulates the conversion of cholesterol to pregnenolone and the conversion of corticosterone to aldosterone. b. It stimulates aldosterone releases by depolarizing the adrenal cell which opens voltage gated Ca^{++} channels, increasing intracellular Ca^{++} . **3- ACTH:** a. ACTH is not an important regulator of aldosterone production, although it is required for optimal secretion. b. ACTH has a tonic role i.e. when ACTH is deficient, the responsiveness of zona glomerulosa is decreased. **4- Plasma Na^+ level:** Acute decline in plasma Na^+ of about 20 mEq/L stimulates aldosterone secretion. b. Dietary Na^+ restriction (slow decline) increases aldosterone secretion: Initially decreased tubular fluid Na^+ are sensed by the macula densa that leads to increased renin secretion. ii. Secondly, a reduction in the ECF volume, through the renin angiotensin system, increased aldosterone secretion.**

Action of Adrenal Androgens Adrenal androgen DHEA & androstenedione are under ACTH control. Their physiological function is due to their peripheral conversion to the potent androgen testosterone. In females, they maintain normal pubic and axillary hair, and stimulate red cell production & have no masculinizing effect in their normal amounts. In males, adrenal



androgens have no physiological importance because the amount of testosterone produced by the testes is greater than that produced by adrenal glands. **Action of Adrenal Androgens** Are either secreted directly from adrenal cortex or result from the conversion of adrenal androgens to estrogens. They are an important source of estrogen in both men and post menopausal women. **Hypersecretion of adrenocortical hormones** **A- Primary hyperaldosteronism (Conn's syndrome):** Cause: Chronic mineralocorticoids excess occurs in patients with aldosterone secreting tumors of the adrenal cortex. Features: 1- Severe K⁺ depletion (hypokalemia) due to prolonged K⁺ diuresis resulting in:- Hypokalaemic nephropathy i.e. damage of the kidney with loss of concentrating ability produces polyuria Muscle weakness due to changes in the electrical excitability of the membranes of nerve and muscle fibers (hyperpolarization). Metabolic alkalosis due to H⁺ loss, decreases the plasma ionized calcium level that leads to tetany either latent or manifest. Decreased in glucose tolerance (utilization): due to inhibition of insulin secretion. 2- Hypertensive: ECF volume is increased due to Na⁺ and water retention resulting in increased of ABP. 3- No edema: Escape phenomenon: Is an escape from the Na⁺ and water retaining effect of excess aldosterone. Expansion of ECF increases central venous pressure and increased the secretion of ANP. ANP increases the responsiveness of the zona glomerulosa to stimuli that normally increases central venous pressure and increases the secretion of ANP. ANP inhibits renin secretion and so lowers plasma angiotensin II levels. **ANP actions are B- Secondary hyperaldosteronism** It is secondary to heart failure, liver cirrhosis, or nephrosis. The level of renin and angiotensin II in plasma in these conditions are elevated and these in turns increases aldosterone secretion. Features: K⁺ depletion due to K⁺ diuresis. 2. Intracellular K⁺ is replaced by Na⁺. 3. Plasma Na⁺ elevation is slight because water is retained with osmotically active Na⁺, so leads to ECF expansion and increased ABP. 4. Edema occurs: Escape phenomenon does not occur and results in continued expansion of ECF volume. C- Glucocorticoid- remediable aldosteronism (GRA): Causes: A genetic error produces a thyroid gene that makes the zona glomerulosa chronically sensitive to ACTH and so produces excessive amounts of all steroids including aldosterone. the secondary effects as hypertension are corrected by glucocorticoids that suppress ACTH secretion (negative feedback)

The Adrenal Medulla The adrenal medulla forms about 20% of the adrenal gland. It secretes catecholamines: epinephrine, norepinephrine and dopamine. It considered as a modified sympathetic ganglion where postganglionic neuron have lost their axons and became secretory cells. Catecholamines are formed from the amino acid tyrosine which is transported and then concentrated by the adrenal medullary cells. The adrenal medullary cells contain the enzyme phenyl ethanol- amine N- methyl transferase (PNMT) which catalyzes the conversion of norepinephrine into epinephrine. Adrenal medullary PNMT is stimulated by glucocorticoids.

Regulation of adrenal medullary secretion Catecholamine secretion is low in basal state and is further reduced during sleep. Increased secretion of adrenal medullary hormones is part of the diffuse sympathetic discharge that occurs in emergency situations. Stressful stimuli such as cold, hypoglycemia, muscular exercise, hemorrhage and anxiety all act on the hypothalamus to stimulate adrenal medullary secretion. Increased catecholamine secretion is an important endocrine response to cold (due to its calorogenic action). Severe hypoglycemia and other stressful states stimulate the hypothalamus, which in turn stimulates the adrenal medulla to release epinephrine that increases glucose production from the liver through glycogenolysis and decreases glucose utilization by peripheral tissues. The concentration of FFA in plasma is increased to enhance utilization. All these effects lead to hyperglycemia during periods of stress. Hemorrhage is a potent stimulus to adrenal medullary secretion. The resulting increases in circulating catecholamines cause generalized vasoconstriction. This pressor response requires the presence of glucocorticoids. **Storage and mechanism of secretion of catecholamines** In the adrenal medulla, norepinephrine are stored in granulated in granulated vesicles bound to ATP associated with a protein chromogranin A that plays a role in hormone storage or secretion. Acetylcholine opens cation channels causing Ca⁺⁺ that influx into the medullary cells that triggers exocytosis and released of catecholamines, ATP and chromogranin A into the blood stream. Adrenal medullary tumors (Pheochromocytomas) Most pheochromocytomas secrete norepinephrine in excessive amounts and the condition is manifested by episodic or sustained hypertension. pheochromocytomas that secrete epinephrine cause hyperglycemia, glucosuria and an elevated metabolic rate.

Role of estrogen on growth of breast ductal system The primordial breasts of females and males are exactly alike. In fact, under the influence of appropriate hormones, the masculine breast during the first 2 decades of life can develop sufficiently to produce milk in the same manner as the female breast. **Estrogens cause:** Development of the stromal tissues of the breasts, (2) Growth of an extensive ductile system, and (3) Deposition of fat in the breasts. The lobules and alveoli of the breast develop under the influence of estrogens alone, but it is progesterone and prolactin that cause the ultimate determinative growth and function of these structures. In summary, the estrogens initiate growth of the breasts and of the milk-producing apparatus. They are also responsible for the characteristic growth and external appearance of the mature female breast. However, they do not complete the job of converting the breasts into milk-producing organs.

Effect of Progesterone on the Breasts Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory in nature.- However, progesterone does not cause the alveoli to secrete milk, milk is secreted only after the prepared breast is further stimulated by prolactin from the anterior pituitary gland.- Progesterone also causes the breasts to swell. - Part of this swelling is due to the secretory development in the lobules and alveoli, but part also results from increased fluid in the subcutaneous tissue. **Initiation of Lactation—Function of Prolactin** Although estrogen and progesterone are essential for the physical development of the breasts during pregnancy, a specific effect of both these hormones is to inhibit the actual secretion of milk. Conversely, the hormone prolactin has exactly the opposite effect on milk secretion—



promoting it. This hormone is secreted by the mother's anterior pituitary gland, and its concentration in her blood rises steadily from the fifth week of pregnancy until birth of the baby, at which time it has risen to 10 to 20 times the normal nonpregnant level. In addition, the placenta secretes large quantities of human chorionic somatomammotropin, which probably has lactogenic properties, thus supporting the prolactin from the mother's pituitary during pregnancy. Even so, because of the suppressive effects of estrogen and progesterone, no more than a few milliliters of fluid are secreted each day until after the baby is born. The fluid secreted during the last few days before and the first few days after parturition is called colostrum; it contains essentially the same concentrations of proteins and lactose as milk, but it has almost no fat, and its maximum rate of production is about 1/100 the subsequent rate of milk production. Immediately after the baby is born, the sudden loss of both estrogen and progesterone secretion from the placenta allows the lactogenic effect of prolactin from the mother's pituitary gland to assume its natural milk-promoting role, and over the next 1 to 7 days, the breasts begin to secrete copious quantities of milk instead of colostrum. This secretion of milk requires an adequate background secretion of most of the mother's other hormones as well, but most important are growth hormone, cortisol, parathyroid hormone, and insulin. These hormones are necessary to provide the amino acids, fatty acids, glucose, and calcium required for milk formation. After birth of the baby, the basal level of prolactin secretion returns to the nonpregnant level over the next few weeks. However, each time the mother nurses her baby, nervous signals from the nipples to the hypothalamus cause a 10- to 20-fold surge in prolactin secretion that lasts for about 1 hour. This prolactin acts on the mother's breasts to keep the mammary glands secreting milk into the alveoli for the subsequent nursing periods. If this prolactin surge is absent or blocked as a result of hypothalamic or pituitary damage or if nursing does not continue, the breasts lose their ability to produce milk within 1 week or so. However, milk production can continue for several years if the child continues to suckle, although the rate of milk formation normally decreases considerably after 7 to 9 months.

Hypothalamic Control of Prolactin Secretion The hypothalamus plays an essential role in controlling prolactin secretion. However, this control is different in one aspect: The hypothalamus mainly stimulates production of all the other hormones, but it mainly inhibits prolactin production. Consequently, damage to the hypothalamus or blockage of the hypothalamic hypophysial portal system often increases prolactin secretion while it depresses secretion of the other anterior pituitary hormones. Therefore, it is believed that anterior pituitary secretion of prolactin is controlled either entirely or almost entirely by an inhibitory factor formed in the hypothalamus and transported through the hypothalamic hypophysial portal system to the anterior pituitary gland. This factor is called prolactin inhibitory hormone. It is almost certainly the same as the catecholamine dopamine, which is known to be secreted by the arcuate nuclei of the hypothalamus and can decrease prolactin secretion as much as 10-fold.

Suppression of the Female Ovarian Cycles in Nursing Mothers for Many Months After Delivery In most nursing mothers, the ovarian cycle (and ovulation) does not resume until a few weeks after cessation of nursing. The reason seems to be that the same nervous signals from the breasts to the hypothalamus that cause prolactin secretion during suckling—either because of the nervous signals themselves or because of a subsequent effect of increased prolactin—inhibit secretion of gonadotropin-releasing hormone by the hypothalamus. This, in turn, suppresses formation of **the pituitary gonadotropic hormones—luteinizing hormone and follicle-stimulating hormone**. However, after several months of lactation, in some mothers, especially in those who nurse their babies only some of the time, the pituitary begins to secrete sufficient gonadotropic hormones to reinstate the monthly sexual cycle, even though nursing continues.

Ejection (or "Let-Down") Process in Milk Secretion—Function of Oxytocin Milk is secreted continuously into the alveoli of the breasts, but milk does not flow easily from the alveoli into the ductal system and, therefore, does not continually leak from the breast nipples. Instead, the milk must be ejected from the alveoli into the ducts before the baby can obtain it. This is caused by a combined neurogenic and hormonal reflex that involves the posterior pituitary hormone oxytocin, as follows. When the baby suckles, it receives virtually no milk for the first half minute or so. Sensory impulses must first be transmitted through somatic nerves from the nipples to the mother's spinal cord and then to her hypothalamus, where they cause nerve signals that promote oxytocin secretion at the same time that they cause prolactin secretion. The oxytocin is carried in the blood to the breasts, where it causes myoepithelial cells (which surround the outer walls of the alveoli) to contract, thereby expressing the milk from the alveoli into the ducts at a pressure of +10 to 20 mm Hg. Then the baby's suckling becomes effective in removing the milk. Thus, within 30 seconds to 1 minute after a baby begins to suckle, milk begins to flow. This process is called milk ejection or milk let-down. Suckling on one breast causes milk flow not only in that breast but also in the opposite breast. It is especially interesting that fondling of the baby by the mother or hearing the baby crying often gives enough of an emotional signal to the hypothalamus to cause milk ejection.

Functions of oxytocin

During sexual intercourse: it is responsible for orgasm. A- In males: contraction of smooth muscle in vas deferens to ejaculate semen. B- In females: the contraction of myometrium followed by relaxation decreases the intra uterine pressure to help semen transport into the uterus after intercourse. 2. During labour: it causes strong contractions of the uterus to expel the baby and placenta. 3. During suckling: it causes squeezing of milk from the breast alveoli into the large ducts and then the nipple.

The Physiology of Pancreatic Hormones



Glucose homeostasis A constant blood glucose concentration is important because it is the only nutrient that can be used under normal conditions by the brain, retina and germinal epithelium of the gonads. On the other hand, flooding blood with glucose is not beneficial, because hyperglycemia has no harmful effects.

Rang of normal glucostasis In the fasting normal person before breakfast, the blood glucose level is about 80-90mg%. This concentration increases to 120- 140 mg% during the first hour after meal, but the feedback systems for control of blood glucose return the glucose level rapidly back to control level within 2 hours after the last absorption of carbohydrates. Most of the in between meals, glucose is formed by glucogeneogenesis and is used for brain metabolism, so, the pancreas does not secrete any insulin during this time to allow the small supplies of glucose to go to the brain so as not be utilized by muscles and peripheral tissues. 4. During starvation, the gluconeogenic function of the liver provides the glucose, require to maintain the fasting blood glucose level.

Insulin receptors Insulin receptors are found on many cells of the body, including cells in which insulin does not increase glucose uptake. IGF- I receptor is similar in structure to that of insulin and so IGF- I and insulin can compete for a common receptor. The insulin receptor is a tetramer made up of 4 subunits held together by disulfide linkages: 2 alpha subunits outside the cell membrane and two beta subunits penetrate the cell membrane and protrude into the cell cytoplasm. 4. The intracellular portions of the B subunit posses tyrosine kinase activity which activated after insulin binding to the extracellular alpha subunit. 5. Activation of tyrosine kinase of the beta subunits produce autophosphorylation of the beta subunits that phoshorylate some cytoplasmic proteins and dephosphorylate others, via phosphorylation of insulin receptor substrates (IRS-1, IRS-2, IRS-3 and IRS-4). 6- The later group activates some intracellular enzymes and inactivates others.

Modulation of insulin receptor The number and affinity of insulin receptor are affected by insulin and other hormones, exercise, food, etc. Exposure to amounts of insulin decreases the number of receptors (down regulation) as in obesity and acromegaly. 2. Exposure to decreased insulin levels increases the number of receptors as in starvation. 3. The affinity of the receptors is increased in adrenal deficiency and in starvation. 4. The affinity of the receptors is decreased by excess glucocorticoids.

Physiological effects of insulin

Effect of Insulin on Carbohydrate Metabolism Immediately after a high-carbohydrate meal, the glucose that is absorbed into the blood causes rapid secretion of insulin. The insulin in turn causes rapid uptake, storage, and use of glucose by almost all tissues of the body, but especially by the muscles, adipose tissue, and liver. **Insulin Promotes Muscle Glucose Uptake and Metabolism** Insulin stimulates glucose uptake of muscles (skeletal, cardiac, smooth), adipose tissue and liver. During much of the day, muscle tissue depends not on for its energy but on fatty acids. The principal reason is that the normal resting muscle membrane is only slightly permeable to glucose, except when the muscle fiber is stimulated by insulin; between meals, the amount of insulin that is secreted is too small to promote significant amounts of glucose entry into the muscle cells. However, under two conditions the muscles do use large amounts of glucose. One of these is during moderate or heavy exercise. This usage of glucose does not require large amounts of insulin, because exercising muscle fibers become more permeable to glucose even in the absence of insulin because of the contraction process itself. The second condition for muscle usage of large amounts of glucose is during the few hours after a meal. At this time the blood glucose concentration is high and the pancreas is secreting large quantities of insulin. The extra insulin causes rapid transport of glucose into the muscle cells. This causes the muscle cell during this period to use glucose preferentially over fatty acids. **Storage of Glycogen in Muscle.** If the muscles are not exercising after a meal and yet glucose is transported cells in abundance, then most of the glucose is stored in the form of muscle glycogen instead of being used for energy, up to a limit of 2 to 3 % concentration. The glycogen can later be used for energy by the muscle. It is especially useful for short periods of extreme energy use by the muscles and even to provide spurts of anaerobic energy for a few minutes at a time by glycolytic breakdown of the glycogen to lactic acid, which can occur even in the absence of oxygen. **Insulin Promotes Liver Uptake, Storage, and Use of Glucose** One of the most important of all the effects of insulin is to cause most of the glucose absorbed after a meal to be stored almost immediately in the liver in the form of glycogen. Then, between meals, when food is not available and the blood glucose concentration begins to fall, insulin secretion decreases rapidly and the liver glycogen is split back into glucose, which is released back into the blood to keep the glucose concentration from falling too low. The mechanism by which insulin causes glucose uptake and storage in the liver includes several almost simultaneous steps: 1. Insulin inactivates liver phosphorylase, the principal enzyme that causes liver glycogen to split into glucose. This prevents breakdown of the glycogen that has been stored in the liver cells. 2. **Insulin causes enhanced uptake of glucose from the blood by the liver cells.** By increasing the activity of the enzyme glucokinase, which is one of the enzymes that causes the initial phosphorylation of glucose after it diffuses into the liver cells. Once phosphorylated, the glucose is temporarily trapped inside the liver cells because phosphorylated glucose cannot diffuse back through the cell membrane. 3. Insulin also increases the activities of the enzymes that promote glycogen synthesis, including especially glycogen synthase, which is responsible for polymerization of the monosaccharide units to form the glycogen molecules. The net effect of all these actions is to increase the amount of glycogen in the liver. The glycogen can increase to a total of about 5 to 6 % of the liver mass, which is equivalent to almost 100 grams of stored glycogen in the whole liver.

Effect of Insulin on Fat Metabolism Insulin increases the utilization of glucose by most tissues of the body, which decreases the utilization of fat, thus, insulin acts as fat sparer. 1. Insulin promotes fatty acid synthesis in liver. Insulin promotes conversion of the excess glucose into FFA which are packaged as triglycerides in VLDL and transported by blood to adipose tissue. 2. Insulin promotes storage of circulating fat in adipose tissue : lipogenesis: a. Insulin activates the enzyme lipoprotein lipase in adipose tissue, which splits triglycerides into FFAs, and helps their transfer into adipose cells. b. FFAs combine with glycerol inside the adipose tissue to be stored in the form of triglycerides. 3. Insulin inhibits release of stored fat from adipose tissue into blood: Inhibits



lipolysis: Insulin inhibits the hormone sensitive lipase enzyme in adipose tissue. So the release of FAs from adipose tissue into blood is inhibited. Insulin stimulates the use of ketoacids by peripheral tissues, thus, insulin is the major antiketogenic hormone. **Effect of Insulin on Protein Metabolism and growth** On protein metabolism: Insulin is a general anabolic hormone. 1. It increases transport of A.A. into cells and so lowers their plasma level. 2. It has a direct effect on ribosomes increasing synthesis of rRNA that leads to formation of new proteins. 3. Insulin also increase the rate of formation of selected DNA in cell nuclei which increases formation of mRNA, which in turn results in more protein synthesis (mostly the enzyme requires for storage of carbohydrates, fats and proteins). 4. Insulin inhibits protein catabolism (proteolysis) in muscle as it suppresses the release of AA from muscle and inhibits their oxidation. 5. Inhibits the rate of gluconeogenesis inside the liver, so AAs are conserved in the form of protein inside the body cells. **B. On growth:** Growth is an anabolic state mainly in cartilage, bone and muscle: Insulin stimulate the synthesis of macromolecules in tissues as cartilage and bones. The gene of insulin and its receptor are released to the gene of IGF-I and IGF-II. Insulin stimulates transcription of related gene of IGF-I and inhibits the gene of one of IGF-I binding proteins. Thus insulin is left free in plasma. The anabolic effect of insulin is aided by the protein- sparing action of adequate intracellular glucose content.

Factors which stimulate or inhibit insulin secretion Feedback effect of blood glucose level: Glucose is the most important stimulant for insulin release in humans. At the normal fasting blood glucose level (80- 90 mg%), the rate of insulin secretion is minimal. If blood glucose level is suddenly increased, insulin secretion increases markedly and reached its maximum at a blood glucose level of 300 mg%. b. The response of insulin secretion to a rise in the blood glucose level provides an extremely important feedback mechanism for regulating blood glucose level: Rise in blood glucose, increases insulin secretion which leads to increased transport of glucose into muscle, adipose tissue and liver and so blood glucose is lowered to normal level. **2. Amino acids:** Insulin secretion is also stimulated by some amino acid (e.g. arginine and lysine) that result from digestion in meal. Amino acid strongly potentiate the glucose stimulus for insulin secretion. This is a purpose response because the secreted insulin in turn promotes the transport of AA into tissue cells and formation of intracellular protein. **3. Gastrointestinal hormones:** Oral glucose leads to an increase in insulin secretion more than when glucose is administered I.V., this is due to: a. The release of glucagon- like polypeptide I (GLP-I), GIP, gastrin, secretin and CCK (insulinogogues). b. AA, potentiate the glucose- stimulated insulin secretion. **4. Other hormones:** glucagon stimulates insulin release. Somatostatin inhibits insulin secretion. Cortisol, growth hormone, estrogen- progesterone, human placental lactogen and thyroid hormones; act by: Directly or indirectly cause hyperplasia of β cells that leads to an increase in insulin secretion. Antagonize the insulin action on peripheral tissues. Prolonged secretion in any one of them in large quantities can lead to exhaustion of β cells and cause diabetes mellitus. Insulin has a negative feedback effect on its own secretion. Leptin released from fat depots act on: The hypothalamus to decrease food intake. B cells to inhibit insulin release. **5. cAMP:** β -adrenergic stimulants, glucagon, theophylline and GIP, increases cAMP levels in β cells, which its turn increases insulin secretion through increasing intracellular Ca^{++} . **6. Autonomic nerves:** Stimulation of vagus nerve increases insulin secretion via action of acetylcholine on M4 receptors that are coupled via G proteins to phospholipase C, are IP3 and intracellular Ca^{++} release. Stimulation of the sympathetic nerves to the pancreas inhibits insulin secretion. The released norepinephrine causes inhibition by acting on α_2 -adrenergic receptors, while β adrenergic receptors increases insulin. The net effect of epinephrine & norepinephrine is usually inhibition.

Glucagon and Its Functions Glucagon, a hormone secreted by the alpha cells of the islets of Langerhans when the blood glucose concentration falls, has several functions that are diametrically opposed to those of insulin. Most important of these functions is to increase the blood glucose concentration, an effect that is exactly the opposite that of insulin. Like insulin, glucagon is a large polypeptide. It has a molecular weight of 3485 and is composed of a chain of 29 amino acids. On injection of purified glucagon into an animal, a profound hyperglycemic effect occurs. Only 1 mg/kg of glucagon can elevate the blood glucose concentration about 20 mg/100 ml of blood (a 25 per cent increase) in about 20 minutes. For this reason, glucagon is also called the hyperglycemic hormone. **Effects on Glucose Metabolism** The major effects of glucagon on glucose metabolism are (1) breakdown of liver glycogen (glycogenolysis) and (2) increased gluconeogenesis in the liver. Both of these effects greatly enhance the availability of glucose to the other organs of the body. **Glucagon Causes Glycogenolysis and Increased Blood Glucose Concentration** The most dramatic effect of glucagon is its ability to cause glycogenolysis in the liver, which in turn increases the blood glucose concentration within minutes. It does this by the following complex cascade of events: 1. Glucagon activates adenyl cyclase in the hepatic cell membrane, 2. Which causes the formation of cyclic adenosine monophosphate, 3. Which activates protein kinase regulator protein, 4. Which activates protein kinase,

5. Which activates phosphorylase b kinase, 6. Which converts phosphorylase b into phosphorylase a, 7. Which promotes the degradation of glycogen into glucose-1-phosphate, 8. Which then is dephosphorylated; and the glucose is released from the liver cells. This sequence of events is exceedingly important for several reasons. First, it is one of the most thoroughly studied of all the second messenger functions of cyclic adenosine monophosphate. Second, it demonstrates a cascade system in which each succeeding product is produced in greater quantity than the preceding product. Therefore, it represents a potent amplifying mechanism; this type of amplifying mechanism is widely used throughout the body for controlling many, if not most, cellular metabolic systems, often causing as much as a million fold amplification in response. This explains how only a few micrograms of glucagon can cause the blood glucose level to double or increase even more within a few minutes. - Infusion of glucagon for about 4 hours can cause such intensive liver glycogenolysis that all the liver stores of glycogen become depleted.

Glucagon Increases Gluconeogenesis Even after all the glycogen in the liver has been exhausted under the influence of glucagon, continued infusion of this hormone still causes continued hyperglycemia. This results from the effect of glucagon to increase the rate of amino acid uptake by the liver cells and then the conversion of many of the amino acids to glucose



by gluconeogenesis. This is achieved by activating multiple enzymes that are required for amino acid transport and gluconeogenesis, especially activation of the enzyme system for converting pyruvate to phosphoenolpyruvate, a rate-limiting step in gluconeogenesis. **Other Effects of Glucagon** Most other effects of glucagon occur only when its concentration rises well above the maximum normally found in the blood. Perhaps the most important effect is that glucagon activates adipose cell lipase, making increased quantities of fatty acids available to the energy systems of the body. Glucagon also inhibits the storage of triglycerides in the liver, which prevents the liver from removing fatty acids from the blood; this also helps make additional amounts of fatty acids available for the other tissues of the body. Glucagon in very high concentrations also (1) enhances the strength of the heart; (2) increases blood flow in some tissues, especially the kidneys; enhances bile secretion; and (4) inhibits gastric acid secretion. All these effects are probably of minimal importance in the normal function of the body. One of the factors that might increase glucagon secretion in exercise is increased circulating amino acids. Other factors, such as β -adrenergic stimulation of the islets of Langerhans, may also play a role.

Somatostatin Inhibits Glucagon and Insulin Secretion The delta cells of the islets of Langerhans secrete the hormone somatostatin, a polypeptide containing only 14 amino acids that has an extremely short half-life of only 3 minutes in the circulating blood. Almost all factors related to the ingestion of food stimulate somatostatin secretion. They include: increased blood glucose, (2) increased amino acids, (3) increased fatty acids, and (4) increased concentrations of several of the gastrointestinal hormones released from the upper gastrointestinal tract in response to food intake. In turn, somatostatin has multiple inhibitory effects as follows: 1. Somatostatin acts locally within the islets of Langerhans themselves to depress the secretion of both insulin and glucagon. 2. Somatostatin decreases the motility of the stomach, duodenum, and gallbladder. 3. Somatostatin decreases both secretion and absorption in the gastrointestinal tract. Putting all this information together, it has been suggested that the principal role of somatostatin is to extend the period of time over which the food nutrients are assimilated into the blood. At the same time, the effect of somatostatin to depress insulin and glucagon secretion decreases the utilization of the absorbed nutrients by the tissues, thus preventing rapid exhaustion of the food and therefore making it available over a longer period of time. It should also be recalled that somatostatin is the same chemical substance as growth hormone inhibitory hormone, which is secreted in the hypothalamus and suppresses anterior pituitary gland growth hormone secretion.

Physiology of disturbed glucose homeostasis

Diabetes mellitus: Insulin deficiency (absolute or relative) produces the disease known as diabetes mellitus. There are two main types of these disease: Type 1 T1DM or insulin dependent diabetes mellitus: (IDDM) is mainly caused by autoimmune destruction of the B cells with a resulting lack of insulin secretion. It usually develops in young age (before the age of 40). Type 2: T2DM or non-insulin dependent diabetes mellitus (NIDDM): is the most common form of diabetes. It is characterized by decreased tissue sensitivity to insulin (insulin resistance), so that larger amounts of insulin are required to produce a normal effect and later by impaired insulin secretion. The rise in plasma glucose that stimulates insulin secretion until B cells reserve is finally exhausted. Factors that predispose to the development of diabetes are: Heredity: Type 2 diabetes may result from genetic defects in: The insulin molecule (0.5%). 2. The insulin receptor (1%). 3. IRS-1. 4. GLUT4 in insulin sensitive tissue (1%). 5. Glucokinase enzyme responsible for metabolism of glucose in cells (1%). Obesity: by down regulation the number of insulin receptors in the target cells throughout the body decreases, thus making the amount of insulin that is available (even if excess) is less effective. Insulin lack/; produces the following abnormalities: Decreased utilization of glucose by the body cells and so hyperglycemia. Increased mobilization of fats from adipose tissue causing abnormal plasma lipoprotein, increased deposition of cholesterol in arterial walls and atherosclerosis. Depletion of proteins in the tissues of the body. **Effects of hyperglycemia:** Increased osmotic pressure: in blood causes osmotic cellular dehydration. Glucosuria: because the renal capacity for glucose reabsorption is exceeded. Polyuria: due to osmotic dragging of water causes more dehydration. Polydipsia: dehydration stimulates hypothalamic osmoreceptors causing thirst. Small amounts of hemoglobin A are non-enzymatically glucosylated glucose attached to the B chain in hemoglobin molecule to form HbA1c. VI. Polyphagia and hyperphagia (excessive eating): its mechanism is: Reduced G1 utilization & activity of the glucostats in the hypothalamus satiety center. Feeding center is released from the normal inhibitory effect of the satiety center. **Hypoglycemia** Glucose is the only fuel used in appreciable quantities by the brain. The carbohydrate reserves in neural tissue are very limited and normal function depends upon a continuous glucose supply. Insulin is not required for glucose utilization by the brain. Hypoglycemia may occur in diabetics as a result of overdose of insulin. In non diabetics, hypoglycemia may result from an insulinoma (insulin secreting tumor of pancreas) or due to large malignant tumors outside the pancreas that secrete excess of IGF-II. As the plasma glucose level falls, the first symptoms are palpitations, sweating and nervousness due to sympathetic autonomic discharge. At lower plasma glucose neuroglycopenic symptoms appear as hunger and confusion. At lower plasma glucose levels, lethargy, coma, convulsions and eventually death occur.

CHAPTER X

Reproduction

An overview for human reproduction The ability to reproduce is one of the properties for living matter. In the human beings the process is one of sexual reproduction, in which the male and female organs differ anatomically and physiologically, and the new individual develops from the fusion of two different sex cells (gametes). Adult males and females produce specialised reproductive germ cells, called gametes. The male gametes are called spermatozoa and the female gametes are called ova. They



contain the genetic material, or genes, on chromosomes, which pass inherited characteristics on to the next generation. Other body cells possess 46 chromosomes arranged in 23 pairs but the gametes contain only 23, one from each pair. Gametes are formed by meiosis. At fertilization, the fusion of an ovum and spermatozoon, the resulting cell is called zygote and possesses the full 46 chromosomes. The zygote embeds itself in the wall of the uterus where it grows and develops during 40-week gestation period before birth. Every body cell contains, within its nucleus, an identical copy of the complement of the individual's genetic material. Two important exceptions are red blood cells (which have no nucleus) and the gametes or sex cells. In a resting cell, the chromatin (genetic material) is diffuse, but when the cell prepares to divide it is collected into chromosomes. Each chromosome is one of a pair, one inherited from the mother and one from the father, so the human cell has 46 chromosomes arranged as 23 pairs [diploid]. Gamete (spermatozoa and ova) with only 23 chromosomes [haploid] instead of 46. The first 22 pairs are known as autosomes, the chromosomes of pair 23 are called the sex chromosomes. The Y chromosome is much shorter than the X and is carried only by males. A child inheriting two X chromosomes (XX), one from each parent, is female, and a child inheriting an X from his mother and a Y from his father (XY) is male. **Male Reproductive System** Male sex organs: 1- Primary sex organ: Testis. 2- Secondary internal sex organs which include a - Duct, Epididymis & Vas deferens. b - Seminal vesicles, prostate & Bulbo-urethral (Cowper's) glands. 3- External organ [The Penis]. The Testis has 2 main functions: (1) **Spermatogenesis**. (2) Production of Testosterone. **Female Reproductive System** Female sex organs: (1) The ovaries (female gonads). (2) Fallopian tubes. (3) Uterus. (4) vagina. (5) Two mammary glands, external genitalia, and Bartholin glands. The ovary has 2 functions: (a) Oogenesis: formation and release of female gametes (ova & oocytes)

(b) Hormonal function: secretion of female sex hormones [estrogens & progesterone] The reproductive system of the female, unlike the male, shows regular menstrual cycle [vaginal bleeding]: Preparation for fertilization & pregnancy. Cause by monthly rhythmic changes in the rates of secretion of hormones. Controlled by cyclic variation in: (1) Hypothalamus releasing hormone (GnRH). (2) Anterior pituitary hormone (FSH & LH). The length of the cycle = 28 ± 3 days. from the start of one menstrual period to the start of the next. The cycle begins from puberty to menopause. Stops only during pregnancy, lactation or disease.

Oogenesis Production of female gametes. Oogenesis very similar to spermatogenesis. In both cases: The diploid primordial germ cells (2N) [44xx or 44xy] multiply mitotically. Then progresses through a number of divisions to become haploid (N) [22x or 22y] gametes. However, in oogenesis: Proliferation of the germ cells occurs in embryonic life with meiotic division of oogonia to give primary oocytes [44xx]

Spermatogenesis Definition: It is the process of producing mature spermatozoa. *At birth: division of the germ cells (spermatogonia) is suppressed until puberty. *At puberty: spermatogenesis begins. Stages: (1) The primary spermatogonia dividing meiotically to produce secondary spermatogonia [same diploid number of chromosomes 44 XY]. (2) The secondary spermatogonia increase in size to form primary spermatocytes, which divided meiotically to produce secondary spermatocytes, each carrying half the number of chromosomes (22X) or (22Y) [haploid number]. (3) The secondary spermatocytes undergo a second stage of meiosis to form daughter spermatids [haploid number of chromosomes]. (4) The final step, the spermatids are converted without further cell division into spermatozoa. The 4 stages of spermatogenesis take 64 days. These stages are equally spaced in time, which means that a new spermatozoa arrive in the tubule lumen every 16 days

Oogenesis Production of female gametes. Stages: During fetal life. During childhood. During Puberty & Adult Life. During Fetal Life: 1] Primordial germinal cell: Migrate from hind gut to the gonadal ridge, then start to differentiate into primordial ova (oogonia). 2] Primordial oogonia: migrate and start to proliferate in fetal ovarian cortex by mitotic division. At 6-7 weeks: 10,000 oogonia are present. At 8 weeks: 600,000 oogonia are present. 3] Primordial follicle: At 11-12 weeks, each oogonia collects a layer from ovarian stroma around it and then change to granulosa cells and form primordial follicle. Primordial follicle = oogonium + surrounding granulosa cells. Granulosa cells = layers of cells from the ovarian stroma. At 20th week of gestation = 6-7 million [degenerate]. At birth = 2-2.5 million are present in the two ovaries. At puberty = 300,000 - 400,000. 13-50 years = 450 develop enough to expel ova, one each month. 4] At 5th month of gestation: The first stage of meiotic division of primordial follicle occurs. **B. During Childhood:** The ovaries remain inactive. The meiotic division of the primordial follicles is still arrested. Primordial follicles increase in size due to active synthesis of mRNA & protein. Granulosa cells proliferate to form stratum granulosum. **C. During Puberty and adult Life** At puberty, the remaining primordial follicles are 400,000. The primary oocyte (containing diploid number of chromosomes) enters the second stage of 1st meiotic division under the effect of FSH before ovulation to give rise to secondary oocyte (haploid number of chromosomes) & 1st polar body. Secondary oocyte starts 2nd meiotic division, which is not completed until fertilization to release 2nd polar body. These polar bodies degenerate outside the oocytes. Thus 23 unpaired chromosomes remain in the secondary oocytes.

Delayed Puberty: The menarche has failed to occur by the age of 17. Testicular development failed to occur by the age of 20. Causes: a) Panhypopituitarism. b) Turner Syndrome. c) Normal gonads can be associated by delayed puberty (In males it is eunuchoidism and in female it is primary amenorrhea). **Non-Dysjunction:** It is the defect in the gametogenesis in which a pair of chromosomes fail to separate so that both go to one of the daughter cells during meiosis. **Turner Syndrome:** It is abnormal zygotes resulting from non-dysjunction to one of the X-chromosomes. Female's zygotes in this syndrome are individuals with XO chromosomal pattern with absent gonads, but development of female external genitalia. No maturation after puberty

Congenital abnormalities. **Klinefelter's Syndrome** The male individuals have XXY chromosomal pattern. This results from non-dysjunction and fertilization of the daughter cell possessing the XX chromosomes by a sperm with a Y chromosome. These individuals have: **Normal male genitalia.** High testosterone secretion at puberty for development of male



characteristics. Abnormal seminiferous tubules Pseudo hermaphroditism Some one having external genitalia of one sex and internal sex organs of the other sex not a true hermaphrodite because there is no ambiguity in the sex of the external genitalia .i.e : having internal reproductive organs of one sex and external sexual characteristics of the other sex .**Female pseudohermaphroditism** Person who is born as XX with female internal organs and on the other hand possesses masculinized genitalia , they can appear to be a male more than a female .Causes :Is congenital adrenal hyperplasia [adrenal glands largely produce testosterone]**Male Pseudohermaphroditism** Individual born with XY chromosome along with testis which is normally in the abdominal cavity . The genitalia which are external are normally female .Causes:It is androgen insensitivity syndrome This happens when the human body does not react to the androgen that is been produced

Fetal physiology The placenta is a circular disc , with diameter of 20 Cm and a thickness of 3.5 m at maturity. It usually weighs 500 grams .The embryo is joined to the placenta by the umbilical cord , which contains 2 fetal arteries and a vein. During the early months of pregnancy , placental permeability is low due to: (1) small surface area of placental membranes . (2) Placental Villi have thick layers in early pregnancy . As placenta gets older ,permeability increases until the last month then decreases. Circulation in the placenta Deoxygenated fetal blood enters the umbilical cord through umbilical arteries then to fetal capillaries of chorionic villi . The exchange of gases , nutrients and other substances takes place between fetal capillaries and maternal sinuses , which are filled with blood coming from uterine arteries. The exchange is aided by: Reduction of blood pressure in the maternal sinuses. Sluggish blood flow in maternal sinuses caused by: (a) Small blood lakes which arise near the chorionic plate which reduce blood velocity (b) Lateral spreading of the blood .(c) Geometry of the maternal blood vessels (perpendicular arteries & parallel venules).(d) Uterine contraction occur during pregnancy which lead to: -1- Weak arterial inflow . -2- No venous out flow , which leads to increase blood flow in the intervillous spaces (maternal sinuses). The blood of fetal capillaries after exchange is returned back to the fetus through the umbilical vein in the umbilical cord .

Placental Functions Diffusion of nutrients : [a] Carbohydrates: The glucose is diffused through the placenta by facilitated diffusion. The placenta can store glycogen .By the action of glycolytic enzymes secreted by placenta , it can convert this glycogen to glucose. [b] Fats: Diffuse more slowly than glucose . [c] Minerals and Vitamins: Na^+ , K^+ , Cl^- are transferred by simple diffusion to fetus . Ca^{++} , Ph^- and Fe^+ are transferred by active transport . Water-soluble & vitamins as vitamins B and C are present in high concentration. Diffusion of gases : [A] Diffusion of O_2 Maternal PO_2 is 50 -60 mmHg, while fetal PO_2 20-30 mmHg. O_2 diffusion through the villi from maternal blood to fetal blood . Most of the O_2 transported by fetal Hb is taken by tissues due to : (1) Fetal Hb is capable of carrying 20%-30% more O_2 than mother's Hb . (2) Fetal Hb has 50% more concentration than maternal Hb . (3) Bohr effect: Large amounts of CO_2 from fetus is diffused to maternal blood. This makes the fetal blood more alkaline, while the maternal blood becomes acidic This allows more O_2 to diffuse to the fetal blood and increases its Hb combining capacity to O_2 . (4) High cardiac output relative to fetal weight. [B] Diffusion of CO_2 : PCO_2 in fetal blood is 2-3 mmHg higher than that of maternal blood , this is sufficient for CO_2 diffusion. The solubility of CO_2 is 20 times more rapid than that of O_2 . The PCO_2 in maternal blood is lower than its normal value due to increase ventilatory by estrogens and progesterone during pregnancy . Diffusion of Fetal Excretory products: These include urea , uric acid , creatinin (non protein nitrogen's). Protective Function of Placenta : Placenta acts as a barrier against invasion of harmful substances to fetus. Thus 1st 3 months of pregnancy before placental development is the period for congenital defects to occur since the fetus is most sensitive to damage by viruses or drugs . Placenta can permit passage of IgG but not IgM which give passive immunity Placenta can permit passage of some harmful materials such as most drugs and viruses fatal death or malformation

Puberty Definition: period of activation of gonads of both sexes by The Gonadotropins to final maturation of reproductive system It also known as adolescence. In females the puberty takes place through the following events: a) Thelarche: Development of breast. b) Pubarche: Development of axillary and pubic hair. c) Menarche: Start of first menstrual period . In males & Females there is also a common event: Adrenarche : Increase adrenal androgens. without any change in ACTH (adreno-cortico trophic hormone) or cortisol secretion. Due to increased secretion of adrenal androgen stimulating hormone (ASH) [from anterior pituitary which acts on adrenal cortex lead to increase androgen . Causes of onset of puberty (1) Genetic factors . (2) State of nutrition. (3) Body composition and fat deposition. -Condition as heavy exercise and severe obesity decrease leptin secretion delayed menarche. (4) Geographic location and exposure to light. -Distance from equator and lower altitudes lead to early onset of puberty . **Control of the onset of puberty** Children's gonads can be stimulated by gonadotropins Their pituitaries contain gonadotrophins & their hypothalamic , contain GnRH (gonadotrophin releasing hormone). But can not be secreted in pulsatile manner . It is suggested that during childhood: Neural mechanism may operate to inhibit the pulsatile release of GnRH .

Puberty in the female The ovaries are stimulated by the gonadotrophins from the anterior pituitary: follicle stimulating hormone (FSH) and luteinizing hormone (LH). A number of changes take place at puberty: The uterus , the uterine tubes and the ovaries reach maturity The menstrual cycle and ovulation begin . The breasts develop and enlarge. Pubic and axillary hair begins to grow. Increase fat deposited in the subcutaneous tissue, especially at the hips and breasts .

Puberty in the male: This occurs between the age of 10 – 14 year. Luteinizing hormone from the anterior lobe of the pituitary gland stimulates the interstitial cells of the testes to increase the production of testosterone . This hormone influences the development of the body to sexual maturity **The changes occurring at puberty include:** Growth of muscle and bone. Enlargement of the larynx and deepening of the voice . Growth of hair on the face , axillae , chest , abdomen and pubis. Enlargement of the penis , scrotum and prostate gland. Maturation of the seminiferous tubules and production of spermatozoa. The skin thickens and become oilier . In the male , fertility and sexual ability tend to decrease gradually. The secretion of testosterone gradually decrease, Usually



beginning at about 50 years of age. **Male reproductive system(1)Primary sex organ : Testis .** a- Seminiferous tubules : spermatogenesis Germ cells(spermatogonia) - Sertoli cells . b- Interstitial cells of Lydig Hormones mainly testosterone which contain lipid granules . (2)Secondary sex organs : a- A system of Tubules and ducts : Epididymis oild duct to storage & maturation of spermatozoa until ejaculated. Vasdeferens which contract to propel spermatozoa to the prostate b- Accessory glands : to produce seminal plasma . 1- Seminal vesicles 60%of seminal plasma & fructose fuel for sperms& prostaglandin 2- Prostate : 30%of seminal plasma& alkaline. oxytocin : for prostatic function. 3- Cowper's gland: 5% secrete mucus which neutralizes the acidity of the urethra C-Penis :-Delivers semen within the female genital tract .-The penis must undergo erection and ejaculation .**Function of sertoli cells :** 1-Nuourishing (glycogen)and protective role for sperm 2-Phagocytic role engulf residual of spermatogenesis 3-Formation of blood-testis barrier . 4-Secreting role: Hormones ex :[Androgen – Activins – Inhibin –Estrogen] . - Aromatase enzyme : convert androgen to estrogen.- Proteolytic enzymes: dissolve tight junction .-Tubular fluid rich in K+ **Mechanism of Erection :**The penis contains erectile tissues ,which consists of cavernous venous sinuses bound by fibro-elastic tissue. During sexual intercourse , the arteries become dilated .Normally erection is terminated by sympathetic vasoconstrictor impulses .Ejaculation : spinal reflex , composed of 2 parts:A- Emission : movement of semen into urethra ,caused byContraction of vas deferens& seminal vesicle B- Ejaculation proper : propulsion of semen out of the urethra bythe contraction of bulbocavernosus muscle**Sperm Capacitation :**Time needed by spermatozoa in female tract(7 hours)to acquire the capacity to fertilize the ova .It involves 2 components in the female genital tract : -a- Increased motility of the sperms .- b- Facilitating the preparation of sperms for a crosomal reaction.Acrosome: is a cap which covers the sperm head and helps the penetration of the ovumControl and Regulation of GnRH & GonadotropinsA)Negative feedback by ovarian steroids:Estrogens and progesterone produced by the ovary will Produce negative feedback on both the hypothalamus & anterior pituitary , and the effect is not direct .Estrogens exert negative feedback at both low and high concentrations .Progesterone is effective at only high concentration .B)Negative feedback by Inhibins:Anterior pituitary decrease FSH Ovary decrease androgen decrease estrogens **C)Positive feedback by Activins:**Anterior pituitary increase FSH.Ovary increase estrogens.**D)Psychic Factors:**Emotional stress decreaseGnRHrelease.Sucklingand lactation Inhibit GnRH secretion lead to Lactating amenorrhea .The Anterior Pituitary secretes the gonadotropins FSH and LH.

Progesterone

Secreted by: Corpus luteum , placenta & small amounts by ovarian follicles and adrenal cortex. Actions of progesterone:**[A] On secondary sex organs: (1)Uterus :** It control s the secretory phase of fertilizing ovum .It help in formation of the placenta.It maintains pregnancy.(2) Fallopian tubes:Stimulates secretion of mucous for nutrition of fertilized ovum .(3)Vagina : Stimulate thick secretion and leukocytes infiltration .(4)Action on mammary gland:Stimulates the development of lobules& alveoli .Strimulates the secretory function of breast during lactation .**[B] Action on the Ovary :**Progesterone in minute amount LH surge.Large oral dose inhibit LH inhibit ovulation **[C] Thermogenic Action:** Progesterone increase basal body temperature(0.5) during post ovulation .**[D] Respiration:**Progesterone stimulates respiration so, decreaseCO₂ tension in alveolar air.**[E]Electrolyte Balance :**Progesterone causes Na⁺ ,CL⁻ and water reabsorption from distal tubule .In large dose: it may increase Na⁺ and water excretion

Relaxin: Polypeptide secreted by placenta.

In female: secreted from corpus luteum, placenta ,uterus & mammary gland.During pregnancy relaxin: (1) Relaxes the pubic symphysis& other pelvic joints .(2) Inhibit the uterine contractility .(3)Play a role in the development of mammary glands.In male : secreted from prostate gland.Found in the semen so, play a role in sperm motility penetration of the ovum.

Inhibin: It is a protein , which inhibits FSH secretion2 forms : testicular origin in male & antral fluid of ovarian follicles in females .The 2 forms are Inhibin A and Inhibin B.Each form of 2 polypeptide units α and β .Inhibin A is composed of $\alpha \beta$ A subunits.Inhibin B is composed of $\alpha \beta$ B subunits .Action: Inhibin B acts directly on the pituitary to inhibit FSH , it decrease androgen production and estrogen formation .

Activins:They are stimulate FSH secretion .They are 2 types of Activin receptors which are Serine Kinases.The receptors are found in : Embryo , gonads , brain and bone marrow(in white blood cell development).Menstrual Cycle(Endometrial Cycle)Phases of **Menstrual Cycle:**(1)Degenerative phase(Menstruation),(2) Proliferative(Estrogen) phase.(3) Secretory (progestational) phase.1- Degenerative phase: Duration: Lasts 3 -5 dayes.If fertilization of the ovum does not occur, the corpus luteum degenerates lead to decrease ovarian hormones[estrogen and progesterone]During normal menstruation70 -100 ml of menstrual discharge is expelled [75% is arterial blood ,25% is venous blood, vaginal epithelial cells , cervical mucus ,bacteria& prostaglandins].This menstrual discharge is non- clotting due to the presence of fibrinolysin released from necrotic endometrial tissue.Factors affecting the amount of menstrual blood Flow:(1)Thickness of endometrium 2)Drugs that dilate the blood vessels .(3)Disease affects clotting mechanism.

2-Proliferative phase It begins on the 5th day from the menstruation and lasts up to 14th day [follicular phaseof ovarian cycle].By the time of ovulation , the endometrium is 3-4 mm thick .Progressive growth of endometrial glands ,but with minimal secretion .Development of endometrial blood vessels. Blood is rich in leucocytes and immunoglobulins **3-Secretory phase:**Begins: from the 14th day i.e. from ovulation till the onest of menstruation.Estrogen causes slight additional proliferation of the endometrium.This phase is dependent on progesterone, secreted from corpus luteum by LH.The endometrium by the end of the



secretory phase reaches a thickness of 5 -6 mm. The aim of these phases (Proliferative & secretory) produce a secretory endometrium for nutrition of fertilized ovum .

The Ovarian (reproductive) Cycle The period between successive ovulations . It occurs in the ovaries under the control of pituitary gonadotrophins (FSH& LH). Aim: Ovulation& release of ovarian hormone , which controls menstrual cycle .Stages: (1) Follicular phases :divided into (I)Follicular Maturation.(II)Full Maturation of one Follicle: Graffian follicle.(2)Ovulation Phase : In 14th Day .(3)After Ovulation: Luteal phase .(1) The follicular phase (i)Follicular Maturation Control: mainly FSH & small dose of LH(from anterior pituitary)Act on 10 -15 primordial folliclesSo undergo these changes:a- Moderate enlargement of the ovum(2-3 folds).b- Proliferation of granulosa cells .The follicles are now called : primary follicle.c-Granulosa cells secreting a glycoprotein which forms the zona pellicida .[develop receptors for FSH]d-The primary follicles change into preantral follicle which have:Thecal cells: a layer of spindle-shaped ovarian stromal cells [develop receptors for LH], which divided into 2 layers1)Glandular theca interna.(secreting steroids)2)Fibrous theca externa.(vascular connective tissue capsule).FSH&LH are necessary for growth of the follicle:-Proliferation of granulosa& theca cells increase in the follicular size.Gap junctions between the ovum& granulosa cells act as a route of transport of nutrients& information.Collects fluid in spaces between the granulosa cells known as antral follicles then vesicular follicles.The ovum & its surrounding granulosa cells are located at one pole of the follicle to form cumulus oophorus .(ii)Full Maturation of one follicle(Graafian follicle): After one week of growth before ovulation occurs: one of the 10- 15 follicles begin to outgrow all the other, while the remainder[14]begins to involutes (Atresia)This is due to:[1] Higher number of FSH receptors in the dominant follicle leading to higher estrogen content , which acts on dominant follicle to increase FSH receptors and increase FSH action.[2] Higher vascularity in the dominant follicle .[3] Presence of 5- α reduced androgen in the remaining slow growing follicle , which Inhibits : a- LH receptor formation . b-Estrogen formation from androgen .Result: increase growth & size of the dominant follicle without further increase in gonadotrophin to give Graffian follicle(1.5 - 2 cm) **(2)Ovulation Phase** Release of a mature ovum(secondary oocyte)[23 chromosomes] from rupture graffian follicle into peritoneal cavity.Time : 14 days after the onset of menstruation.Control: LH is essential for final follicular growth and ovulation.2 days before ovulation, LH secretion is increased(6-10 fold)and reach a peak 18-hours before ovulation& FSH is also increased.Both FSH & LH act to cause very rapid growth of follicle & protrusion of stigma.Beginning of progesterone secretion in minute amount which progressively increase FSH& less LH stimulate the release of plasminogen activator from granulosa cells that converts plasminogen in follicular fluid to plasmin, Plasmin dissolves blood clots.Just before ovulation,1st meiotic division is completed with the formation of secondary oocyte & 1st polar body, which is discarded .**Few hours before ovulation** Both LH& progesterone increase the activity of collagen(proteolytic enzyme) within the follicle degeneration of stigma oozing of fluid from the follicle through it .Prostaglandin cause vasodilatation and contraction of the smooth muscle of theca externa.Rapid growth of new blood vessels into the follicular wall with local secretion of prostaglandins More swelling rupture of follicle release of ovum surrounded by a layer of granulosa cells(corona radiata), then fallopian tube pick the ovum .After ovulation , the secondary oocyte begins the 2nd meiotic division , which is only completed after fertilization .**(3)After Ovulation(Luteal Phase)** :-The theca cells differentiate into stroma cells and theca lutein cells . The process is known as Luteinization , which forms corpus luteum .**The corpus luteum lasts 10 -14 days after ovulation** If pregnancy does not occur, it begins to stop secretion and becomes fibrous tissue (corpus albicans) 4 days before the next ovarian cycle.If pregnancy occurs , it persists 2 - 4 months under the effect of chorionic Gonadotropin of placenta

physiological control of ovarian hormones. Generally estrogen is the hormone of femininity , while progesterone is the hormone of pregnancy .

Action of Estrogens : In embryonic life :Minute amounts of estrogen secreted by ovarian cells are essential for development of uterus and vagina during intrauterine life .In male embryos , testosterone is converted to estrogen to masculinize the male brain thus contributing to the male sex behavior .**Prepubertal effect of estrogen** During childhood , estrogens are secreted with very low levels to cause developmental changes in the female reproductive organs .The hypothalamus is hypersensitive to this very low estrogen levels and then suppression of GnRH secretion. There are 2 estrogen receptors($\alpha + \beta$) mediate the ovarian function and hypothalamic-pituitary ovarian axis. The estrogens secreted in ovarian follicles act through estrogen β - receptors which located in lung , bladder , prostate ,brain and bone Estrogens act through estrogen α - receptors to regulate the hypothalamic- pituitary- axis , these receptors are located in uterus , kidney , adrenal gland , testis and Epididymis . **Postpubertal effects of estrogens** : (a)On primary sex organ:1-Estrogen facilitate the growth of ovarian follicles .2-Estrogen stimulate LH , essential for ovulation & corpus luteum formation .(b)On secondary sex organs :Estrogens are responsible for the growth and development of : uterus , cervix , vagina ,fallopian tubes and mammary glands .**Effect of Estrogen on Mammary glands:**Estrogens are considered the growth hormone of the breasts , by stimulating:- a- Enlargement at puberty in girls .b-The growth of ducts , nipple and stroma.c-Deposition of fat .d- The increase in the blood flow of breast **Effects on Secondary sex characters** (1)Female body configuration : narrow shoulders , broad pelvis and characteristic fat deposition in breasts and hips (2)Voice.(3)Hair: less body hair and growth of pubic & axillary hair is due to adrenal androgen .(4)Skin: Excess estrogens cause dry skin and its deficiency cause greasy skin .(5)Behavior effects: Estrogens increase libido and are responsible for sex behavior of the female**Effect of estrogen on metabolism** It have a protein anabolic effect on the sexual organs & bones .It have anti- insulin effect .It stimulate maturation and increasing osteoblastic activity & epiphyses of bones .**Effect on Endocrine glands:**1-Increase the size of pituitary gland .2- Regulation of gonadotropin secretion .

Progesterone

It is steroid secreted by the corpus luteum , placenta and by small amounts by the ovarian follicles and adrenal cortex. There are 2 progesterone receptors A&B in which these receptor bound to heat shock proteins(stress protein. It has effect on secondary sex organs: uterus, fallopian tubes and vagina **Actions of progesterone on mammary glands** 1-Stimulate the development of lobules and alveoli 2-Supports the secretory function of breast during lactation. **Action on the ovary** Progesterone in minute amounts in the preovulatory stage leads to LH, while large oral doses of progesterone inhibit LH secretion and inhibit ovulation .Thermogenic Action It is responsible for the rise in basal body temperature during post ovulation **Electrolyte Balance:**Progesterone



causes Na^+ , Cl^- and water reabsorption from distal tubule. **Respiration:** It stimulates respiration and decreased CO_2 tension in alveolar air & arterial blood. **Physiology of pregnancy** The spermatozoa remain capable of fertilization for 1-2 days. However, freshly ejaculated spermatozoa are incapable of fertilizing for the first 6-7 hours after their release in the vagina, the cause of this incapability is: a- During these few hours, a process known as capacitation takes place, which involves a change in the surface coating of spermatozoa, and requires the environment of the female genital tract. b- The ascent of spermatozoa to the ampulla takes about one hour, aided by uterine and fallopian tube contractions during and after sexual intercourse. Although millions of sperms are deposited in the vagina, only 1000-3000 sperms succeed in reaching the ovum. In addition to the uterine contractions there are factors that help and protect the sperm: (1) Presence of the alkaline seminal fluid, which reduces the acidity of the vaginal fluid. (2) Ability of newly ejaculated semen to coagulate to prevent the leakage of sperms from the vagina. (3) Highly viscous cervical mucus changes at ovulation under the influence of estrogen and becomes more liquefied to allow the sperms to pass through, and suction of sperms into the uterus. **Maturation of an ovum** Before ovulation, the primary oocyte completes its first meiotic division in the presence of LH to give a secondary oocyte with haploid number and the first polar body. Before fertilization, the secondary oocyte begins its second meiotic division, which is not completed unless fertilization occurs. If a sperm, which is bearing an X chromosome, fuses with the X chromosome of the ovum, an XX will result, and a female child is formed, and when XY a male child is formed. For a sperm to enter the ovum, it must first penetrate the multiple layers of granulosa cells (corona radiata) which surround the ovum. One sperm reaches the membrane of the ovum, the fusion with the membrane is mediated by specific proteins on the surfaces of the two cells. **Fertilization involves:** (1) Chemo-attraction of the sperm to the ovum by substances produced by the ovum. (2) Adherence of sperm to the zona pellucida surrounding the ovum at Zp3 receptor. Then the sperm cell undergoes acrosomal reaction. **Transport of a mature ovum:** After ovulation, the ovum and the corona radiata (surrounding granulosa cells) is expelled into the peritoneal cavity, then picked up by fallopian tube (finger-like processes) and then directed to the intermediate portion of the fallopian tube "the ampulla" where fertilization occurs. The fertilization takes place at the 14th – 16th day of ovarian cycle. The released ovum retains the capacity for fertilization for 12 – 14 hours.

Capacitation It is the ability of spermatozoa to produce fertilization. It is caused by exposure of the sperms to the female genital tract. It involves 2 components, which occur after 7 hours in the female genital tract: 1- Increased motility of the sperms. 2- Facilitating the preparation of sperms for acrosomal reaction. The role of capacitation appears to be facilitatory as fertilization occurs in vitro. Characteristics of the sperm: A mature sperm is a motile cell, rich in DNA. It is formed of: Head and a motile tail. Head: made up of chromosomal material, a crosome is a cap covering the head and is a lysosome-like organelle rich in enzymes involved in sperm penetration of the ovum. A motile tail: with the proximal portion covered by a sheath rich in mitochondria. The placenta can act as an endocrinal organ and secrete the following hormones: A- Human chorionic Gonadotropin (HCG) HCG secreted by syncytial trophoblast cells into the fluids of the mother. It is a glycoprotein with the same function of LH, but not inhibited by the high levels of progesterone and estrogens. It increases rapidly to reach its maximum level 7-9 weeks of pregnancy. Functions: It prevents degeneration of the corpus luteum, which maintains pregnancy by its secretion of estrogens and progesterone.

B- Estrogens:

The secretion of estrogens by placenta syncytial trophoblasts is characterized by: Most of the estrogens is estrone, which is converted to estradiol, estrone and estrone. **Functions of Estrogens in pregnancy:** 1- Growth of uterus. 2- Growth and enlargement of mammary glands. 3- Relaxation of pelvic ligaments, which helps the easy passage of fetus through birth canal. 4- Increase number & sensitivity of Oxytocin receptors in uterus.

C- Progesterone: It is secreted by syncytial trophoblast. Functions: Development of decidual cells needed for fetal nutrition. (2) Decrease uterine contractility during pregnancy. (3) Increase secretions of fallopian tube and endometrium before implantation to provide the necessary nutrition for the zygote development. (4) Prepares breast for lactation. D- Human chorionic Somatomammotropin (HCS) = human placental lactogen (hPL) = Chorionic growth hormone prolactin (CGP) It may function as maternal growth hormone of pregnancy. Functions: Partial development of breast. Deposition of protein in tissues. Provides great amount of glucose from mother to the fetus. Other Hormonal secretions Relaxin: polypeptide. In female: secreted from corpus luteum, placenta, uterus & mammary gland. During pregnancy relaxin: (1) Relaxes the pubic symphysis & other pelvic joints. (2) Softens & dilates the cervix to facilitate labor. (3) Play a role in the development of mammary glands. (4) Inhibits the uterine contractility. In male: secreted from prostate gland. Found in semen so, play a role in sperm motility penetration of the ovum. CRH: A- Stimulate fetal adrenal gland so, increases dihydro-androstenedione (DHE) thus increasing the circulating estrogen. B- Increase ACTH & Cortisol. Inhibin and GnRH: GnRH stimulates HCG. Inhibin inhibits HCG. Prolactin Pituitary Hormones: Pituitary gland of the mother is stimulated by placental hormones to secrete increase amounts of: Corticotrophin – Thyrotrophin – Prolactin. Other glands A) Pancreas increase insulin. B) Thyroid gland increase thyroid hormones. C) Parathyroid gland maintain normal Ca^{++} . D) Cortical secretion increase Glucocorticoid increase Aldosterone.

Parturition (Labor)

It is the process of expulsion of the fetus, the surrounding membranes and the placenta from the uterus. It requires strong coordinated uterine contractions aided by voluntary abdominal muscle contraction. The mechanism which initiates labor involves a combination of these factors: (1) Hormonal factors. (2) Mechanical factors.



(1) Hormonal factors A) Ratio of estrogen/ progesterone during pregnancy: Progesterone inhibits uterine contractions thus it prevents expulsion of fetus. Estrogen tends to stimulate uterine contraction. The 2 hormones are secreted in increasing amounts throughout pregnancy until the 7th month after which: Progesterone levels remain constant or slightly decrease, estrogen secretion continues to increase. Ratio of estrogen/ progesterone increases to increase uterine contractility. B) Oxytocin Action: Increased levels of fetal Oxytocin to initiate labor, while maternal Oxytocin maintains uterine contractions during labor. High levels of estrogen at the end of pregnancy increase the synthesis and sensitivity of oxytocin receptors. C) Fetal hypothalamic – pituitary axis: It stimulates uterine contraction. D) **Prostaglandin**: It is secreted from fetal membranes. Direct stimulation of uterine contractions. Dilates and thins out the cervix during early labor with invasion of leucocytes

(2) Mechanical factors Stretch of uterine muscles induces uterine contractions. Stretching or irritation of cervix stimulates reflex uterine contractions. Positive Feedback theory of labor: Once the uterine contraction becomes greater than a critical level, there is a positive feedback, which initiates a vicious circle of even stronger contractions. It depends on: (1) Cervical stretch: (by descent of baby's head in the cervix) stimulate reflex contractions in the fundus and body of uterus. (2) Cervical stretch and dilatation also stimulates posterior pituitary gland to secrete oxytocin, which increases the uterine contractility. Stages of labor: 1- First stage: involves the stretching of cervix and initiation of uterine contractions. 2- Second stage: involves the expulsion of the baby from the birth canal. 3- Third Stage: involves the expulsion of fetal membranes and placenta after separation from its implantation site

Abdominal muscle contraction during Labor Once uterine contractions become strong during labor, pain signals originate both from the uterus itself and from the birth canal. These signals elicit neurogenic reflexes in the spinal cord to abdominal muscles causing intense contraction of the muscles. The abdominal contractions add greatly to the force that cause expulsion of the baby. Each uterine contraction tends to force the baby downwards towards the cervix. In the early part of labor, contraction occurs every 30 minutes, finally appear every 3 minutes. The combined contractions of the uterine and abdominal musculature during delivery of the baby cause downward force on the fetus. In about 95% of births, the head is the first part of the baby to be expelled, in which to open the birth canal. Towards the end of pregnancy, the cervix becomes soft, which allows it to stretch when labor contraction begins in the uterus. Once the cervix has dilated fully, the fetus membranes rupture and the amniotic fluids are lost through the vagina. The fetus's head is rapidly moved into the birth canal and with additional force enters the canal. **Separation of the placenta**: For 10 -45 minutes after birth of the baby, the uterus continues to contract, which causes shearing effects between the wall of the uterus and placenta thus separating the placenta from its implantation site, which causes bleeding. The contraction of the uterus after delivery of the baby constricts the vessels supplied blood to the placenta. In addition, vasoconstrictor prostaglandins formed at the placental implantation site cause additional blood vessel spasm

Lactation

Development of the breast begins at puberty by the action of estrogen and progesterone. Additional growth occurs during pregnancy, especially the glandular tissue. During pregnancy: [A] Increased estrogen level causes: 1- Growth of ductal system. 2- Increased stroma. 3- Increased fat deposition. These estrogen effects on the breast are aided by other hormones: Prolactin – Growth hormone – Insulin and adrenal glucocorticoids. [B] Increased progesterone levels causes: 1- Growth of breast lobules & alveoli. 2- Development of secretory characteristics in alveolar cells. Secretion of milk is due to: (1) Hormones [Prolactin – Human chorionic somatomammotropin (HCS)]. (2) Sucking Milk ejection or milk letting down. [1] Hormones: (a) Prolactin promotes milk secretion: It is secreted in the mother from 5th week of pregnancy until birth. (b) Human chorionic somatomammotropin (HCS): Secreted by placenta, has also lactogenic properties. It is promoted at 5th week after labor. These hormones provide elements necessary for milk synthesis as: fatty acids, amino acids, glucose and calcium. **2] Sucking**: Baby begins sucking Transmits sensory impulses to reach the spinal cord Hypothalamus which stimulates: oxytocin secretion from posterior pituitary prolactin secretion from anterior pituitary Oxytocin reaches the breasts contract myoepithelial cells squeeze milk from alveoli and fine ducts Milk flows down in the large ducts to reach the nipples. -Sucking of one breast causes milk to flow in that as well as the other. **Initiation of Lactation** is due to high levels of estrogens, prolactin, progesterone and human chorionic somatomammotropin (HCS). At first in very small amount into the duct at 5th month of gestation. Expulsion of placenta at labor leading to sudden decrease in estrogens & progesterone, this sudden drop initiates lactation **Colostrum**: Is an initial yellowish sticky secretion produced by breast 1st week after birth contains more immunoglobulins and proteins. **True Milk** Produced on 2nd – 3rd week, contains more lactose and fat. **Effect of lactation on menstrual cycles** Lactation stimulates prolactin secretion which acts to: 1- Inhibit Gonadotrophic Releasing Hormone (GnRH) secretion from hypothalamus. 2- Inhibit the action of GnRH on the pituitary. 3- Antagonize the action of gonadotropins on ovaries Inhibit ovulation, inactive ovaries and decreased estrogen and progesterone output

The changes occurs in the maternal physiology: There is an increase in size of sexual organs. The uterus increases from 50 grams to 1100 grams. The breasts become double in size, at the same time the vagina enlarges and opens more widely. Various hormones can cause marked change in pregnant woman's appearance such as edema, acne and masculinization. The changes in the maternal weight gain The average weight gain during pregnancy is about 24 pounds during the last trimester (3 months) of pregnancy, about 4 pounds in fetus and 4 pounds in amniotic fluid, placenta and fetal membrane. The uterus increases about 2 pounds and the breast about 2 pounds, an average increase of 9 pounds, about 6 pounds of this extra fluid in the blood and extracellular fluid and the remaining 3 pounds is fat accumulation. During pregnancy, woman has increased desire for food as a result of removal of food substrates from the mother's blood by the fetus. **Metabolism during pregnancy** During pregnancy: Increased secretion of many hormones such as: Thyroxine, Adrenocortical hormones and sex hormones. The basal metabolic rate of pregnant woman increases about 15% during latter half of pregnancy as a result she has sensation of overheated **Nutrition during pregnancy** The greater growth of the fetus occurs during the last period of pregnancy. Its weight is double during the last 2 months. The mother does not absorb sufficient protein, calcium, phosphates and iron from her diet to supply these extra needs of the fetus. The mother's body already storing these substances, some in placenta, but



the most in the normal storage depots of the mother .If nutritional elements are not present in pregnant woman 'diet a number of deficiencies occurs . Without sufficient iron will produce Hypochromic anemia.Calcium ,Vitamin D and also vitamin K (sufficient Prothrombin) to avoidHemorrhage(brain hemorrhage during birth)**cardiovascular changes in maternal physiology**About 625 milliliters of blood flows through the maternal circulation of placenta each minute .The general increase in mother's metabolism, increases cardiac output and increase the blood volume due to Aldosterone and estrogens which increased during pregnancy and also the bone marrow which produces extra red blood cells to go with excess fluid volumethe respiratory changes in maternal physiology:Increased basal metabolic rate of pregnant woman, the total amount of O₂ used by the mother is increased about 20%, this causes increase ventilation .Also during pregnancy progesterone increases respiratory center's sensitivity to CO₂ , the net result: increase ventilation and decrease Pco₂.The growing uterus presses upward against theabdominal contents ,and these press upward against the diaphragm ,.So the respiratory rate is increased to maintain extra ventilation . changes in renal function in maternal physiologyThe rate of urine formation usually increasedbecause of increased fluid intake and increased excretory products The renal tubules ' reabsorptive capacity for Na⁺ , Cl⁻ , and water is increased as increased production of steroid hormones by placenta and adrenal cortex . Also the Glomerular filtration rate increases 50% during pregnancy ,which tends to increase the rate of water and electrolyte excretion in the urine

Menopause

Menopause: Definition:Stoppage of female sexual cycle(ovarian & menstrual), which lack of sex hormones . It occurs at the age of 45 -50 years .Cause:*At the age of 45 years:

Only a few primordial follicles are left to be stimulated by FSH and LH . Decrease estrogen secretion by ovary .Insufficient , neither to inhibit FSH and LH nor causing their ovulatory surge .Few years later: The remaining follicles become atretic and estrogen production = zero .Manifestations of menopause:1- Amenorrhea(loss of menstruation).2- Osteoporosis due to absence of the estrogen anabolic effect on bones.3- Gradual loss of secondary sex characters .4- Psychic disorders as: anxiety , irritability, depression , dyspnea .5- Hot flushes ,characterized by extreme flushing of the skin .6- FatigueTreatment :(1) Administration of small amounts of estrogen .(2) Intake of milk and vitamin D to avoid Osteoporosis .(3) Psychotherapy in severe psychic disorders .Hormonal changes:Decrease estrogen and progesterone increase gonadotrophine releasing hormone GnRH increase FSH,LH (but no surge) increase androgen .Although the functions of the tests tend to decrease slowly with advancing age , there is no male menopause similar to that in females .

CHAPTER XI

CENTRAL NERVOUS SYSTEM

Functional organization of the CNS

Different Divisions Of The Nervous System The nervous system is comprised of two major parts: 1. The central nervous system (CNS) and 2. The peripheral nervous system (PNS). The CNS includes the brain and spinal cord. The brain is the body's "control center" which consists of:CEREBRUM, MIDE BRAIN, PONS, "MEDULLA OBLONGATA AND CEREBELLUM" (THE BRAIN STEM)The PNS is then subdivided into the autonomic nervous system and the somatic nervous system. The autonomic has involuntary control of internal organs, blood vessels, smooth and cardiac muscles. The somatic has voluntary control of skin, bones, joints, and skeletal muscle.

spinal cord The spinal cord extends from the skull (foramen magnum) to the first lumbar vertebra. The spinal cord consists of gray matter and white matter. The gray matter of the cord is located centrally & is surrounded by white matter (myelinated axons). The white matter of the spinal cord consists of ascending and descending fiber tracts.**Function:** 1. The ascending tracts transmitting sensory information (from receptors in the skin, skeletal muscles, tendons, joints, & various visceral receptors) 2. The descending tracts transmitting motor information (to skeletal muscles, smooth muscle, cardiac muscle, & glands). 3. The spinal cord is also responsible for spinal reflexes. **Brain Stem** Connects the brain to the spinal cord; consists of the midbrain, pons, & medulla oblongata. **Function:** 1. provides the main motor and sensory innervation to the face and neck by the cranial nerves. 2. Plays an important role in the regulation of cardiac and respiratory function. 3. Regulates the central nervous system, and has a vital role in maintaining consciousness and regulating the sleep cycle.

Midbrain short section of the brain stem, it contains bundles of myelinated nerve fibers that join lower parts of the brain stem & spinal cord with higher parts of the brain; helps with eye & head movements

Pons A rounded bulge on the underside of the brain stem, helps regulate rate & depth of breathing

Medulla oblongata extends from the level of the foramen magnum to the pons; transmits all ascending & descending impulses & contains several vital & non vital reflex centers.



Reticular formation A complex network of nerve fibers scattered throughout the medulla oblongata, pons & midbrain; That connect centers of the hypothalamus, basal nuclei, cerebellum, & cerebrum with fibers in all the major ascending & descending tracts. It is responsible for: Normal and paradoxical sleep

Cerebellum The cerebellum is the part of the brain that is located posterior to the medulla oblongata and pons. 1. The main function of the cerebellum is coordination. 2. The cerebellum receives information from our eyes, ears, muscles, and joints about what position our body is currently in (proprioception). 3. The cerebellum is also responsible for balance and posture. 4. It also assists us when we are learning a new motor skill, such as playing a sport or musical instrument.

Cerebrum The cerebrum, or top portion of the brain, is divided by a deep crevice, called the longitudinal sulcus which separates the cerebrum in to the right and left hemispheres that contains: the cerebral cortex, basal ganglia and the limbic system. The right hemisphere is responsible for the left side of the body while the opposite is true of the left hemisphere. Each of the two hemispheres are divided into four separated lobes: The frontal lobe :Specialized for motor control, learning, planning and speech Parietal lobe: Somatic sensory functions; Occipital lobe: Control vision; Temporal lobe: Hearing centers and some speech.

Connections of the cerebral cortex The cerebral cortex is connected to various subcortical structures such as the thalamus and the basal ganglia, sending information to them along efferent connections and receiving information from them via afferent connections.

Function the cerebral cortex:Thought Voluntary movement Language Reasoning Perception Special Sensory Cortexes1. Visual cortex: information from sight receptors2. Auditory cortex: information from sound receptors3. Olfactory cortex: information from odor receptors4. Gustatory cortex: information from taste receptors

The basal ganglia The basal ganglia (or basal nuclei) are a group of nuclei in the brains of vertebrates, situated at the base of the forebrain and strongly connected with the cerebral cortex, thalamus and other areas. It is responsible for: 1. Motor control and learning. 2. Neurological conditions, including several movement disorders.

The Limbic System The Limbic System is a complex set of structures found just beneath the cerebrum and on both sides of the thalamus. Is a functional grouping that: 1. Establishes emotional states 2. Links conscious functions of cerebral cortex with autonomic functions of brain stem 3. Facilitates memory storage and retrieval.

The diencephalon Is the part of the forebrain that contains such important structures as the thalamus, hypothalamus and the posterior portion of the pituitary gland. Integrates sensory information and motor commands

Thalamus

Thalamus Filters ascending sensory information for primary sensory cortex. • Relays information between basal nuclei and cerebral cortex

The Hypothalamus The Hypothalamus is a small part of the brain located just below the thalamus on both sides of the third ventricle. **Functions:** 1. Provides subconscious control of skeletal muscle 2. Controls autonomic function 3. Coordinates activities of nervous and endocrine systems 4. Secretes hormones: antidiuretic hormone (ADH) – oxytocin 5. Produces emotions and behavioral drives: the feeding center (hunger), sexuality, combativeness. – the thirst center (thirst) 6. Coordinates voluntary and autonomic functions 7. Regulates body temperature 8. Controls circadian rhythms (day–night cycles). 4 Classifications of Cranial Nerves 1. Sensory nerves: carry somatic sensory information: • Touch, Pressure, Vibration, Temperature, and Pain 2. Special sensory nerves: carry sensations: Smell, Sight, Hearing, Balance 3. Motor nerves: axons of somatic motor neurons 4. Mixed nerves: mixture of motor and sensory fibers.

Sensory areas (cortex) The sensory areas are the areas that receive and process information from the senses. The senses of vision, audition, and touch are served by the primary visual cortex, primary auditory cortex and primary somato sensory cortex. In general, the two hemispheres receive information from the opposite (contralateral) side of the body. Alpha and Gamma Motor Neurons There are three types of neurons in the body: Sensory neurons, Interneurons, and Motor neurons. Neurons are a major class of cells in the nervous system. Their main role is to process and transmit information.

Somatic motoneurons are further subdivided into two types:

alpha efferent neurons and gamma efferent neurons. (Both types are called efferent to indicate the flow of information from the central nervous system (CNS) to the periphery.) When a muscle is stretched, sensory neurons within the muscle spindle detect the degree of stretch and send a signal to the CNS. The CNS activates alpha motoneurons in the spinal cord, which cause muscle fibers to contract. This process is also called the stretch reflex.



Sensory receptors, Sensory transduction and Information processing

Sensory receptors They are specialized structures or modified nerve endings present at the peripheral termination of afferent nerve fibers. **Functions:** Detectors: They detect adequate stimuli (change in the internal or external environment) and inform CNS about different sensations. Transducers: They transform any form of energy in the stimulus (chemical, mechanical, thermal, etc.) into action potentials that lead to generation of nerve impulses in the sensory nerve.

Classification

Mechanoreceptors: Detect mechanical deformity in the receptors or cells adjacent to them as: a. Touch and pressure receptors: in skin and deep tissues. b. Proprioceptors: In the ligaments & joints: position, stretch and tension. c. Vestibular receptors: Equilibrium. d. Cochlear receptors: Sound. e. Baroreceptors: Blood pressure.

2. Thermoreceptors: Detect thermal of energy Cold receptors. **Warm receptors.**

3. Pain receptors: Free nerve endings that respond to tissue damage.

4. Electromagnetic receptors: Detect light: rods and cones. Detect electric damage of tissues.

5. Chemoreceptors: Respond to chemical changes: Taste and smell O₂, CO₂, H⁺ conc. in blood. Osmo and glucoreceptors in the hypothalamus.

Properties of receptors

Specificity: Each type of receptor is most sensitive to specific stimulus e. g. light, sound, pressure, etc. And once the receptor is stimulated, it gives rise to one type of sensation.

2. Excitability: When adequately stimulated, a receptor generates a state of partial depolarization, known as Receptor or generator potential → an action potential

3. Electronic spread of receptor potential: The receptor potential induces a local circuit of current flow or current skin that spread passively to the adjacent part of the sensory nerve.

4. Generation of action potential: If the amplitude of the receptor potential is strong enough to depolarize the first node of Ranvier to threshold (about 10mV), it opens voltage gated Na channels and an action potential is produced in the sensory nerve and spreads to the CNS.

Properties of Receptor Potential (RP) It is a non propagated state of depolarization, which spreads passively. Its amplitude is increased by increasing the intensity of the stimulus. It has no absolute refractory period. It initiates a propagated action potential. Its duration (5- 10msec.) is longer than action potential duration (2 msec.) so can cause repeated action potentials. Relationship between the strength of the stimulus to the magnitude of the receptor potential (RP) As the strength of the stimulus increases, the magnitude of the RP increases. Relation of the receptor potential magnitude to number of impulses generated in the sensory nerve The number of impulses produced in the sensory nerve is proportional to the amplitude of the receptor potential

Adaptation of receptors Means decrease of the receptor potential and number of impulses emitted inspite of constant stimulus. **Causes of adaptation:** In mechanoreceptors, adaptation occurs by one of two mechanisms: 1. Readjustment and remodeling in the structure of the receptor itself. 2. Accommodation of the terminal nerve fiber to the stimulus, due to inactivation of Na channels as result of continuous current flow. According to the rate of adaptation, receptors are classified into: Slowly adapting receptors (tonic receptors): As pain receptors and alveolar stretch receptors. They are either slowly adapting or they do not adapt at all. Their function is to keep the brain continuously informed about the status of the body, and its relation to the surroundings. They also protect and warm the body against any dangerous change in the internal environment.

2. Moderately adapting: As temperature, smell and taste receptors.

3. Rapidly adapting: (phasic receptors) As touch and pressure receptors (Paccinian corpuscles, Meissner's corpuscles and hair cells. They adapt rapidly to continuously applied stimuli, but they discharge strongly while a change is actually taking place. So they are called movement receptors. They can predict the next position of the body because they can measure the rate of change.

Sensory Code Definition: Coding of sensory information means the ability of CNS to recognize the type, the site and the degree of sensation. All stimuli produce action potentials which are all alike. Modality of sensation: depends on: Adequate stimulus: Each receptor is specialized to receive a particular type of stimulus.

2. Muller's law of specific nerve energy: Whatever may be the method of stimulation of the receptor, the sensation given is that the receptor is specialized to. E.g. if the rods and cones in the retina are stimulated mechanically or electrically, the sensation perceived is always light.

3. Labeled line principle: Which stated that there is a specific pathway for each sensation which transmits it to a specific area in the cortex.

a. Intensity of sensation: It is coded by change in: . The number of receptors activated by the stimulus. 2. The frequency of impulses. C. Locality of the stimulus (The Law of Projection): There is a separate representation area for each part of the body in the cerebral cortex. When an impulse reaches the specific area in the cortex, it projects this stimulus to its original site.

Physiology of the eye (Anterior chamber accommodation)

The Eye as a Camera Parallel rays falling on the eye converge by lens system to focus on the retina, which is similar to the sensitive film of the camera. Within the layers of the retina, light impulses are changed into electrical signals. Then they are sent through the optic nerve, along the visual pathway, to the occipital cortex at the posterior (back) of the brain. Here, the electrical signals are interpreted or "seen" by the brain as a visual image.

The Eye The normal eye focuses light and produces a sharp image

Essential parts of the eye Cornea: light passes through this transparent structure Aqueous Humor: clear liquid behind the cornea The pupil: A variable aperture, An opening in the iris The crystalline lens Most of the refraction takes place at the outer surface of the eye. Where the cornea is covered with a film of tears. The iris: is the colored portion of the eye – It is a muscular diaphragm that controls pupil size – The iris regulates the amount of light entering the eye by dilating the pupil in low light conditions and contracting the pupil in high-light conditions.

The Eye – Operation

- The cornea-lens system focuses light onto the back surface of the eye (retina) – The retina contains receptors called rods and Cones → send impulses via the optic nerve to the brain
- The brain converts these impulses into our conscious



Rods and Cones – Chemically adjust their sensitivity according to the prevailing light conditions. The adjustment takes about 15 minutes. This phenomenon is “getting used to the dark.” **The Eye – Focusing** • The eye can focus on a far object – The ciliary muscle is relaxed – The zonules (sensory ligaments) tighten – This causes the lens to flatten, increasing its focal length – For an object at infinity, the focal length of the eye = fixed distance between lens and retina • This is about 1.7 cm. The eye can focus on near objects – The ciliary muscles stretch – This relaxes the zonules – The lens little bulged a bit and the focal length decreases – The image is focused on the retina

The Eye – Near and Far Points • The near point is the closest distance for which the lens can accommodate to focus light on the retina – Typically at age 10, this is about 18 cm – It increases with age • The far point of the eye represents the largest distance for which the lens of the relaxed eye can focus light on the retina – Normal vision has a far point of infinity **Conditions of the Eye** • Eyes may suffer a mismatch between the focusing power of the lens-cornea system and the length of the eye. Eyes may be – Farsighted • Light rays reach the retina before they converge to form an image – **Nearsighted** • Person can focus on nearby objects but not those far away. **Farsightedness** • Also called hyperopia • The image focuses behind the retina • Can usually see far away objects clearly, but not nearby objects

Correcting Farsightedness • A converging lens placed in front of the eye can correct the condition • The lens refracts the incoming rays more toward the principle axis before entering the eye – This allows the rays to converge and focus on the retina **Nearsightedness** • Also called myopia • In axial myopia the nearsightedness is caused by the lens being too far from the retina • In refractive myopia, the lens-cornea system is too **powerful for the normal length of the eye**

Correcting Nearsightedness • A diverging lens can be used to correct the condition • The lens refracts the rays away from the principle axis before they enter the eye. This allows the rays to focus on the retina

Accommodation It is the changes that occur in the lens to see near objects. The emmetropic eye: At rest, parallel rays are brought to a focus on the retina. Light rays from an object at a distance more than 6 meters from the eye are considered parallel and focus on the retina. When objects are brought closer to the eye, the rays proceeding are divergent. If the eye remained unchanged the rays will be focused behind the retina. In order to bring the image of the near object to focus on the retina, the eye lens increases its dioptric power by increasing its curvature (accommodation).

Mechanism of accommodation: The lens has a strong elastic capsules, which encircles proteinaceous fibers. When the lens is in a relaxed state with no tension on its capsule, it tends to consider a spherical shape due to elasticity of the capsule. However, this is opposed by the constant tension of zonular fibers (sensory ligaments).

Power of accommodation It is the difference in power of the lens of the resting eye (non accommodated) during far vision and its power during maximal accommodation during near vision. The power of the accommodation decreases with age as the elasticity of the lens decreases. It is about 14 D at age of 10 years, 10 D at 20 years and 2 D at 50 years and only 1 D at age of 60 years. **Far point:** It is the short distance from the eye, which can be seen clearly without accommodation. This is 6 m or more in emmetropes. **Near point:** It is the short distance from the eye at which an object may be seen clearly using maximum accommodation. It is about 10 cm in young adults and 80 cm at age of 60 years. This near point distance increases with age. **Range of accommodation** It is the distance between far and near points. The range of accommodation decreases with age **The cornea** Is the window through which the light rays pass on their way to the retina. It acts as a powerful convex lens (45D), which causes marked bending of the light rays. This because it has: 1. High degree of curvature and its diameter is 11 mm(which helps the formation of sharp retinal images). 2. A refractive index 1.38 compared with 1.0 for air. 3. It contributes to about 2/3 of the eye's refractive power. 4. The cornea protects the delicate inner structure of the eye through the corneal reflex and it has the ability to absorb ultraviolet rays.

The Corneal Reflex It is a superficial reflex. Touching the cornea of one eye by a foreign body causes blinking of both eyes. Stimulation of corneal receptors leads to afferent impulses (along the ophthalmic division of the 5th cranial nerve) ►the pons ►the facial nerve (efferent) **The Aqueous Humor** Is a thick watery substance filling the space between the lens and the cornea. **Functions** Maintains the intraocular pressure and inflates the globe of the eye. Provides nutrition (e.g. amino acids and glucose) for the a vascular ocular tissues; posterior cornea, trabecular meshwork, lens, and anterior vitreous. May serve to transport ascorbate to act as an anti-oxidant agent. Presence of immunoglobulins indicate a role in immune response to defend against pathogens.

The Lens 1. The lens is that part of the human eye that is located immediately behind the iris. 2. It is transparent, elastic and crystalline. Its role is to focus the light and move towards the retina. 3. The lens is a transparent, biconvex structure in the eye that, along with the cornea, helps to refract light to be focused on the retina. 4. The lens, by changing shape, functions to change the focal distance of the eye so that it can focus on objects at various distances, thus allowing a sharp real image of the object of interest to be formed on the retina. 5. The lens is flexible and its curvature is controlled by ciliary muscles.

Light reflex, and Retinal function (dark adaptation, and electrophysiology of Rods and Cones) Retina It is formed of 10 layers from outside to inside: Pigment layer 2. Photoreceptors layer (rods and cones) 3. Outer limiting membrane



4. Outer nuclear layer (contains nuclei of photoreceptors) 5. Outer plexiform layer (synapses between layers 4& 6) 6. Inner nuclear layer 7. Inner plexiform layer (synapses between layers 6& 8) 8. Ganglion cell layer 9. Optic nerve fibers layer 10. Inner limiting membrane

Parts of the Retina of Physiologic Importance Macula lutea: yellow spot opposite to the posterior pole of the eye lies lateral to optic disc. Optic disc: the exit of optic nerve from the retina. Fovea centralis: the central part of the macula & it is composed of cones only. Photoreceptors: each receptor is formed of 4 functional segments Outer segment: Rods and Cones. It contains 1000 discs containing the photosensitive pigment. Inner segment: contains abundant mitochondria. Nucleus. Synaptic body: area of junction with other retinal cells.

Spectral sensitivity of rods and cones

Purkinje Sift Phenomenon Is the shift from max. sensitivity of photopic function (at 505 nm) to max. sensitivity of scotopic function (at 500nm). Is studied by Luminosity Curves During day time: red, blue flowers appear equally bright But at night: blue flowers appear bright but red flowers appear black.

Retinal adaption It is the ability of retina to adjust its sensitivity to different light intensities: Light adaption ↓↓ retinal sensitivity to light and ↑↑ retinal threshold when a person shifts from dim lighted place to bright lighted place **Mechanism** Breakdown of rods and cones (it takes 5 minutes). Changes 1. Constriction of the pupil (miosis). Breakdown of photopigments in rods and cones. 3. ↓↓ retinal sensitivity to light. ↓↓ signal intensity to retinal neurons. **2. Dark adaption** ↑↑ retinal sensitivity to light max. 100,000- 500,000 times) & ↓↓ retinal threshold when a person shifts from bright lighted place to dim lighted place. **Mechanism** Regulation of photopigments in rods and cones it takes 30 minutes and has 2 stages:

Photoreceptors Potentials and Signal Transmission in Retina Photochemical changes (Bleaching) The photochemical substances (pigments) are 2 types: Rhodopsin: present in rods. Iodopsin: present in cones. II. Genesis of electrical response in the retina. III. Linkage between rhodopsin and Na channels (excitation cascade) IV. Signal transmission in the retina.

Visual Pathway As the optic nerve leaves the back of the eye, it travels to the optic chiasm, located just below and in front of the pituitary gland (which is why a tumor on the pituitary gland, pressing on the optic chiasm, can cause vision problems). In the optic chiasm, the optic nerve fibers emanating from the nasal half of each retina cross over to the other side; but the nerve fibers originating in the temporal retina do not cross over. From there, the nerve fibers become the optic tract, passing through the thalamus and turning into the optic radiation until they reach the visual cortex in the occipital lobe at the back of the brain. This is where the visual center of the brain is located. The visual cortex ultimately interprets the electrical signals produced by light stimulation of the retina, via the optic nerve, as visual images. A representation of parasympathetic pathways in the pupillary light reflex can be seen here: parasympathetic response.

The pupillary light reflex Is a reflex that controls the diameter of the pupil, in response to the intensity (luminance) of light that falls on the retina of the eye, thereby assisting in adaptation to various levels of darkness and light, in addition to retinal sensitivity. Greater intensity light causes the pupil to become smaller (allowing less light in), whereas lower intensity light causes the pupil to become larger (allowing more light in). Thus, the pupillary light reflex regulates the intensity of light entering the eye. **Mechanism** Pathways in the Ciliary ganglion. Green = parasympathetic; Red = sympathetic; Blue = sensory The optic nerve, or more exactly, the photosensitive ganglion cells through the retino hypothalamic tract, is responsible for the afferent limb of the pupillary reflex - it senses the incoming light. The oculomotor nerve is responsible for the efferent limb of the pupillary reflex - it drives the muscles that constrict the pupil. **Neuron 1** The pupillary reflex pathway begins with the photosensitive retinal ganglion cells, which convey information to the optic nerve (via the optic disc). The optic nerve connects to the pretectal nucleus of the upper midbrain, bypassing the lateral geniculate nucleus and the primary visual cortex. These "Intrinsic photosensitive ganglion cells" are also referred to as "Melanopsin", which regulate both the circadian rhythms and the pupillary light reflex. **Neuron 2** From the pretectal nucleus, axons connect to neurons in the Edinger-Westphal nucleus, whose axons run along both the left and right oculomotor nerves. **Neuron 3** Oculomotor nerve axons synapse on ciliary ganglion neurons. **Neuron 4** Neuron #4 innervates the constrictor muscle of the iris.

The physiological role of the external and middle ear in the process of hearing

The Middle Ear

The middle ear is an air filled cavity in which are located three middle ear ossicles, the malleus, incus and stapes Transformer action: allows sound wave travelling in air (outer ear) to become sound wave travelling in fluid (inner ear) without reflection at interface Transformer action of middle ear allows over 60% of sound energy reaching eardrum to be transmitted to inner ear No middle ear, sensitivity to sound reduced by 30x (eg. mucous filled during ear infection)

Auditory Ossicles Bones (named for their shape) are: malleus (hammer) Incus (anvil) Stapes (stirrup) Connected by synovial joints Malleus connected to tympanic membrane Base of stapes connected to oval window (fenestra vestibuli) Vibration of the tympanic membrane causes movement of the ossicles. In this way, the vibrations of the tympanic membrane are transmitted to



the oval window at the base of the cochlea. The eustachian tube in the middle ear opens into the pharynx. It functions to equalise air pressure between the outside air and the middle ear cavity. What may happen if the pressures become unequal?

Functions of the Middle Ear in Hearing The middle ear transforms sound pressure variation in the air-filled (moist) ear canal to sound pressure variations in the fluid-filled cochlea. Damage to the ossicles may affect this transfer function and impair hearing. The middle ear also acts as an impedance matcher- it matches the impedance of the auditory meatus to the much higher impedance of the cochlear fluids. Without this impedance matching function, a lot of sound would be reflected to the external auditory meatus

Functions of the Middle Ear Muscles There are 2 middle ear muscles: Tensor tympani that is attached to the malleus. This muscle is innervated by the Trigeminal (V) nerve. Tensor stapedius that is attached to the stapes. This muscle is innervated by the Facial (VII) nerve. Contraction of the middle ear muscles increases the stiffness of the ossicular chain. This helps to reduce the transmission of loud sounds and prevent damage to the cochlea. Which of these muscles will be affected in Bell's Palsy and how may this affect hearing? Cochlea and hearing process: "Changing sound energy into neural activity & Neural Mechanisms for Pitch and Loudness Discrimination

The Inner Ear The inner ear can be thought of as two organs: - the semicircular canals which serve as the body's balance organ - the cochlea which serves as the body's microphone, converting sound pressure impulses from the outer ear into electrical impulses which are passed on to the brain via the auditory nerve.

The Inner Ear The inner ear consists of bony tunnels that are located inside the temporal bone. The bony labyrinth of the inner ear consists of the cochlea (involved in hearing), the vestibule and the semicircular canals (involved in balance). The cochlea is divided longitudinally into 3 fluid-filled compartments, the scala vestibuli, the scala tympani and the scala media. The middle compartment, the scala media contains the organ of Corti

Inner Ear Semicircular Canals Cochlea The semicircular canals are the body's balance organs. Hair cells, in the canals, detect movements of the fluid in the canals caused by angular acceleration. The canals are connected to the auditory nerve. The inner ear structure called the cochlea is a snail-shell like structure divided into three fluid-filled parts. Two are canals (Scala tympani and Scala Vestibuli) for the transmission of pressure and in the third is the sensitive organ of Corti, which detects pressure impulses and responds with electrical impulses which travel along the auditory nerve to the brain.

The organ of Corti can be thought of as the body's microphone. Perception of pitch and perception of loudness is connected with this organ. It is situated on the basilar membrane in the cochlea duct. It contains inner hair cells and outer hair cells. There are some 16,000 -20,000 of the hair cells distributed along the basilar membrane. Vibrations of the oval window causes the cochlear fluid to vibrate. This causes the Basilar membrane to vibrate thus producing a traveling wave. This causes the bending of the hair cells which produces generator potentials. If large enough will stimulate the fibers of the auditory nerve to produce action potentials. The outer hair cells amplify vibrations of the basilar membrane. The cochlea works as a frequency analyzer. It operates on the incoming sound's frequencies. Frequency Theory Place Theory Frequency Theory. BM vibrates in synchrony with the sound entering the ear, producing action potentials-- in auditory nerve cells -- at the same frequency (e.g., 50 Hz sound -> 50 APs/sec). Limitations: max APs/sec = 200 Hz. Use this theory for Frequencies <100Hz. Auditory Neuron The auditory nerve takes electrical impulses from the cochlea and the semicircular canals. Makes connections with both auditory areas of the brain. Information from both ears goes to both sides of the brain - binaural information is present in all of the major relay stations. Left ear information Right ear information

Auditory Neurons Adaptation When a stimulus is suddenly applied spike rate of an auditory neuron fiber increases rapidly. If the stimulus remains (a steady tone for eg.) the rate decreases exponentially. Spontaneous rate: neuron firings in the absence of stimulus. Neuron is more responsive to changes than to steady inputs. Perception of Sound Threshold of hearing How it is measured Age effects Equal Loudness curves Bass loss problem Critical bands Frequency Masking Temporal Masking Threshold of Hearing Hearing area is the area between the Threshold in quiet and the threshold of pain. Note: Shift in threshold of quiet for those who listen to loud music. The sound intensity required to be heard is quite different for different frequencies. Threshold of hearing at 1000 Hz is nominally taken to be 0 dB. Marked discrimination against low frequencies so that about 60 dB is required to be heard at 30 Hz. The maximum sensitivity at about 3500 to 4000 Hz is related to the resonance of the auditory canal.

Deafness Conductive - damage to the outer and middle part of the ear; it usually can be treated & hearing aids can be used. E.g. ear infections. Sensorineural: some or most of hair cells in the cochlea die. Hearing aids can only amplify sounds they can hear. Mixed-combination Mild hearing loss (35 to 54 dB) Moderate hearing loss (55 to 69 dB) Profound hearing loss (90 dB and beyond) Neurophysiological principles of synaptic transmission (interneuronal communication)

SYNAPTIC TRANSMISSION

The process by which neurons transfer information at a synapse



Different Types of Synapses The human nervous system uses a number of different neurotransmitter and neuroreceptors, and they don't all work in the same way. Synapses can group into 5 types: 1. **Excitatory Ion Channel Synapses.** These synapses have neuroreceptors that are sodium channels. When the channels open, positive ions flow in, causing a local depolarization and making an action potential more likely. Typical neurotransmitters are acetylcholine, glutamate or aspartate.

2. Inhibitory Ion Channel Synapses. These synapses have neuroreceptors that are chloride channels. When the channels open, negative ions flow in causing a local hyperpolarization and making an action potential less likely. So with these synapses an impulse in one neuron can inhibit an impulse in the next. **Typical neurotransmitters are glycine.** **3. Non Channel Synapses.** These synapses have neuroreceptors that are not channels at all, but instead are membrane-bound enzymes. When activated by the neurotransmitter, they catalyse the production of a "messenger chemical" inside the cell, which in turn can affect many aspects of the cell's metabolism. These synapses are involved in slow and long-lasting responses like learning and memory. Typical neurotransmitters are adrenaline, noradrenalin, dopamine, serotonin, endorphin, angiotensin, and acetylcholine. **4. Neuromuscular Junctions.** These are the synapses formed between motor neurones and muscle cells. They always use the neurotransmitter acetylcholine, and are always excitatory. **5. Electrical Synapses.** In these synapses the membranes of the two cells actually touch, and they share proteins. This allows the action potential to pass directly from one membrane to the next. They are very fast, but are quite rare, found only in the heart and the eye. **Summation** When one postsynaptic neuron is excited/inhibited by more than one presynaptic neuron. Thus several neurons converge and release their neurotransmitters towards one neuron. One neuron can have thousands of synapses on its body and dendrites. So it has many inputs, but only one output. The output through the axon is called the Grand Postsynaptic Potential (GPP) and is the sum of all the excitatory and inhibitory potentials from all that cell's synapses. This summation is the basis of the processing power in the nervous system.

Types of Synapses

CNS Synapses – Axodendritic: Axon to dendrite • Axoaxonic: Axon to axon – Axosomatic: Axon to cell body – Gray's Type I: Asymmetrical, excitatory – Gray's Type II: Symmetrical, inhibitory **An electrical synapse** Is a mechanical and electrically conductive link between two neurons that is formed at a narrow gap between the pre- and postsynaptic neurons known as a gap junction. At gap junctions, such cells approach within about 3.5 nm of each other, a much shorter distance than the 20 to 40 nm distance that separates cells at chemical synapse. In organisms, electrical synapse-based systems co-exist with chemical synapses. Electrical synapses are often found in neural systems that require the fastest possible response, such as defensive reflexes. **Chemical synapses** Are specialized junctions through which neurons signal to each other and to non-neuronal cells such as those in muscles or glands. Chemical synapses allow neurons to form circuits within the central nervous system. Underlie perception and thought. They allow the nervous system to connect to and control other systems of the body.

Principles of Chemical Synaptic Transmission 1. **Synthesis of the Chemical Transmitter** 2. Transport and Storage of the Transmitter 3. Release of the Neurotransmitter 4. Receptor Sites for the Neurotransmitter 5. Inactivation of the Neurotransmitter Neuropharmacology Transmission

The study of effect of drugs on nervous system tissue – Receptor antagonists: 1. Inhibitors of neurotransmitter receptors • e.g. Curare binds tightly to Ach receptors of skeletal muscle. 2. Mimic actions of naturally occurring neurotransmitters E.g. Nicotine binds and activates the Ach receptors of skeletal muscle (nicotinic Ach receptors) – Toxins and venoms 3. Defective neurotransmission: Root cause of neurological and psychiatric disorders **Cortical Control of Motor Functions, functions of motor descending tracts & Processing Of Signals In The CNS** Most "voluntary" movements initiated by the cerebral cortex are achieved when the cortex activates function stored in lower brain areas: the cord, brain stem, basal ganglia, and cerebellum. These lower centers, in turn, send specific control signals to the muscles. The motor cortex is divided into three subareas: The primary motor cortex, (2) The premotor area, and (3) The supplementary motor area. Some Specialized Areas of Motor Control Found in the **Human Motor Cortex Broca's Area and Speech: A premotor area responsible for "word formation".** Damage to it does not prevent a person from vocalizing, but it does make it impossible for the person to speak whole words rather than uncoordinated words or simple word such as "no" or "yes." **"Voluntary" Eye Movement Field** In the premotor area immediately above Broca's area is a point for controlling voluntary eye movements. Damage to this area prevents a person from voluntarily moving the eyes toward different objects. Instead, the eyes tend to lock involuntarily onto specific objects, an effect controlled by signals from the occipital visual cortex. This area also controls eyelid movements

Head Rotation Area. Slightly higher in the motor association area, electrical stimulation elicits head rotation. This area is closely associated with the eye movement field; it directs the head toward different objects. **Area for Hand Skills** In the premotor area immediately anterior to the primary motor cortex for the hands and fingers important for "hand skills." That is, when tumors or other lesions cause destruction in this area, hand movements become uncoordinated, a condition called motor apraxia. **Transmission of Signals from the Motor Cortex to the Muscles** Motor signals are transmitted directly from the cortex to the spinal cord through the corticospinal tract and indirectly through the basal ganglia, cerebellum, and various nuclei of the brain stem. In general, the direct pathways are concerned more with discrete and detailed movements, especially of the distal segments of the limbs, particularly the hands and fingers.

Corticospinal (Pyramidal) Tract The most important output pathway from the motor cortex is the corticospinal tract. The corticospinal tract originates about 30 % from the primary motor cortex, 30 % from the premotor and supplementary motor areas, and 40 % from the somatosensory areas.



“Extrapyramidal” System The term extrapyramidal motor system is widely used in clinical circles to sign all those portions of the brain and brain stem that contribute to motor control but are not part of the direct corticospinal-pyramidal system. These include pathways through the basal ganglia, the reticular formation of the brain stem, the vestibular nuclei, and often the red nuclei. **Stimulation of the Spinal Motor Neurons** In the cervical enlargement of the cord where the hands and fingers are represented, large numbers of both corticospinal and rubrospinal fibers allowing a direct route from the brain to activate muscle contraction. **Effect of Lesions in the Motor Cortex or in the Corticospinal Pathway—The “Stroke”** The motor control system can be damaged by the common abnormality called a “stroke.” This is caused either by a ruptured blood vessel that hemorrhages into the brain or by thrombosis of one of the major arteries supplying the brain. In either case, the result is loss of blood supply to the cortex or to the corticospinal tract.

Role of the Brain Stem in Controlling Motor Function The brain stem consists of the medulla, pons, and mesencephalon. It contains motor and sensory nuclei that perform motor and sensory functions for the face and head regions. But in another sense, the brain stem provides many special control functions, such as the following: 1. Control of respiration 2. Control of the cardiovascular system 3. Partial control of gastrointestinal function 4. Control of many stereotyped movements of the body 5. Control of equilibrium 6. Control of eye movements

CNS reflexes (Spinal cord reflexes) Development of Reflexes A reflex is a rapid, predictable motor response to a stimulus. Innate reflexes are unlearned and involuntary. Acquired reflexes are complex, learned motor patterns. **Nature of Reflex Responses** Somatic: Reflexes involving skeletal muscles and somatic motor neurons. Autonomic (visceral) Reflexes controlled by autonomic neurons. Heart rate, respiration, digestion, urination, etc. Spinal reflexes are integrated within the spinal cord gray matter while cranial reflexes are integrated in the brain. Reflexes may be monosynaptic or polysynaptic.

Components of a Reflex Arc 1. Activation of a Receptor: site of stimulus 2. Activation of a Sensory Neuron: transmits the afferent impulse to spinal cord (CNS) 3. Information processing at the Integration center: synapses (monosynaptic reflexes) or interneurons (polysynaptic) between the sensory and motor neurons. In CNS Spinal reflexes or cranial reflexes 4. Activation of a Motor Neuron: transmits the efferent impulse to effector organ 5. Response of a peripheral Effector: Muscle or gland that responds. **Spinal Reflexes** 4 important somatic spinal reflexes: Stretch Tendon Flexor(withdrawal) Crossed extensor reflexes

Stretch Reflexes 1. Stretching of the muscle activates a muscle spindle (receptor) 2. An impulse is transmitted by afferent fibers to the spinal cord 3. Motor neurons in the spinal cord cause the stretched muscle to contract 4. The integration area in the spinal cord Polysynaptic reflex arc to antagonist muscle causing it to relax (reciprocal innervation)

Stretch Reflex Example Patellar Reflex

Tap the patellar tendon muscle spindle signals stretch of muscle motor neuron activated & muscle contracts Quadriceps muscle contracts Hamstring muscle is inhibited (relaxes) Reciprocal innervation (polysynaptic- interneuron) antagonistic muscles relax as part of reflex Lower leg kicks forward Demonstrates sensory and motor connections between muscle and spinal cord are intact.

Tendon Reflexes Monitors external tension produced during muscular contraction to prevent tendon damage Controls muscle tension by causing muscle relaxation Golgi tendon organs in tendon (sensory receptor) activated by stretching of tendon inhibitory neuron is stimulated motor neuron is hyperpolarized and muscle relaxes Both tendon & muscle are protected Reciprocal innervation (polysynaptic) causes contraction

Superficial Reflexes Elicited by gentle cutaneous stimulation Important because they involve upper motor pathways (brain) in addition to spinal cord neurons Superficial Reflexes Plantar Reflex Tests spinal cord from L4 to S2 Indirectly determines if the corticospinal tracts of the brain are working Draw a blunt object downward along the lateral aspect of the plantar surface (sole of foot) Normal: Downward flexion (curling) of toes

Abnormal Plantar Reflex: Babinski’s Sign Great toe dorsiflexes (points up) and the smaller toes fan laterally Happens if the primary motor cortex or corticospinal tract is damaged Normal in infants up to one year old because their nervous system is not completely myelinated.

Visceral Reflexes Provide automatic motor responses Can be modified, facilitated, or inhibited by higher centers, especially hypothalamus

Visceral Reflex Arc Receptor → Sensory neuron → Processing center interneuron(s) 1 or 2 visceral motor neurons Pre- and post-synaptic neurons (long reflex) Just a post-synaptic neuron (short reflex) **Long Reflexes** Autonomic equivalents (target visceral effectors) of polysynaptic somatic reflexes Coordinate activities of the entire organ Visceral sensory neurons deliver information to CNS along dorsal roots of spinal nerves: within sensory branches of cranial nerves within autonomic nerves that innervate visceral effectors **Short Reflexes** Bypass CNS Involve 1 small part of target organ Involve sensory neurons and



interneurons located within autonomic ganglia Interneurons synapse on ganglionic neurons Motor commands distributed by postganglionic fibers Control simple motor responses with localized effects

The stretch reflex and skeletal muscle tone Structure of the muscle spindles Each muscle spindle consists of 8- 10 intrafusal muscle fibers : Enclosed in spindle shape connective tissue capsule. Smaller than the extrafusal muscle fiber . Are parallel with the rest of muscle fiber. The central region (receptor) has no actin & myosin filaments so , do not contract . The peripheral ends are striated & contractile .

There are 2 types of intrafusal fibers : (1)Nuclear bag fibers[contain many nuclei in central area] 2) Nuclear chain fibers[have one lie of nuclei spread in a chain through the receptor] .

Excitation of the spindle receptors The muscle spindle receptor can be stimulated by : (1)Stretch of the whole muscle: The passive stretch Stretch of the sensory endings of the spindle . Reflex contraction of the stretch muscle . (2)Contraction of the end portion of the intrafusal fibers : By increasing γ efferent discharge stretch of the central part , as the following : Stimulating the sensory endings(receptor). Stimulation of the primary ends . Initiating impulses in the afferent that enters the spinal cord Stimulation of α motor neurons of the anterior horn cell . Send impulses along type A α efferent fibers to extrafusal muscle to contract (3)Maximal stimulation occurs when : 1-Stretch of whole muscle . 2- Increase the rate of discharge of γ efferent, Stimulation of both [a & b] . (4) Minimal stimulation occurs when : [Unloading] If there is shortening of extrafusal fibers without shortening of intrafusal fibers. Unloading is: Decrease the firing from spindle receptors during active muscle contraction. Unloading is functionally disadvantageous: because CNS stops receiving information about the rate& extent of muscle shortening. α contract the extrafusal fibers. γ contract the intrafusal fibers. So, central part of the spindle is remain stretched during muscle contraction which allow C.N.S to receive information about rate & extend of muscle contraction[loading] .

Types of the Stretch reflex

•	Dynamic (phasic) reflex :	static (Tonic) reflex :
Stimulus	Sudden quick stretch	Slow sustained stretch
Receptor	Nuclear bag fibers	Nuclear bag fibers&Nuclear chain fibers
Afferent	Primary endings	Primary & secondary endings
Center	All of α motor neuron	Some of α motor neuron
Efferent	Alpha –fibers .	Alpha –fibers .
Effector Organ .	Extra fusal muscle fibers	Extrafusal muscleFibers .
Efferent	Strong reflex contraction	Continuesmuscle contraction .

Thus , the primary endings respond to both : Changes in length of the muscle (static response) Changes in the rate of stretch in the muscle (dynamic response) . While , secondary endings respond only to changes in length (static response) Physiological **importance of the stretch reflex** : (1) Help to maintain the muscle length (2) Controls of voluntary movements. [a] Servo-assist function during muscle contraction: During voluntary contraction , impulses from higher center stimulate :- α motor neurons direct contraction of extrafusal muscle fibers . γ motor neurons reflex contraction of extrafusal muscle fibers . So, α & γ linkage potentiates voluntary contraction [b] Damping or smoothing function of the stretch reflexes :- The ability to prevent oscillation& jerkiness of body movements . During voluntary contraction signals are transmitted from brain [pyramidal tracts] sends irregular signals to AHCs(anterior horn cells)which lead to Jerky movement . Stretch reflex prevent Oscillation& smoothens muscle contraction . 3- The static stretch reflex is the basis of muscle tone :-

Skeletal Muscle tone: Is continuous , alternating , reflex subtetanic contractions of skeletal muscle fibers . Or: Resistance of the muscle to the stretch . During rest the muscle spindles is continuously stretched because : a- The length of muscles is shorter than distance between origin & insertion. b- The attractive force of the earth’s gravity causes lengthening of the muscles: Especially the antigravity muscles . C- There is a continuous γ efferent discharge stretching the muscle spindles Skeletal muscle tone is maintained without fatigue because : (1)Muscle tone is due to alternative activity of different muscle fibers . (2)The type of contraction is subtetanic . (3)Muscle fibers contracting are low[red] muscle fibers which can sustain force in the muscles for a long time . **The importance of the muscle tone:-** (1) Keeping body in erect upright position against gravity . (2) Provides a background for voluntary muscle activity (3)Helps in body temperature regulation (4)Helps venous return & lymph drainage . Supra-spinal regulation of Stretch Reflex Stretch reflex is a spinal reflex , regulated by certain brain areas :

Facilitatory centers	Inhibitory centers
1-Primary motor area (4)	1-Cortical suppressor area (45).



2- Neo cerebellum . 3- Facilitatory reticular formation. i.e: pontine reticular nuclei(pons) 4- Vestibular nuclei (VN)	2- Paleocerebellum . 3-Inhibitory reticular formation Medullary reticular nuclei . 4- Red nucleus (RN) 5- Basal ganglia .
Send impulses through facilitatory reticular formation along Ventral reticulo spinal tract	Send impulses through Inhibitory Reticular formation along lateral Reticulo spinal tract
Facilitatory reflex formation has intrinsic activity . -Vestibular nuclei sends via Vestibulo spinal tract -Act on γ motor neurones reflexly	Inhibitory reflex formation has no Intrinsic activity. -Red nucleus sends through Rubro-spinal tract . -Act on γ motor neurones reflexly .

The function & importance of Golgi tendon’s organs[Inverse stretch Reflex]

Definition : It is the reflex relaxation of muscle in response to strong stretch (autogenic inhibition) Up to a point , the harder a muscle is stretched; the stronger is the reflex contraction . However , when the tension becomes great enough , contraction suddenly stops & muscle relaxes. **Stimulus:** Marked tension in the muscle **Aim:** To maintain muscle tension constant

Clonus Definition: Regular rhythmic (repeated) contractions of hypertonic muscles in response to sudden maintained stretch . Cause: increased γ efferent discharge . Ex: Ankle clonus when sudden maintained dorsi flexion of foot Response rhythmic planter flexion at ankle .**Mechanism:** Alternating stretch reflex & inverse stretch reflex sequence . Sudden stretch of the gastronomies muscle . stimulates the hyper-sensitive muscle spindles. strong reflex muscle contraction [planter flexion]. Stimulates the Golgi tendon organs . Reflex relaxation of the muscle [dorsiflexion] & the cycle is repeated .

Lengthening Reaction i.e : Clasp knife effect(Pocket knife). It is finding characteristic of increased γ efferent discharge . It is the sequence of: Resistance followed by disappearance of resistance when limb is moved passively. passive extension of the elbow meets immediate resistance due to: stretch reflex in the biceps muscle Further stretch produce the inverse stretch reflex Disappear the resistance to extension suddenly. The arm extends quick easily . Moderate stretch of hypertonic muscle muscle contraction . Marked stretch of hypertonic muscle muscle relaxation . Motor function of the cerebellum & basal ganglia

Neural connections of basal ganglia Functionally important pathways: Connect the basal ganglia with each other & with other areas of the nervous system . [1] Cortical Connections: The basal ganglia are connected with the cerebral cortex through 2 main circuits a- The caudate circuit. b- The putamen circuit. a-The caudate circuit: Large proportion of nerve fibers arise from the cortical association areas[i.e: motor association area , somatic sensory association area , visual association area and Auditory area] . Integrate different types of motor & sensory information into thought .

Caudate nucleus internal globus pallidus . Thalamus . Prefrontal , promoter and area of cerebral cortex . planning the sequence of pattern of movement. b- The putamen circuit : Fiber originating from the premotor area Putmen Internal globus pallidus . Thalamus primary motor area . Putmen receives input mainly from movement area . Putmen sends output back to primary motor cortex. Fibers from cerebral cortex to thenceostriatum secrete acetyl choline[excitatory] . Pathways between the neostriatum and substantia Axon from neurons in the neostriatum (caudate & putamen) pass to substantia nigra secrete GABA . Fibers from substantia nigra pass to neostriatum & secrete dopamine[inhibitory]. [II] Efferent pathway from the basal ganglia: The globus pallidus[chief efferent]: Subthalamic nuclei & substantia nigra .

Reticular formation . Motor neurons of the spinal cord . Extra pyramidal tract . Normal function of the basal ganglia is maintain balance between the excitatory and inhibitory transmitters .

Chemical transmitter of basal ganglia

Inhibitory Dopamine - GABA	Excitatory Acetylcholine -Noradrenaline
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Functions of the basal ganglia The basal ganglia play a very important role in motor control . **(1)The caudate nucleus** , in association with the cerebral cortex : a- helps in planning sequences of patterns of movements to achieve a goal : Ex: when one is subjected to a danger. He responds immediately by turning away from it then begins to run . b- Modifying the timing of these patterns of movement i.e: [rapidly or slowly] . C- Modifying their spatial dimensions. Ex : one can write very small or very large letter . **(2)The putamen circuit :** Help the corticospinal system in subconscious learning patterns such as writing lletters of alphabet & cutting with scissors . **(3)Basal ganglia** responsible for initiation ®ulation of: The gross intentional movements of the body ex : swinging of the arms while walking and facial expressions. **(4)The globus pallidus responsible for :** The posture taken by the body to perform a voluntary movement i.e: it locks the different parts of the body into a specific position So as to facilitate



the fine movements of the hand. (5) **The basal ganglia is mainly inhibitory to the muscle tone** The manifestations of parkinsonism It is one of diseases of the basal ganglia in human. Due to: Degeneration of dopamine containing neurons in the Substantia nigra .

Mechanism of disease: -Imbalance between excitation and inhibition in basal ganglia -Created by the loss of dopaminergic inhibition of the putamen . Characters : (1)**Rigidity: Both flexor & extensor muscles are affected.** Types: a- Lead -pipe rigidity: continuous resistance to bending b- Cowheel Rigidity: there is a series of catches during passive movement . **Mechanism:** due to excess impulses transmitted along the cortico -spinal tract to both α & γ ACHs . (2) **Tremors: Static Tremors** . Rhythmic involuntary alternating contractions of the antagonistic muscles. **Characters:** Present at rest & disappears with activity . Occurs in the form of pill rolling movement at the hand. (3)**Akinesia:** It is the difficulty in initiating voluntary and spontaneous movements . **Characters: 1-Speech; monotonous** . 2-Loss of associated movements: ex: swinging of arms during walking . 3- Loss of facial expression (masks face).

Division of the cerebellum Anatomically : Cerebellum is divided into 3 areas with different function: **Structure & connections of the cerebellum** The cerebellum has a cortex of grey matter covering a mass of white matter . All afferent fibers to the cerebellum are consists of 3 layers : (1) A superficial molecular layer . (2) A middle layer of purkinje cells . (3) A deep granular layer . Afferent fibers coming to cerebellum synapse directly or indirectly with purkinje cells . Efferent impulses to the cerebral nuclei . i.e : dentate , interpositus & fastigial nuclei . Areas of the brain i.e : brain stem & thalamus . The cerebellum functions to coordinate motor activity initiated in the CNS .

Function of the cerebellum in voluntary movement [1] Servo-comparator function:

(a) The motor cortex, transmits a signal to a group of muscle to execute a particular movement . (b) The motor cortex also transmits the same information simultaneously to the intermediate zone of the cerebellum to inform the cerebellum about the order given from cortex to muscles . (c) As the muscles respond to cortical signals by contraction : Receptors such as muscle spindles Sends signals upward through spinocerebellar tract to cerebellum . The motor areas of cerebral cortex on one side are connected to the intermediate zone of the cerebellar hemisphere of the opposite by : A closed feedback circuit (Cortico-ponto -fastigial-thalamo -Cortical [2] **The braking effect of the cerebellum** After the muscles have begun to move.

The cerebellum: Assesses the rate of movement . Calculate the length of time needed to reach the intended point . Transmits inhibitory impulses to the motor cortex , to inhibit the agonist & excite the antagonist muscles . Thus , brakes are applied to stop the movements at the precise intended point . -Cerebellum must act to inhibit the motor cortex at the appropriate time at intended point . [3] Planning and timing function of the cerebellum **Cortical association areas (site for voluntary movement):** sends signals to the lateral zones of the cerebellum. The lateral zones plan movements . sends efferent signals to the motor area of the cerebral cortex . Corticospinal tract movement . The lateral cerebellum: plans for the next movement at the same time the present movement is occurring so , has the ability to progress smoothly from one movement to the next . The lateral cerebellum: provides appropriate timing for each movement . **Function of the cerebellum in equilibrium** The flocculonodular lobe plays an important role in equilibrium . The vestibular apparatus sends signals to the cerebellum Brain stem . Maintain equilibrium through changes in muscles tone Damage to the flocculonodular lobe lead to disturbance of equilibrium

Function of the cerebellum in muscle tone (A) The neocerebellum is facilitatory to the stretch reflex [muscle tone] Since its feedback time is longer than the simple spinal cord stretch reflex which helps further in the maintenance of posture .

B) The Paleocerebellum is inhibitory to the stretch reflex [muscle tone] . Posture and equilibrium (vestibular apparatus and the cerebellum) The Utricle & Sacculae (U & S) Within each membranous labyrinth: An otolith organ (macula): on the floor of the utricle (U) Another macula is located in the wall of the sacculae (S) **Function of the Utricle & sacculae:** [A] Maintenance of static equilibrium : (1) In the vertical position of the head: The impulses from the right and left utricles balance each other No sensation of mal equilibrium . (2) When head tilted in space : Calcium carbonate crystals in gelatinous material fall by their weight. Rate of discharge of impulses increases on that side but decreases on other side . Unbalanced discharge from the bases of hair cells . Sensation of mal equilibrium is created . Stimulate the equilibratory centers in the brain stem & cerebellum . stimulate the appropriate muscles to restore equilibrium **[B] Detection of linear acceleration** : * Linear acceleration means acceleration in a straight line. Types: 1-Horizontal : Sensed by utricle. 2-Vertical : Sensed by sacculae Structure of the macula Contains sustentacular cells and hair cells . Surrounded by an otolith membrane . Crystals of calcium carbonate , the otolith . - Embedded in the otolith membrane . -Range from 3 -19 μm in length in humans . Are denser than the endolymph . Nerve fiber from hair cells joins those from the cristae vestibule-cochlear nerve . Orientation of the maculae in the Utricle & Sacculae (U&S) Each macula has a group of hair cells oriented on its surface in all directions: So that different groups are stimulated with different positions of the head . The macula of the utricle lies in the horizontal plane :

The processes of hair cells pointing upwards . The macula of the sacculae , lies in vertical plane: The processes of the hair cells pointing laterally, allows them to operate only when the head is not in the vertical position. Ex :when one is lying down . **The Semicircular Canals (SCCs) The Structure of the SCCs** : On each side of the head . Perpendicular to each other so that they are oriented in the 3 planes of space . The membranous canals are suspended in perilymph . **The function of the SCCs:** Detection of head rotation or stoppage of head rotation in one direction or another . Detect early that a person is turning . Send impulses to the nervous system : Applies its control equilibratory corrective measures . Relative degree of contraction of individual antigravity muscles so , that the person does not start to fall before he begins to correct the situation. **The role of the SCCs in**



angular acceleration Rotational(angular) acceleration in the plane of a given SCCs . RMP of hair cell = -60 mv When Stereocilia are pushed towards kinocilium lead to open cation(K+& Ca++) channels depolarization Under resting condition :The SCCs on both sides transmit a continuous series of impulses about 200 impulses/sec .leads to balanced discharge gives the sensation of stability . During sudden rotation of head from left to right in horizontal plan : Endolymph by inertia flows to left deflection of both cupula . Right Rotation : cupula is bent towards utricle i.e: stereocilia are pushed towards kinocilium increase frequency of impulses in right rotation horizontal SCCs . Left rotation cupula is bent away from utricle decrease frequency of impulses .Result: persons has a true feeling of rotation to the right . With continuous of rotation with constant speed , the endolymph rotate at the same rate as the canal: the cupula swings back into upright position disappears of sensation of rotation . When rotation is stopped: The canal stop rotating , the endolymph continuous to move due to its momentum to the right[in the same direction of rotation] So , both cristae bend to the right . Thus left crista bend towards utricle depolarization. While right crista bend away from utricle hyperpolarization Thus the person feels a false sensation of rotation to the left **[Vertigo] After few seconds** : The endolymph stops moving , the cupula recoil to the resting position the false sensation of rotation (vertigo) disappears . **Methods of stimulation of the SCCs** (1)Rotational method : through rotating chain Stimulates 2 SCCs canals in 2 ears adjusted to lie on horizontal plane . (2)Caloric method : through washing ear by warm water (43o C) to produce convection current in endolymph . Stimulates one canal in one ear adjusted to lie on vertical plane . e.g: litting head 60o back wards orients the horizontal canal in vertical plane . (3)Electrical method : through vestibular nerve by galvanic current(2 -5 m.amp) . Stimulates all canals in one ear .

Effects of stimulation of the SCCs [1] Sensation of rotation : In the same direction of rotation . **[2] Nystagmus** : Definition: Jerky movements of eye observed at the beginning and at the end of rotation . Components : A- Slow component : opposite to direction of rotation . B-Fast component : in direction of rotation at beginning of rotation . Time : At the start and at the end of rotation . Aim : To fix objects in visual field during rotation . Types : Horizontal[when the head rotated horizontal]. Vertical [when the head rotated sideward] . Rotatory [when the head rotated forward] **Causes of nystagmus** :

Physiological nystagmus	Pathological nystagmus
1- With head rotation: (Vestibule- ocular reflex = VOR) -Initiated by SCCs impulses -Can occur in blind person . 2-Optokinetic nystagmus : -Initiated by visual impulses -e.g: When person looks from a window of a moving train .	1- Neocerebellar syndrome . 2- Menier’s disease . 3-Searching nystagmus : in defective vision .Focus image on healthy part of retina . 4- SCCs or Vestibular nerve pathway irritation or lesion .

[3] Vertigo : Definition: False sensation of rotation that a person feels when rotation is stopped . -The sensation is always in the opposite direction to that of original rotation . **Mechanism: Movement of endolymph** Causes : a- Stoppage of rotation . b- Irritation of SCCs by drugs ex: Streptomycin . c-Motion sickness ex : sea travel . d- Toxicity by alcohol . [4] Maintenance of balance [support the body] Increased muscle tone of the ipsilateral side & decreased on the opposite side **[5] Autonomic responses : Nausea , vomiting , pallor , hypotension and sweating** . Impulses from the SCCs[vestibular apparatus] autonomic centers in the brain stem . [6]Post rotatory reactions : past pointing test of Barany: After stoppage of rotation , Cortical voluntary movements of limbs & body compensatory to vertigo . It results in past pointing or even fall on opposite side . Physiology of the Limbic system: (Emotion, behavior), Reticular activating system and reticular formation

Limbic system consists of : a- A ring of cortex on the mediale side of each hemisphere : Surrounds the corpus callosum , called the allo-cortex. Compsed of:-The orbito-frontal area , subcallosal gyrus , cingulated gyrus , para-hippo cample gyrus & uncus . b- Subcortical nuclei of limbic system : include Hypothalamus , septum , para - olfactory area , thalamus , portions of the basal ganglia , the hippocampus & amygdale . **Functions of the limbic system** **1- Olfaction** : It has a role in analysis of olfactory signals . **2-Sexual behavior** : Sexual intercourse regulated by limbic system & hypothalamus . Modification of sexual functions and behaviors done by: higher cerebral functions& psychic factors . **3-Control of autonomic behavior** : Produces the autonomic changes that accompany emotional state . Ex: Changes in blood pressure , heart rate , and respiration .

4- Control of emotions :Fear and rage are closely related Phemenon . Are instinctive & protective against threats of the environment . A) Fear : [avoidance reaction] : occurs when the animal is threatened External manifestation : sweating , pupillary dilatation , tachycardia , dryness of the mouth & escape reaction. Produced by : (fear center) Stimulation of periventricular nuclei of hypothalamus & amygdaloidal nuclei **Disappear by** : Lesions of the amygdaloidal nuclei . B)Rage :[fighting reaction] occur when the animal threatened and cornered . The rage center present in the lateral hypothalamus & amygdala. -Is inhibited by the neocortex or ventromedial nucleus of the hypothalamus . So , lesion in the neocortex would produce rage in response to minor stimuli . **C)Placidity : opposite to rage** . Caused either by stimulation of the placidity area or destruction of the amygdala . **5- Motivation** : It is the force that activates a certain behavior to achieve a goal . - There are 2 areas for motivation : Rewarding



sensation: at medial band of tissue Punishment sensation :at lateral portion of posterior hypothalamus . The sensation are important in : a- Motivating our behavior to get reward or avoid punishment . b- The process of learning .c The reticular formation of the brain stem Is a large structure occupying the center of the brain stem . It consists of areas of diffuse neurons of 2 types: **1- Sensory neurons** -Are greater in number -make multiple connections within the reticular formation itself . **2- Motor neurons** -Are large in size.- Receive impulses from sensory neurons. **-Divided into:** A- The Pontine reticular system (facilitatory reticular formation) B- The medullary reticular syst.(Inhibitory reticular formation)

Reticular activating system(RAS) Control of the brain activity , consciousness & electric activity . It is composed of multi-synaptic pathway . Located within the reticular formation of the brain stem . Some of the branches of RAS pass directly to the cortex . Most of the branches of the RAS synapse in non- specific thalamic nuclei cortex .

Factors affecting the activity of the Reticular activating system(RAS)

A- Factors that increase RAS activity : The impulses from all sensory pathways : Pain & Proprioceptive stimuli are particularly effective & can arouse a person from sleep (2) Descending impulses from cerebral cortex have a strong excitatory effect on RAS : Emotions and voluntary movement help in keeping a person awake . (3)Epinephrine & Nor epinephrine from adrenal medulla produce alerting response .

B- Factors that decrease the Reticular activating system activity : Impulses from the sleep – producing centers of the reticular formation . (2) Lesions that damage the RAS ex :Vascular lesions , poisons , tumors & hypoxia . (3) Drugs ex: barbiturates as they cause hyper -polarization of the neurons .

physiology of the speech

Speech : It is the highest function of the nervous system . It involves: Understanding of spoken & printed words . The ability to express ideas in speech & written words .

Speech Centers : [1]The primary visual cortex in the occipital lobe (Area 17): Enable the person to see visual images .ex : written words

(2)The primary auditory cortex in the temporal lobe(Area 41 , 42): Enables the person to hear spoken words . **(3) The visual association area** (Area 18 , 19): Enables the person to understand and recognize the meaning of written words . **(4) The auditory association area** (Area 22): Enables the person to understand sounds or spoken words . **(5) General Interpretative area :** “ Wernicke’s area” Located in the superior temporal lobe . Located where somatic , visual & auditory association areas meet . It is much more highly developed in one cerebral hemisphere than the other . It has a great rote in the interpretation of auditory & visual information . It forms a thought that is expressed . Wernicke’s area project to: **(6) Hand skill area [Exner’s area]** Located in the premotor area . Form a coordinated program for hand movement . It projects to the primary motor area of the hand . **(7) Broca’s area [Area 44]** Located in the promotor area . Forms a coordinated program for vocalization . It projects to face area in primary motor cortex

Aphasia Are abnormalities of language functions . Due to injury of language centers in the cerebral cortex . It usually follows thrombosis or embolism of cerebral vessels .

Type	Defect	Area Damaged
(1)Auditory aphasia = word deafness	- Person is unable to uderstand spoken words	Auditory association area in superior temporal gyrus .
2)Visual aphasia = Word blindness	Person is unable to understand the written words .	Visual association area In Occipital Loop
3)Wernicke’s aphasia = Fluent aphasia .	-Unable to interpret the meaning of the spoken or written words or express thoughts into words .Talk is excessive & meaningless	Wernicke’s area
4)Broca’s aphasia = non fluent aphasia =	-Unable to produce words instead of noises	Broca’s area
Motor aphasia	The speech is poorly produced slowly with great effort [2 or 3 words]	Hand skill area
Motor apraxia = Agraphia .	Unable to express his thoughts by written words in absence of paralysis	
	Hand movements become uncoordinated & useless	



Dysarthria: This is a disorder of articulation resulting from lesions in the centers that control voluntary movement namely , cortical motor areas , cerebellum and basal ganglia or their nervous pathways . **Dysarthria causes :** 1- Parkinsonism: in which speech becomes slow and monotonous due to muscle rigidity . 2-Neocerebellar syndrome: which produces staccato speech .

Functions of the hypothalamus

The hypothalamus is an important center for the integration of : Visceral reflexes & maintain the constancy of internal environment . The hypothalamus receives afferents from: 1-Pre-olfactory area . 2- The limb lobe . 3- The amygdale . 4- The hippocampus . 5-The non-specific thalamic nuclei . 6-The globus pallidus 7- Collaterals from the sensory ascending tracts .

The hypothalamus sends efferents to : 1- Neurohypophysis . 2- The anterior thalamic nuclei . 3-The brain stem reticular formation .

Functions of the hypothalamus : [1] **Autonomic functions :** Stimulation of the anterior nuclei parasympathetic effects . Stimulation of the posterior dorsomedial & lateral nuclei sympathetic effects [2] **Behavioral function :** The hypothalamus is part of the limbic system . Concerned with the affective nature of sensation . Stimulation of certain areas pleases the animal Stimulation of other areas unpleasant response ex : terror , pain , fear and aversion. [3] **Defensive reaction :** As a component of the limbic system expression of rage & fear . [4]**Relation to cyclic phenomenon :** Adjusts bodily rhythms to the 24-hour light- dark cycle (circadian rhythm) [5] **Neuro-endocrine function :** a- **Control of posterior pituitary :** Along hypothalamic - hypophyseal tract . Control synthesis of ADH & Oxytocin . b- **Control of anterior pituitary :** Through releasing of at least 9 releasing hormones . Hypothalamo- hypophyseal portal circulation [6] **Food intake regulation :** This is regulated by a balance between two centers: a- The feeding center : in lateral hypothalamus (hunger) b- The satiety center : in ventromedial nucleus (anorexia) . [7] **Control of sexual function :** Hypothalamus Afferent anterior pituitary regulates sexual function . [8] **Wakefulness and sleep :** a- As part of the Reticular Activating System RAS, it initiates and maintains wakefulness . b- Stimulation of the anterior hypothalamus promotes sleep . [9]**Body water regulation :** Thirst center located in the supra-optic region of the hypothalamus Make the animal drink . [10] **Temperature regulation :** Posterior hypothalamus Reflex responses activated by the cold weather (Cutaneous VC & Shivering) . Anterior hypothalamus Heat-losing mechanism(Cutaneous vasodilatation , sweating) Rage :[fighting reaction] occur when the animal threatened and cornered . The rage center present in the lateral hypothalamus & amygdala. Is inhibited by the neocortex or Ventromedial nucleus of the hypothalamus So , lesion in the Neocortex would produce rage in response to minor stimuli . **Placidity : opposite to rage .** Caused either by stimulation of the placidity area or bilateral destruction of the amygdaloid nuclei .

PHYSIOLOGY OF SLEEP

Sleep : Is a state of loss of consciousness from which a person can be aroused by proper stimuli . Different stages can be identified from an EEG(electro – encephalogram) recording during sleep : [1] Alert wakefulness , characterized by high-frequency beta waves . [2] Quiet wakefulness : The person relaxed with eyes closed Associated with alpha waves . [3] This is followed by : a- **Slow-wave sleep(Non-Rapid Eye Movement[NREM]** Stage 1 : low voltage &high frequency beta waves . Stage 2 : Sleep spindles i.e. bursts of alpha like waves . Stage 3 : Lower frequency& increased amplitude of waves . Stage4 :Maximum slowing[lowest frequency] with large waves is seen . Thus during deep sleep:rhythmic slow waves , indicating marked synchronization . b- **Rapid Eye Movement Sleep(REM sleep)** Irregular low voltage ,high frequency waves which resembles to beta waves

Types of sleep

1- Occurrence	Non rapid eye movement [NREM] slow wave sleep	Rapid eye movement [REM] paradoxical sleep
2- Eye movement	Most [80%] of the sleep during night	Occurs in episodes of 5- 30 min
3-Talking & Walking	Eye deviate up . Present .	Recur every 90 min Occupies20% of sleep
4-Dreams .	It present , but are not remembered (Not consolidated in the memory)	Rapid eye movement Absent .
5-Threshold of waking	Low .	Dreams which are remembered .
6- Heart rate	Decreased	High , difficult to a
Respiratory rate , ABP & metabolic rate .	Hypotonia .	Waken .
7-Muscle tone 8 – EEG .	Theta + Delta with sleep spindles .	Increased Marked hypotonia . -Beta waves –Irregular fast ,low waves



Distribution of sleep stages A young adult first enters NREM sleep & spends in stages & spends in stages 3 & 4 70-100 min. Sleep then lightens & followed by REM sleep This cycle is repeated at intervals of 90 min. throughout the night .So , there are 4-6 REM period per night . The percentage of REM sleep[dreams] falls with long age .

Mechanisms of sleep (a)Genesis of slow –wave sleep[Non Rapid Eye Movement]: **[1]slow-wave sleep [Non REM]** : Can be produced by 3 subcortical regions 1- Diencephalic sleep zone in posterior hypothalamus . 2-Medullary synchronizing zone in reticular formation . 3- Basal forebrain sleep zone . **[2]Slow –wave sleep** is produced by decreasing serotonin & increasing adenosine and release of prostaglandin D2 in preoptic area of hypothalamus **[b] Genesis of REM sleep** The pontine reticular formation cholinergic discharge

REM sleep Sleep disorder : 1- Insomnia : Insufficient sleep that occur in adults due to psychological factors . Ex :anxiety or intake of analeptics e.g. coffee . **2- Somnambulism : [sleep walking]** More common in male children . The person walks with eyes opened , and avoid obstacle . When awakened can not remember what he did **3-Narcolepsy** : Irresistible sleep during daytime activities . Start s with sudden onset of REM sleep .

4- Sleep apnea : Caused by obstruction of the air ways during sleep . Effort to overcome the obstruction awakens the person from sleep .

5- REM behavior disorder : Hypotonia fails to occur . The patients with his condition act out their dreams . They even jump out of bed to do battle with imagined aggressors .

Cognitive function of the brain

Cognition is a term referring to the mental processes involved in gaining knowledge and comprehension, including thinking, knowing, remembering, judging and problem-solving. These are higher-level functions of the brain and encompass language, imagination, perception and planning.

Role of the Basal Ganglia for Cognitive Control of Sequences of Motor Patterns—

The Caudate Circuit The term cognition means the thinking processes of the brain, using both sensory input to the brain plus information already stored in memory. Most of our motor actions occur as a consequence of thoughts generated in the mind, a process called cognitive control of motor activity. The caudate nucleus plays a major role in this cognitive control of motor activity.

The neural connections between the caudate nucleus and the corticospinal motor control system, Part of the reason for this is that the caudate nucleus, extends into all lobes of the cerebrum, beginning anteriorly in the frontal lobes, then passing posterior through the parietal and occipital lobes, and finally curving forward again like the letter “C” into the temporal lobes. Furthermore, the caudate nucleus receives large amounts of its input from the association areas of the cerebral cortex overlying the caudate nucleus, mainly areas that also integrate the different types of sensory and motor information into usable thought patterns.

Thoughts, Consciousness, and Memory Our most difficult problem in discussing consciousness, thoughts, memory, and learning is that we do not know the neural mechanisms of a thought and we know little about the mechanisms of memory. We know that destruction of large portions of the cerebral cortex does not prevent a person from having thoughts, but it does reduce the depth of the thoughts and also the degree of awareness of the surroundings. Each thought certainly involves simultaneous signals in many portions of the cerebral cortex, thalamus, limbic system, and reticular formation of the brain stem. Some crude thoughts probably depend almost entirely on lower centers; the thought of pain is probably a good example because electrical stimulation of the human cortex seldom elicits anything more than mild pain, whereas stimulation of certain areas of the hypothalamus, amygdala, and mesencephalon can cause excruciating pain. Conversely, a type of thought pattern that does require large involvement of the cerebral cortex is that of vision, because loss of the visual cortex causes complete inability to perceive visual form or color. We might formulate a provisional definition of a thought in terms of neural activity. Thought results from a “pattern” of stimulation of many parts of the nervous system at the same time, probably involving most importantly the cerebral cortex, thalamus, limbic system, and upper reticular formation of the brain stem. **This is called the holistic**

theory of thoughts. The stimulated areas of the limbic system, thalamus, and reticular formation are believed to determine the general nature of the thought, giving it such qualities as pleasure, displeasure, pain, comfort, crude modalities of sensation, localization to gross areas of the body, and other general characteristics. However, specific stimulated areas of the cerebral cortex determine discrete characteristics of the thought, such as (1) specific localization of sensations on the surface of the body and of objects in the fields of vision, (2) the feeling of the texture of silk, (3) visual recognition of the rectangular pattern of a concrete block wall, and (4) other individual characteristics that enter into one’s overall awareness of a particular instant. Consciousness can perhaps be described as our continuing stream of awareness of either our surroundings or our sequential thoughts.



How did you find that? Did you navigate your rooms one by one? Represent images of your rooms and house, and visit each one, as in a computer game?

visual imagery. Experiencing a sensory impression in the absence of sensory input. What is imagery for? In a memory test, visualizing images of words help remember more accurately. Many top athletes use visual imagery to enhance their athletic performance. People use imagery to solve problems. Einstein developed the theory of relativity by imagining himself traveling beside a beam of light. Good mathematicians are good at visualizing math problems.

Imagery and Perception

Perception You get physical input. And your neurons are responding to it.

Imagery You don't have physical input, but your neurons are responding to it. **Do they share the same mechanism? How are they related? Can you form imagery of** Red apple, green apple, yellow apple, Blue apple, orange apple, purple apple **Can you form imagery of a zebra? Can you see stripes in your zebra? Can you count how many stripes the zebra has?**

Imagery debate How do we create mental images? Analogue Mental images and perceptual images both involve spatial analogs of the stimulus. Propositional Mental images are created by the same mechanism that creates language (propositional mechanism) The spatial experience of mental images are an "epiphenomenon".

Analog Hypothesis Mental images are internal representations that operate in a way that is analogous to the functioning of the perception of physical objects. Coglab Mental rotation Example: Want to compare whether or not the two figures are the same. How do you make a judgment?

Cognitions & Trauma Cognitions refers to any conscious thought, belief, value, idea, image, attitude in the person's mind Hindsight Bias (Brewin, 2003) Assumptive World Views (Janoff-Bulman 1989) Key Thoughts at moment of danger Attribution Theory (Heider, 1958) Heuristic Biases (Kahneman & Tversky, 1974)

The state or condition of being conscious. A sense of one's personal or collective identity, including the attitudes, beliefs, and sensitivities held by or considered characteristic of an individual or group: Love of freedom runs deep in the national consciousness. Special awareness or sensitivity: class consciousness; race consciousness. Alertness to or concern for a particular issue or situation: a movement aimed at raising the general public's consciousness of social injustice.

In psychoanalysis, the conscious. Two major themes that govern the nature and organization of memory in the brain: (1) Memory is a fundamental property of brain, and its storage is intimately tied to ongoing information processing in the brain; (2) Memory is manifested in multiple ways by multiple, functionally, and anatomically distinct brain systems. What parts of the brain burn glucose most intensely when someone reads?

Broadly speaking, one system recognizes patterns, one generates patterns, and the third determines priorities. All three systems are crucial to reading and to learning to read. A brief description of how they work will provide the scientific grounding we need to understand how technology can help teachers teach reading and students learn to read.

Memory processes and Learning theory

Learning and memory

It is the ability to alter behavior on the basis of experience. Learning is the acquisition of the information that makes this possible. Memory is the retention and storage of the information. Learning and memory are closely related and should be considered together.

Memory is divided into : (1) Explicit memory . (2) Implicit memory . (1) Explicit memory : declarative or recognition memory. It is associated with consciousness . Dependent on the hippocampus & medial lobes of the brain . It is divided into: **a- Episodic memory: memory for events . b- Semantic memory: memory for words & language** (2) Implicit memory : non-declarative memory or reflexive memory . Does not involve awareness . Its retention does not involve processing in the hippocampus . It includes skills , habits & conditioned reflexes once acquired become unconscious & automatic . Includes priming = facilitation of recognition of words or objects by prior exposure . An example: improved recall of a word when presented with the first few letters of it .



Implicit memory can be divided into : (a) Non –associative learning : The person learns about a single stimulus , by either habituation or sensitization . 1-Habituation : Is a simple form of learning . Repeated stimulus decrease response Caused by :inactivation of Ca⁺⁺channels in pre- synaptic neurones . 2- Sensitization : Is in sense , the opposite reaction . Repeated stimulus increase response . [If it is coupled one or more time with pleasant or unpleasant stimulus] - The mother who sleeps through many kinds of noise wakes when her baby cries .

(b)Associative learning: The person learns about the relation of one stimulus to another . This includes classic conditioning and operant conditioning .

1- Conditioned reflexes: A conditioned reflex is a reflex response to a stimulus ex: bell-ringing beside a dog . Previously elicited no response . Repeatedly pairing the stimulus with another stimulus [that normally produce the response] (Unconditioned stimulus ex : placing a meat in the dog's mouth) **Pavlov's proved that** : If this is repeated many times : The dog would salivate when the bell was rung.[even though no meat was placed in its mouth] . -Most somatic , visceral& other neural changes occur as conditioned reflex responses .

2-Operant conditioning : The animal is taught to perform some task (operate on the environment) To obtain a reward or avoid punishment . The Unconditioned stimulus is the pleasant or unpleasant event . The Conditioned stimulus is a light or some other signal that alerts the animal to perform the task . Explicit memory & many forms of implicit memory involve :

Consolidation of memory It is the process that encodes the memory & makes it remarkably resistant to erasing . Before it ,memory can be erased easily . Following it ,there is a stable resisting memory engrains . Involves the hippocampus & its connections .

Centers for memory encoding and storage :

(1)Implicit memory : Encoded in the stratum of the basal ganglia & cerebellar folliculus . **(2)Explicit memory** : Short term memory is encoded in the hippocampus . Emotional aspect of long term memories are stored in neocortex & amygdaloid .

Types of Amnesia

Amnesia means loss of memory : can occur following injuries .

(1)Retrograde amnesia : inability to remember events happened before the injury .

(2) Ante grade amnesia : inability to store the memory events happened after the injury .

Alzheimer's disease Progressive loss of short term memory followed by loss of cognitive and other brain functions . Cause : Degeneration of the hippocampal neurons

Skin and Immunity

The skin is the largest organ in the body and has surface area of about 1.5 - 2 m². It includes glands , hair and nails. It consists of 2 layers : the epidermis and the dermis . The epidermis is the most superficial layer of the skin and is composed of stratified keratinised squamous epithelium, which varies in thickness in different parts of the body . The dermis is tough and elastic .It is formed from connective tissue and the matrix contains collagen fibers & elastic fibers. - Fibroblasts ,macrophages and mast cells are the main cells found in the dermis

The skin has three main functions: protection, regulation and sensation.. The skin is an organ of protection. The primary function of the skin is to act as a barrier. The skin provides protection from: mechanical impacts and pressure, variations in temperature, micro-organisms, radiation and chemicals. The skin is an organ of regulation. The skin regulates several aspects of physiology, including: body temperature via sweat and hair, and changes in peripheral circulation and fluid balance via sweat. It also acts as a reservoir for the synthesis of Vitamin D. The skin is an organ of sensation. The skin contains an extensive network of nerve cells that detect and relay changes in the environment. There are separate receptors for heat, cold, touch, and pain.

Immunity

Immunity can be either natural or artificial, innate or acquired=adaptive, and either active or passive. **Active natural (contact with infection):** develops slowly, is long term, and antigen specific. **Active artificial (immunization):** develops slowly, lasts for several years, and is specific to the antigen for which the immunization was given. **Passive natural (transplacental = mother to child):** develops immediately, is temporary, and affects all antigens to which the mother has immunity. **Passive artificial (injection of gamma globulin):** develops immediately, is temporary, and affects all antigens to which the donor has immunity.



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