BLOOD

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ESSAYS

* 1. Anemia

Anemia is a clinical condition characterized by reduction in no. of RBC or their hemoglobin content below the lower limit of normal range for age and sex of individual.

i.e.; below 14 g/dl for man
below 12g/dl for woman

Grading: Mild anemia Hb 8-12g/dl
Moderate anemia Hb 5-8g/dl
Severe anemia Hb <5g/dl

Classification

Morphological/Wintrobe's Classification

Based on MCV & MCHC

A. Normocytic normochromic anemia
MCV normal, MCHC normal
E.g. Acute post hemorrhagic anemia
Aplastic anemia
Hemolytic anemia

B. Microcytic hypochromic anemia
MCV reduced, MCHC reduced
E.g. Chronic post hemorrhagic anemia
Iron deficiency anemia
Sideroblastic anemia
Thalassemia

C. Macrocytic normochromic anemia
MCV increased, MCHC normal
E.g. Megaloblastic anemia

Etiological/Whitby's Classification

A. Due to increased blood loss
Acute post hemorrhagic anemia
Chronic post hemorrhagic anemia

B. Due to impaired RBC production
a.cytoplasmic maturation defect
E.g:IDA, Thalassemia
b.Nuclear maturation defect
E.g:Megaloblastic anemia
c.Defect in stem cell proliferation and maturation
E.g:Aplastic anemia
d.Bone marrow Infiltration
Eg.:Leukemia,Multiple myeloma
e.Congenital anemia
E.g:Sideroblastic anemia

C. Due to increased RBC distruction
E.g:Hemolytic anemia

Pathophysiology of anemia

Subnormal level of Hb causes lowered O_2 carrying capacity of blood. This in turn initiates compensatory physiological adaptations such as increased release of O_2 from Hb, increased blood flow to tissues, maintenance of blood volume, and redistribution of blood flow to maintain cerebral blood supply. Tissues with high O_2 requirement such as heart, CNS & skeletal muscle during exercise are affected more by anemia.

Effect of anemia on functioning of circulatory system

In anemia, as RBC count decreases, viscosity of blood decreases. This decreases the resistance to blood flow in the peripheral blood vessels so that greater quantities of blood flows through tissues and return to heart, thereby increasing cardiac output. Moreover, hypoxia resulting from diminished transport of O_2 by blood causes peripheral tissue blood vessels to dilate allowing increased return of blood to heart & increased cardiac output to a still higher level. Thus one of the major effects of anemia is greatly increased cardiac output as well as increased pumping work load on heart.

The increased cardiac output partially compensates for the reduced O_2 carrying effect of anemia by increasing the blood flow to tissues. However, when a person with anemia begins to exercise, the heart is not capable of pumping much greater quantities of blood as at rest. Therefore during exercise, which greatly increases the tissue demand for O_2, extreme tissue hypoxia results and acute cardiac failure ensures.

General clinical features

- Generalized weakness, tenderness & fatiguability
- Pallor of skin & mucous membrane
- Respiratory symptoms like breathlessness
- CVS manifestations like palpitation, tachycardia & cardiac murmurs
- CNS features due to cerebral hypoxia like lethargy, headache, tinnitus, confusion
- Ocular manifestations like visual disturbance, retinal hemorrhage
- Gastrointestinal symptoms like anorexia, nausea,constipation
- Reproductive system-menstrual disturbances like amenorrhoea, menorrhagia in females
- Renal system involvement
- BMR increases in severe anemia

Iron deficiency anemia

It is the commonest nutritional deficiency disorder present throughout the world. In India, iron deficiency is the commonest cause of anemia

Causes:

- Inadequate dietary intake of iron
- Increased loss of iron
- Increased demand of iron
- Decreased absorption of iron

Clinical features:

- General features of anemia
- Characteristic features of anemia
  - Nail- spoon shaped

- Tongue- becomes angry red (atrophic glossitis)
- Mouth- angular stomatitis
- Esophagus- may develop thin membranous webs at post cricoid area leading to dysphagia (Plummer-Wilson syndrome)

Lab findings:

1. Blood picture & red cell indices
   - Hb concentration is decreased
   - RBCs are microcytic & hypochromic. Also show anisocytosis & poikilocytosis
   - MCV, MCH & MCHC are reduced
2. Bone marrow findings
   - Hyper cellular
   - Erythroid Hyperplasia
3. Biochemical findings
   - Serum iron decreased
   - Serum ferritin decreased
   - Total iron binding capacity increased

Treatment:

- Oral administration of Fe^{2+} salts.
- Correct the cause
- Prognosis by reticuloyte count

Megaloblastic anemia

It is c,haracterized by abnormally large cells of erythropoietic series. These are caused by defective DNA synthesis due to deficiency of vit.B_{12} or folic acid.

Megaloblastic anemia due to vitamin B_{12} deficiency

Causes:

1. Inadequate dietary intake
2. Poor absorption of vit.B_{12} from gastrointestinal tract due to lack of intrinsic factor – Pernicious anemia

A common cause of blood cell maturation failure is failure to absorb vitamin B_{12} from GIT. This often occurs in disease Pernicious anemia. Here the basic abnormality is an atrophic gastric mucosa that fails to produce normal gastric secretions. The parietal cells of gastric glands secrete a glycoprotein called intrinsic factor which combines with vit.B_{12} in food and makes vit.B_{12} available for absorption by gut.

Lack of intrinsic factor causes diminished availability of vit.B_{12} because of faulty absorption of vit.B_{12}. Pernicious anemia is an autoimmune disease & in about 50% patients, antibodies to intrinsic factor can be demonstrated.

Megaloblastic anemia due to folic acid deficiency

Causes:

1. Inadequate dietary intake
2. Malabsorption.
3. Excess urinary folate loss – liver disease
4. Drugs- Phenytoin, Contraceptive pills

Clinical features of megaloblastic anemia

1. Blood picture and blood indices
   - Hb level low
   - RBC – macrocytic, normochromic
   - MCV & MCH increased; MCHC normal
   - Peripheral smear – nucleated RBC with anisocytosis & poikilocytosis
   - Multilobular neutrophils are present in the peripheral smear
   - Lifespan of RBC decreased
2. Bone marrow picture
   - Hyper cellular
   - Megaloblastic cell with abnormal mitosis
3. Biochemical findings
   - Serum bilirubin increases due to excessive destruction of RBC
   - Serum iron & ferritin is increased as iron is not utilized by immature RBC

Treatment

Administration of Vit.B_{12} & folic acid
Hydroxy cobalamine as IM injection

Hemolytic anemia

Anemia resulting from an increase in rate of RBC destruction.RBC lifespan decreases in hemolytic anemia.

2 Types

1.Acquired (extra corpuscular)
Causes:Antibody mediated,Hypersplenism
2.Heriditary (Intra corpuscular)
Heriditary Spherocytosis,G6PD Deficiency

General features

- General features of anemia
- Mild jaundice due to unconjugated hyperbilirubinemia
- Dark colored urine due to excess urobilinogen
- Splenomegaly
- Gall stones

Lab investigations

1. Tests for increased RBC destruction
   - Serum unconjugated bilirubin is increased
   - Urine urobilinogen increased
   - Fecal stercobilinogen increased
2. Tests for increased RBC production
   - Reticulocyte count increases
   - Bone marrow shows erythroid hyperplasia with increased iron stores
   - X-ray of bones show expansion of marrow space especially in skull & long bones
3. Tests for damage to red cells
   - Blood film – microspherocytosis & fragmented RBC
   - Osmotic fragility increased
   - Electrophoresis for abnormal Hb
   - Tests for sickling
   - Screening tests for G6PD deficiency

Treatment

Treat the cause

Aplastic anemia

It is defined as pancytopenia i.e., simultaneous presence of anemia, leucopenia & thrombocytopenia

resulting from aplasia of bone marrow. The underlying defects in all cases appear to be sufficient decrease in number of hemopoetic stem cells which make them unable to divide and differentiate.

Causes

A. Primary aplastic anemia
   1. Congenital - Fanconi's anemia
   2. Acquired - Immunologically mediated
B. Secondary aplastic anemia
   1. Drugs – antimetabolites, mitotic inhibitors
   2. Toxic chemicals such as benzene derivatives, insecticides
   3. Infections – infectious hepatitis, AIDS
   4. Miscellaneous – associated with SLE, X-rays

Clinical features

1. General features of anemia
2. Hemorrhage from various site due to thrombocytopenia such as from nose, skin, gums etc.
3. Increased susceptibility to infections.

Lab findings

1. Anemia – Hb decreases, normocytic normochromic anemia
2. Leucopenia – absolute granulocyte count decreases with relative lymphocytosis
3. Thrombocytopenia
4. Bone marrow aspiration – severe depression of myeloid cells, erythroid cells & megakaryocytes

Treatment

1. Treat the cause
2. Supportive blood transfusion
3. Marrow stimulating agent
4. Bone marrow transplantation

2. Erythropoiesis:

It refers to the production of RBCs. It is a part of hemopoeisis, the production of blood cells.

Site of Erythropoiesis:

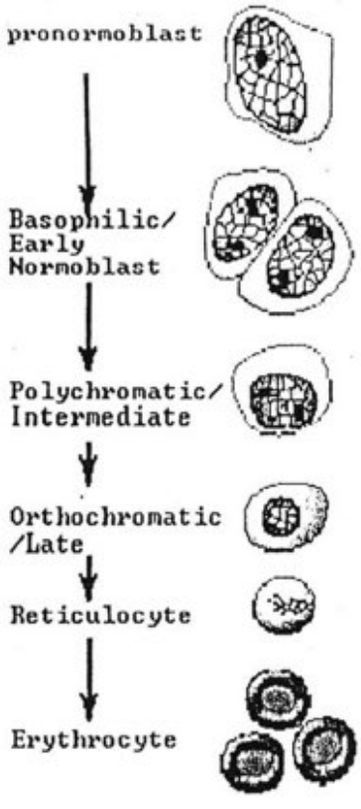
Primitive blood cells appear in the third week of embryonic life.From third weeek upto third month erytropoiesis occurs in mesoderm of yolk sac.This is known as Meroblastic stage.This is the only stage in life where this process occurs in blood vessels. During the middle trimester erythropoiesis mainly takes place in liver, but considerable production also takes place in lymph nodes and spleen. This is Hepatic stage. From the fifth month onwards it mainly takes place in the bone marrow and this stage is known as myeloid or medullary stage. In the adults only lymphocytes are produced from lymphoid organs like spleen, lymph gland and thymus. RBCs are produced only from bone marrow. Only when bone marrow is restricted due to any disease, extramedullary erythropoiesis takes place from spleen, thymus and lymphoid tissue. Bone marrow produces RBCs until a person is 5 yrs old. Except the proximal portions of femur and humerus, the marrow of long bones become fatty and stop the production of cells after an age of 20 yrs. Beyond this stage the cells are produced from the marrow of membranous bones like vertebrae, sternum, ribs and ileum. Even in these bones,marrow becomes less productive as age increases.

Genesis of Blood cells:

Blood cells begin their life as a single type of cell in the bone marrow called pleuripotent hematopoietic stem cell(PHSC).PHSC possess two fundamental properties, Self renewal and Differentiation.

Daughter cells formed from PHSC cannot produce all type of cells.They become commited to a particular cell line.These cells are called Commited stem cells(CSC).One type of CSC give rise to cells of myeloid series(RBC,Granulocyte,Monocyte and Platelet).Another type of CSC give rise to lymphoid series(T&B lymphocytes)The committed stem cell then form colonies of progenitor cells called colony forming units. It is found that these units go to form erythrocytes(CFU-E), neutrophils and granulocytes(CFU-GM), monocytes, eosinophils and basophils.

Stages of Erythropoiesis:



The erythropoietic stem cell first forms the proerythroblast which is the first recognizable RBC. Then it passes through different stages to form the mature cell. The cells undergo division and maturation to form the late normoblast. Hb is acquired in the intermediate normoblast.

1. Pronormoblast :
   - Cell size is large(15-20μm)
   - Cytoplasm is basophilic due to RNA
   - Nucleus with nucleoli
   - Chromatin forms fine stippled reticulum
   - No Hb is present
   - Mitosis is present
2. Early/Basophilic normoblast
   - Cell is smaller(14-16μm)
   - Cytoplasm is basophilic
   - Nucleoli disappeared
   - Fine chromatin network seen
   - No Hb
   - Active mitosis is seen
3. Intermediate/Polychromatic normoblast
   - Cell is smaller(10–14μm)
   - Cytoplasm polychromatic with basophilic RNA and acidophilic Hb
   - Hb begins to appear
   - Mitosis still present
   - Fine chromatin network seen
4. Late/Orthochromatic normoblast
   - Cell size is again reduced(8–12μm)
   - Cytoplasm acidophilic with diffuse basophilic hue
   - Mitosis absent
   - Hb increase in amount
   - Nucleus pyknotic , small with few chromatin and is dark
   - Last stage in which nucleus is present
5. Reticulocyte
   - Premature cells of erythroid series
   - Size slightly greater than erythrocyte
   - Juvenile RBC devoid of nucleus
   - Still contain some RNA so they are still able to synhesise Hb
   - They are acidophilic with slight basophilic hue due to fine reticulum of RNA
   - About 1% of the total RBCs are reticulocytes.
6. Erythrocyte
   - The mature RBC
   - Biconcave disc shaped
   - Size 7.5μm

Regulation & Factors involving erythropoiesis:

1. Hematopoietic growth factor-erythropoietin:
2. Growth factors
3. Maturation factors
4. Minerals
5. Vitamins
6. Hormones
7. Proteins

• Erythropoeietin

Tissue oxygenation is the most essential regulator of RBC production.Tissue hypoxia due to any cause will try to increase the production of a hormone called erythropoietin.It is a glycoprotein with a mol wt of about 34000.It is the major regulator of erythropoiesis. In the absence of erythropoietin hypoxia has little effect in stimulating RBC production.In adults about 85% of erythropoietin comes from kidney and 15% from liver. Erythropoietin is produced by interstitial cells of peritubular capillary bed of kidney and perivenous hepatocytes of liver. It is also produced in brain where it exerts a protective effect against excitotoxic damage triggered by hypoxia. It is also produced in uterus and fallopian tube where it is introduced by oestrogen and appears to mediate oestrogen-dependant angiogenesis.The actions of erythropoietin are,

-Stimulate the production of pronormoblast from hemopoeitic stem cells on bone marrow.

-Stimulate synthesis of Hb in devoloping RBC

-Causes the cells to pass through different stages more rapidly and hence speeds the production of RBCs.

The production continues till the person is relieved of hypoxia or enough RBCs are produced to carry enough amount of oxygen from lungs to tissues. Recent evidences suggest that the oxygen sensor is a heme protein that in deoxy form activates and in oxy form deactivates the transcription of erythropoietin gene to mRNA. The secretion is also stimulated by cobalt and androgens,TSH and thyroid H,small doses of cortisol and ACTH, epinephrine, NE and prostaglandins.

• Growth factors

- The proliferation and self renewal of pleuripotent stem cells depend on the stem cell factor
- GM-CSF(Granulocyte Monocyte Colony Stimulating Factor)
- IL1 and IL6 followed by IL5 act in a sequence to convert pleuripotent stem cells to committed stem cells.
- The genes for all these are located in the long arm of chr 5 together. The loss of one factor can be compensated for the other.

• Maturation factors:

Vitamin B_{12} and folic acid.

Both these are required for the synthesis of DNA since both in different ways are essential for the synthesis of thymidine tri phosphate, a building block of DNA. Therefore the deficiency of either of these will lead to abnormal and diminished and consequeontly failure of nuclear maturation and cell division.

• Minerals

Mainly Iron and traces of Cu,Mn,Ni,Zn and Co are necessary for erythropoiesis.

• Vitamins

-Vit C

Required for the absorption of Fe from GIT .

Scurvy is associated with hypochromic and normocytic anemia.

-Vit B6

Pyridoxine is essential for the synthesis of heme.

-Riboflavin deficiency leads to hypoplasia of bone marrow and normocytic normochrom

•Hormones:

– Testosterone causes red cell proliferation in the bone marrow and hence RBC count is higher in males.

- In hypo function of adrenal, pituitary and thyroid gland, there is mild to moderate anemia usually normochromic type. Endocrine disorder treated with apparent hormone, anemia is prevented.

3. Steps of hemostasis :

Haemostasis: The process of forming clots in the walls of damaged blood vessels and maintaining blood in the fluid state within the vascular system and preventing blood loss.

Steps

- Vasoconstriction
- Formation of platelet plug
- Formation of definitive clot
- Clot retraction
- Clot lysis after repair

•**Vasoconstriction:**

Immediately after injury, the blood vessel constricts inorder to stop the bleeding.It is due to,

- The constriction results from local myogenic spasm initiated by direct damage to blood vessel and degree of spasm is directly proportional to the degree of trauma to the blood vessel.
- Neuronal reflexes initiated by pain nerve impulses or other sensory impulses that originate from traumatized or nearby tissue.
- Local autacoid factors are released from the traumatized tissue to blood. The initial vasoconstriction is transient but it is maintained for several minutes by humoral facilitation in activated platelets. The activated platelets release powerful vasoconstrictors serotonin, thromboxane A2, epinephrine and nor-epinephrine.

•**Formation of platelet plug:**

It is the plugging of platelets at the site of injury.

- Platelet adhesion:

The platelet adhere to subendothelial collagen which is exposed whenever the vascular endothelium is constricted. It requires Von Willebrand factor(VWF), which is a protein synthesized from vascular endothelium secreted both into the plasma and subendothelium.Receptors for platelets to VWF is Glycoprotein 1b(Gp 1b) receptors. The unstimulated platelets on binding with VWF are linked to the subendothelium.Platelets also adhere to subendothelial collagen directly through Gp1a.

•Platelet activation and secretion :

Platelet binding to exposed collagen leads to its activation.A lot of changes occurs during activation.It changes its shape and become spherical,throws pseudopodia and discharge their granules.Surface expression of phospholipids also occurs.Agonist activates G protein in the platelet which inturn activates phospholipase C and phospholipase A2 which releases arachidonic acid from platelet phospholipids.The arachidonic acid then converted in to endoperoxide by cyclooxygenase.Endoperoxide then dissociates in to thromboxane A2 and prostacyclin by the enzymes thromboxane synthase and prostacyclin synthase respectively.Thromboxane A2 is a vasoconstrictor and prostacyclin is a vasodialator.An increase in the thrombin and agonist like ADP and arachidonic oxidation products maintain and amplify activation.As this progresses contraction in the pletelet cytoskeleton presses them together and appears to fuse.

• Platelet aggregation:

Platelet aggregation is defined as the attachmend of activated platelets to one another.The released ADP and thromboxane A2 activates nearby platlets and ADP activates fibrinogen receptors to cause further accumulation. Fibrinogen and thrombospondin from α granules bind to their receptors on 2 opposing activated platelets and cause their aggregation.Platelet activating factor and thromboxane A2 promotes aggregation while prostacyclin inhibits it and keeps the plug localized and prevents the intravascular spread of clot.The damaged vessel wall gets activated.More and more platelets get attracted and forms the plug. They set forth a small plug worth preventing the loss of blood if the vascular opening is small.During the subsequent coagulation fibrin threads are formed and these attach tightly to the platelets and form a definitive clot.

•**Formation of definitive clot**

It includes,

- Formation of prothrombin activator(complex of activated factor Va,Xa,PL,Ca) by intrinsic and extrinsic pathways.
- Conversion of prothrombin to thrombin by prothrombin activator.
- Conversion of soluble fibrinogen to insoluble fibrin by thrombin.

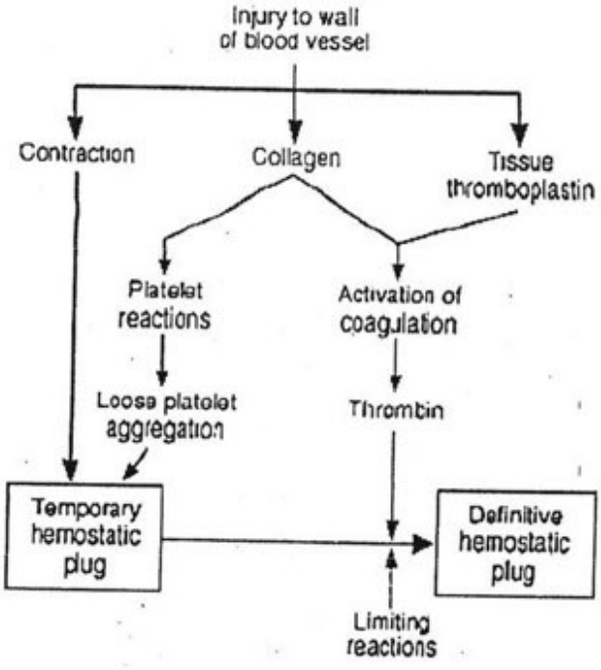
step 1: formation of prothrombin activator

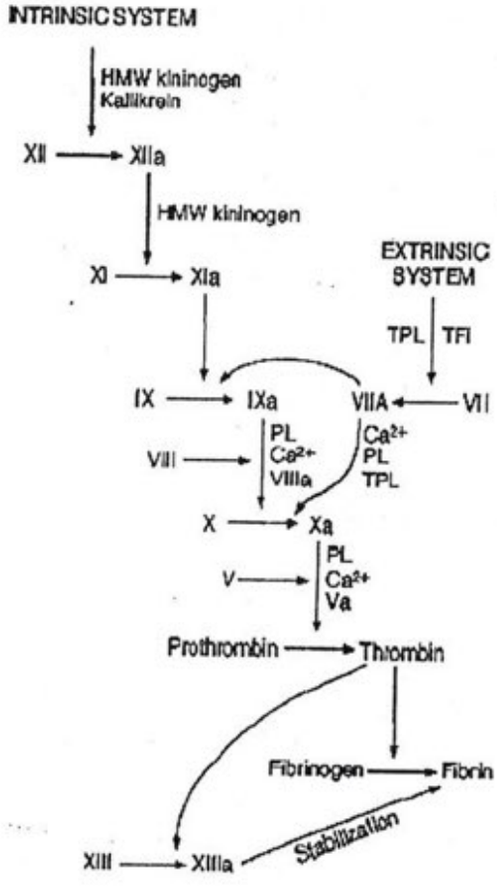
It is formed by intrinsic and extrinsic pathways.it requires clotting factors.They are designated by roman numerals.Synthesised mainly in liver and thereby decreases in liver diseases.Once activated they are transformed to enzyme which activates other factors.Thus they first act as a substrate and then an enzyme.they are,

I	Fibrinogen
II	Prothrombin
III	Tissue Thromboplastin
IV	Calcium
V	Proaccelerin, Labile factor, Accelerator globulin
VI	It is not a separate entity and has been dropped.

VII	Proconvertin, Stable Factor, SPCA(Serum Prothrombin conversion accelerator)
VIII	Anti-haemophilic factor A, Antihaemophilic Globulin
IX	Antihaemophilic Factor B, Christmas Factor
X	Stuart-Prower Factor
XI	Plasma Thromboplastin Anticedant, Anti-haemophilic Factor C
XII	Hagemann's Factor, Glass Factor
XIII	Fibrin Stabilizing Factor, Laki-Lorand Factor
HMW-K	High Molecular Weight Kininogen, Fitz-Gerald Factor
Pre-Ka	Pre-Kallikrein, Fletcher Factor
PL	Phospholipid

In spite of the presence of all clotting factors in blood, the blood does not clot spontaneously unless a vessel wall has been injured. This is due to the fact that all the factors are present in an inactive form and Prothrombin Activator is absent from blood. Moreover blood contains small amounts of naturally occurring anti-coagulants. Prothrombin Activator is formed by a cascade of reactions in which the activation of one factor leads to the activation of the next. The sequence of changes can occur in 2 pathways i.e. Extrinsic and Intrinsic Pathways, ultimately leading to the generation of Prothrombin Activator. These two pathways ultimately converge to form a common pathway which leads to Fibrin formation. Both begin when a blood vessel is injured and bleeding has occurred.





Extrinsic pathway

Takes place invivo. It is activated when tissue factors(Tissue thromboplastin) present in the cell membrane are exposed by cellular injury. Tissue Thromboplastin is an acellular lipoprotein exposed at the site of tissue injury. Released TPL converts factor VII toVIIa(activated). VIIa in presence of calcium, PL, and TPL converts factor X to Xa and factor IX to IXa. Factor IX and X are activated both during intrinsic and extrinsic mechanisms. Whenever more Xa is formed tissue factor inhibitor inhibit VIIaand TPL.

Intrinsic pathway

Both in vivo and vitro.

In vivo : Exposure to subendothelial collagen

In vitro : Electrical discharge and exposure to wettable surfaces like glass or collagen fibers.

The initiating factor of this mechanism is factor X. Factor XII form a complex with HWK and Pre-K on vascular subendothelial collagen.

- The first reaction is the activation of factor XII to XIIa by Ka and HMW K. XIIa in turn activates factor XI to XIa and pre Ka to Ka.

- Factor XIa in the presence of Calcium activates Factor IX to IXa

- Factor IXa forms a complex with Factor VIIa(which is activated when separated from VWF). This complex activates Factor X. Phospholipid from aggregated platelets and Calcium are necessary for full activation of Factor X.

- Phospholipid, Calcium, Factor Va and Factor Xa together form Prothrombin Activator which converts Prothrombin to Thrombin

Intrinsic Pathway	Extrinsic Pathway
Occurs in vivo and invitro	In vivo only
Activated by contact with sub-endothelial collagen	By release of Tissue Thromboplasin
Requires Factors XII, XI, IX, VIII, Ka and HMWK	Requires Tissue Thrombo-plastin and Factor VII
Slower-requires 1 to 6 minutes	Fast and explosive in severe trauma and occurs in 15 seconds

Step2: Formation of Thrombin

Prothrombin ⟶ Thrombin

Prothrombin activators converts prothrombin to thrombin.Prothrombin Activator acts as a proteolytic enzyme and splits prothrombin to Thrombin.prothrombin is a plasma protein formed in liver.Vitamin K is required for its synthesis.When Thrombin is formed the process of clot formation is accelerated. It activates several clotting factors.

Step 3: Formation of Fibrin

Fibrinogen is a soluble high molecular weight plasma protein synthesized in liver.Thrombin removes 4 polypeptides from each molecule of Fibrinogen to form fibrin monomer which polymerise with other monomer to form long fibrin fibreswithin seconds.Fibrin is initially a loose mesh of interlacing strands.In the presence of Calcium and Factor XIIIa covalent linkages form between Fibrin threads thus a dense mesh of Fibrin thread is formed which traps the RBCs and WBCs to form a solid mass called blood clot.

•Clot Retraction Within 5 to 30 minutes the clot retracts down to 40% of the original volume with the liberation of a yellow fluid called Serum. Serum has essentially the same composition of plasma except the clotting factors I, II, V and VIII and high levels of Serotonin from platelets.

Platlets directly contribute to clot retraction by activating platelet contractile proteins like actin,myosin and thrombosthenin.

•Clot lysis: Fibrinolytic system

The tendency of blood to clot in vivo by limiting reactions that tend to prevent clotting inside the blood vessels and to break down any clots that do form. These reactions include aggregating effect of Thromboxane A2 and Anti-aggregating effect of Prostacycline.Fibrinolytic system is a clot lysing system which includes,

-plasminogen
-plasmin
-plasminogen activators
-plasminogen activator inhibitors
-plasmin inhibitors

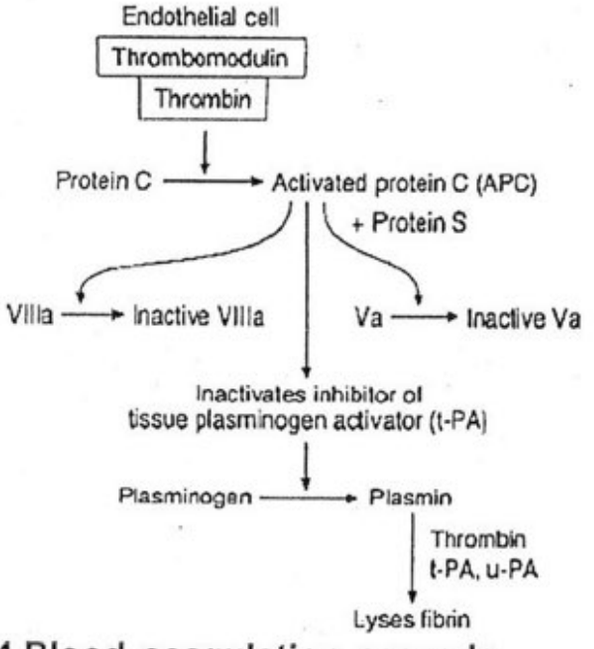
Plasminogen: Plasminogen is a plasma protein produced in liver.When clot is formed large amount of plasminogen is entraped in the clot along with other proteins.Plasminogen receptors are present on surface of different type of cells and are plentiful on endothelial cells. Binding of Plasminogen to its receptors causes its activation to Plasmin by plasminogen activators.In intact blood vessels there are mechanisms that discourages clot formation. Human TPA is now produced by r-DNA technology and is available for clinical use as Alteplase. It lyses clots in the coronary arteries and is given to patients soon after the onset of MI.(Urokinase also).

- Plasmin:This is the active form of plasminogen produced by plasminogen activators.Plasmin cleaves the fibrin thread as well as other coagulants like fibrinogen,factor V,VIII,XII and forms fibrin degradation product.This inhibit thrombin and inhibit the polymerisation of fibrin monomer and also compete with fibrinogen for bindingsites on platelets.This impaires the formation of hemostatic plug.
- Plasminogen activators:These convert plasminogen to plasmin.There are 2 type of PA,tissuePA and urokinasePA.These are secreted by injured endothelial cells.
- Plasminogen activator inhibitors and Plasmin inhibitors:Fibrinolytic system is regulated by plasminogen activator inhibitors and plasmin inhibitors.PAI are 2 type ,PAI-1 and PAI-2. Endothelial cells of blood vessels except those in cerebral micro-circulation produce Thrombomodulin, a Thrombin binding protein and express it on their surfaces. Thrombin is a Pro-coagulant which activates Factors V and VIII. But when Thrombin binds to Thrombomodulin it acts as an anti-coagulant as the complex activates Protein C. Activated Protein C along with its co-factor Protein S inactivates Factors VIII and V and inhibitors of Tissue Plasminogen Activator and increases the formation of Plasmin.

Plasmin inhibitors, α2 antiplasmin released from the liver inactivate the plasmin thus prevent degradation of fibrinogen and protect the clot from excessive lysis.

Anti-Thrombin III: Circulating serine protease inhibitor that binds to serine proteases in the coagulation system blocking their activity as clotting factors

Annexins: Homologous proteins associated with coagulation and fibrinolysis. Total 20 (10 in mammals). Annexin II form a platform on endothelial cells on which the components of the fibrinolytic system interacts producing fibrinolysis. Annexin V forms a shield around Phospholipids involving coagulation and exerts an anti-thrombotic effect



4.Blood coagulation cascade (intrinsic and extrinsic systems):Refer essay 3.

5.Blood groups, blood transfusion and complications

Blood Grouping:

ABO system invented by Landsteiner in 1901. 30 common antigens discovered in blood cells on the surface of cell membrane. Important types are ABO and Rh(Landsteiner and Weiner in 1940). Other systems are MN, P, S, Lutheran, Lewis, Kidd, Duffy etc. They are weakly antigenic and not significant. Previously MN system was used to settle paternity disputes.

•ABO System:

A and B antigens are seen on the surface of cell membrane. Classified into 4 groups based on presence or absence of antigen.

A	AAg
B	B Ag
AB	A&B Ag
O	No antigen.

These antigens are also found in tissues like salivary glands, saliva , kidney, liver, lung, testis, semen and AF

Structure of Antigens: Complex oligosaccharides differing *in their terminal sugar on the H- antigen.* Glycosphingolipids in Red cells and Glycoproteins in other tissues. H gene codes for Fucose transferase which forms H-antigen.

- Type A have a gene that codes for transferase that has terminal N-Acetyl galactosamine on the H-Ag.
- Type B have a gene that codes for transferase that has terminal Galactose on the H-antigen.
- Type AB has both transferases.
- Type O has neither but only the H-antigen.

Genetic determination of Agglutinogen: Inherited as Mendelian dominant. 2 genes, one on each of the two paired chromosomes determining the ABO blood group. These genes are of 3 types.

- Type O: Functionless
- Type A:
- Type B

Based on this 6 possible combinations of genes called genotypes are seen.

- O OO
- A AO/AA
- B BO/BB
- AB AB

Development: A and B antigens first appear in 6th week of fetal life. Concentration at birth is 1/5 of the adult level and progressively rises during puberty and adolescence.

Antibodies: Called agglutinins, present in serum. They are Gamma globulins of IgM type and do not cross the placenta. IgG antibodies are seen during mismatched transfusion and incompatibility during pregnancy. Produced in the bone marrow and lymphoid cells. Antibodies to A antigen known as anti-A or á. Antibodies against B are known as anti-B or b. They act best at low temperature (5-20°C) and are called cold antibodies. 2 to 8 months after birth infants produce antibodies because antigens similar to A and B are present in food and they initiate development of antibodies. Peaks at 8-10 years and gradually declines.

Group A	Anti-B
Group B	Anti-A
Group O	Both
Group AB	Neither

Landsteiner's Laws:

- If an agglutinogen is present on the red cell membrane of an individual, the corresponding agglutinin must be absent in the plasma.

Applicable to both ABO and RH system.

o If an agglutinogen is absent on the red cell membrane of an individual, the corresponding agglutinin must be present in the plasma.

Applicable only to ABO blood group system.

Frequency distribution of Blood Groups:

Group	Western	Indian
O	45 %	45 %
A	41 %	25 %
B	10 %	25 %
AB	4 %	5 %

Agglutination: Reaction between blood group antigens and its corresponding antibodies leads to clumping or agglutination. The agglutinins have several binding sites and binds to 2 or more RBCs at the same time.When plasma of type A is mixed with type B red cells,anti-B antibody of A group person cause type B red cell to clump.

Group	Agglutinins in plasma	Plasma agglutinates red cells of type
O	Anti-A,Anti-B	A,B,AB
A	Anti-B	B,AB
B	Anti-A	A,AB
AB	None	None

In ABO system the O group is the universal donor because they contain no agglutinogens and are not agglutinated by antibodies or members of other groups. AB is the universal recipient. They contain no antibody in the serum and can receive blood from any group.

✶ Bombay blood group:In Bombay in 1952 a group of people have RBCs that lacked H-antigen as well as A and B antigens. They are designated as O_H. They do not have H-gene from either parent and so even if they have A and B gene they are not formed. Their serum contains all types of antibodies and so if they need transfusion special blood of the same type should be given. They were known as Bhende group.

✶ **Rh System:**

Second most important blood group. First studied in Rhesus monkey. There are 6 common types of antigens. C, D, E, c, d, e. Among these C, E, c, e are less immunogenic. d produces less antibodies. D is most antigenic and widely prevalent. Rh positive refers to the presence of D and Rh negative do not have D antigen.

Frequency distribution:

Group	Western	Asia
Rh Positive	85	99
Rh Negative	15	1

Locus of Rh gene is present on chromosome 1.No secretors, no naturally occurring antibodies. Antibodies are found only when Rh negative blood is exposed to Rh positive either by transfusion or entry of fetal blood. Antibodies are IgG type. They can cross the placenta. They act best at body temperature and hence called warm antibodies. The gene corresponding to antigen D is D. If D is absent in the chromosome it is occupied by alternate form or allallomorphs d. DD and Dd will be Rh positive. dd will be negative.

Importance of blood grouping:

- To prevent mismatched transfusion and organ transplantation.
- To prove disputed paternity
- Accused person's blood stains if collected from the site of crime confirms his presence.
- Some diseases are more common in particular blood groups. Duodenal ulcer in O group. Pernicious anemia and GIT disorders in A,Urinarytract infection in B and AB. Duffy negative resistant to Plasmodium vivax.
- To prevent Rh incompatibility in pregnancy.

✶ **Blood transfusion**:Injection of large quantities of blood from a healthy donor to the vein of a patient or recipient. Whole blood or components can be transfused. Whole blood can increase the volume as well as the O_2 carrying capacity of blood.

- Indications :
  - To restore blood volume after hemorrhage or burns
  - To maintain the conc of circulating hemoglobin at an adequate level
  - Anemia not responding to vit B_{12} and Fe and aplastic or hemolytic anemia
  - Bleeding disorders like hemophilia and clotting defects.
  - Symptomatic treatment in agranulocytosis
  - Shocks of various type
  - CO poisoning
- Criteria for an ideal donor
  - Must be of the same blood group and rh type
  - Healthy individual between 18 – 60 yrs of age
  - BP normal less than 180/100 mmHg
  - Body wt > 50 kg to donate 450 ml
  - Shouldn't be suffering from infectious diseases like AIDS, syphilis, malaria , hepatitis
  - Hb normal >12.5 g/dl
  - Hematocrit -3.8%
  - Once in 3 months
- Precautions taken before transfusion
  - Consent taken from donor
  - Donor's and recipient's blood should be typed and cross matched

✶ 2 types of crossmatching

- Major/direct crossmatching : Donor's cells are mixed with recipient's plasma and checked for agglutination. The Donor's plasma gets diluted with recipient's plasma so that agglutination of recipient's RBC's occur rarely. But Donor's cells are easily agglutinated by recipient's plasma.

- Minor /indirect crossmatching : The Donor's plasma reacted with recipient's RBC's and checked for agglutination. This rarely happens

o Screening tests done for syphilis,AIDS, hepatitis B&C, HTLV I& II
o Blood collected in sterile precaution and proper anti coagulant added
o Transfusion not rapid, rate is 100 -200 ml/hr
o I unit is transfused over 2-3 hrs
o In pediatric transfusion rate is 2 -5 ml/kg body wt/hr

- Collection and storage of blood

o Collected from median cubital vein by phlebotomy
o About 400-450 ml of blood is collected at a time
o For every 100 ml of blood 14 ml of anti coagulant is added
o Stored in sterile plastic bags made of PVC
o Stored at 4°c (1°c to 6° c). low T decreases the metabolism of RBC's and increase their viability. Also prevents the growth of pathogenic bacteria.

- Anticoagulants used:

o Citrate is used in combination with dextrose in the following forms
  - Acid Citrate Dextrose(ACD)
  - Citrate Phosphate Dextrose (CPD)
  - Citrate Phosphate Dextrose Adenine(CPDA)

-Citrate chelates Ca and prevents Ca dependent stages of coagulation.

-Dextrose provides suitable medium for RBC metabolism.It liberates lactic acid and helps in the invivo and invitro survival of RBC's.

-Action of adenine is to prevent loss of red cell ATP.

-In ACD & CPD the shelf life of RBC's is 21 days, but in CPDA it will remain viable up to 35 days.

o Heparin

- Storage lesions and preservation injuries :

These are biochemical changes that take place in blood during storage which reduces life span of RBCs

o Decrease in pH : Though glycolysis is slowed down by low temperature it does not stop. So lactate is produced it will reduce pH.
o Loss of ATP due to glycolysis.So viability of RBC decreases.
o Loss of K^+ and gain of Na^+: the Na^+ - K^+ gradient is maintained by Na^+ - K^+ ATPase which fails to work at 4° c.Also the loss of K^+ will be > than the gain of Na^+
o Loss of K^+ and gain of Na^+ leads to increase in net water inside and red cells becomes spherical and osmotic fragility
o Decrease in 2,3 DPG: increases the affinity of Hb for O_2 and shifts the dissociation curve to left and thereby decreases tissue oxygenation.
o Increase in plasma Hb levels because of the RBC lysis.

- In-vivo recovery of stored red cells

Becomes spherical (re-conditioned in 24 hrs with respect to Na & K content, size, shape and osmotic fragility). Their metabolism increases. Na is extruded *from the cells by Na^+-K^+ pump and K^+ is drawn back* and ionic pattern returns to normal.Blood products intended for transfusion are collected as whole blood Then it is processed into components.

Hazards of Transfusion:

Complications due to mismatched transfusion

•Acute Hemolysis: It is one of the most serious transfusion reactions,begins few minutes to few hours. ABO incompatability is the most common cause. Donor's RBCs agglutinating with recepient's naturally occurring antibodies resulting in complement activation and subsequent hemolysis leading to renal dysfunction and failure.

•Delayed hemolysis: Occurs in patients previously sensitized to RBC alloantigen and who have a negative alloantibody screen on pre-transfusion testing. When a patient is transfused an antigen positive blood there will be production of alloantibodies that bind to donor's RBCs. Antibodies detected in 1-2 weeks after administration of incompatible blood later hemolysis occurs due to phagocytosis of agglutinated cells. Usually seen in Rh incompatibility.

Clinical features based on severity:

- Mild degree of hemolysis: No apparent hemolysis be cause the destroyed RBCs are replaced within a week. No symptoms.
- Moderate type: Post- transfusionional hemolytic jaun dice. Transfused red ells are destroyed and hemoglobin released. Hemoglobin is degraded to bilirubin which leads to jaundice.
- Severe degree of hemolysis: Agglutination of RBCs form clumps and causes the blockage of blood vessels of vital organs coronary, pulmonary and renal vessels causing ischemia of organs.Hemoglobin released from destroyed RBCs degrade to bilirubin and causes jaundice
- Acute Renal Shutdown: It begins a fewminutes to a few hours after transfusion and progresses till death. Antigen-antibody reaction causes the release of toxic substances from hemolysed blood leading to renal va soconstriction.
- Circulatory shock: Due to loss of circulating RBCs in the recipient and production of toxic substances from nemolysed cells. BP falls. Renal blood flow and renal output decreases.

- Free hemoglobin released to circulating blood if greater than that can bind to Haptoglobulin , the excess leaks through glomerular membrane to renal tubules. If free Hb is very high it precipitates and blocks the renal tu bules. In general vasoconstriction, circulatory shock and renal tubular blockage
- Symptoms: Fever, chills, breathlessness, jaundice, sudden onset of pain in the lumbar region or precordium, oliguria, BP fall

Causes other than mismatching:

- Infections: AIDS, Syphilis, Malaria, Hepatitis B and C, Bacterial, viral and Parasitic infections. CMV.
- Fluid overload or circulatory overload because they are volume expanding.
- Pulmonary congestion and cardiac failure.
- There will be fever. It is the most frequent reaction associated with the transfusion of cellular component (due to bacterial contamination of blood) due to HLA antigen on WBCs and platelets of donor and antibodies developed in the recipient and successive release of IL-I, VI and TNF-alpha.
- Hypothermia: Immediate transfusion without bringing back to normal temperature.
- Cardiac dysrhythmia
- Thrombophlebitis: if complete sterile precautions are not taken.
- Air embolism due to entry of air from transfusion tube. It can even lead to death.
- Repeated transfusion can lead to iron overload. Iron gets deposited in tissues (Hemosiderosis). It will lead to endocrine hepatic or cardiac dysfunction
- Electrolyte Imbalance: Hyperkalemia due to movement of potassium into plasma from RBCs during storage. Hypocalcemia: citrate chelate calcium which inhibits coagulation cascade.

- **Blood substitutes**: various substitutes are used if volume substitution has to be done before blood transfusion. Volume expansion only. No oxygen carrying capacity.
  - Crystalloids: Poor substitutes because they cannot remain inside the blood vessel. They are used if there is fluid loss hemoconcentration and also in dehydration. Also they can be used as a media for administration of drugs and hormones. Eg; Saline, Glucose.
  - Colloids: They can replenish the fluid and also keep it within the blood vessel due to osmotic pressure exerted by them. Eg: Dextran, Gelatin. Dextran is the best colloid used.

6. Plasma Proteins and their functions:

Major organic constituents of blood. More than 100 individual plasma proteins have been recognized. Broadly

Albumin : 3.5-5 g/dl
Globulin : 2-3.5 g/dl
Fibrinogen : 200-450 mg/dl
Prothrombin : 0.03g/100 ml
Total : 6-8 g / 100 ml
A-G ratio : 1.2-2.1 : 1

Synthesis of Plasma proteins

In embryo till 3 months is produced from from mesenchyma.In adults,

Albumin, 50-80 % of globulin and fibrinogen is from hepatocytes of liver

Gamma globulins from plasma cells or B lymphocytes

Macrophages of reticuloendothelial system of liver, spleen and bone marrow synthesise some cells of complement protein system.

Intestine : some apoproteins (lipoproteins and transport of lipids)

Endothelial cells : Plasminogen activator and VWF

Seperaton of plasma proteins

Colin's fractionation
Ultra centrifugation
Precipitation by salting out
Immunoelectrophoresis
RIA,ELISA

Albumin:

- Major fraction
- Mol wt :69000
- Plasma conc : 3.5-5 g/dl
- Smallest plasma protein
- Total exchangeable pool : 4-5 g/kg body wt. Of this 2/5th is intravascular and 3/5 th is extravascular. The extravascular part reaches ECF by vesicular transport across the capillary network.
- Half life is 19 days, degraded at the rate of 6-10 % of exchange pool per day. Replaced by hepatic synthesis at the rate of 200-400 mg/kg/day. Total : 12-15 g/day. The aminoacids are reutilized for protein synthesis.

•Variations:

- Physiological decrease in,
  - New-born
  - Pregnancy
  - Fasting
- Pathological decrease in,
  - Imoaired synthesis in Liver Diseases
  - Exessive loss in Renal Diseases
  - Chronic Malnutrition
  - Mal absorption in GIT Diseases
  - Haemorrhage
- Increase in,
  - Burns
  - Dehydration

Diabetes Insipidus

Globulins:

- Mol wt: 80000-1,90000
- Plasma conc : 2-3.5 g/dl
- Classes are $\alpha_1\alpha_2$, $\beta_1\beta_2$ and gamma globulins
- Based on function divided into
  - o Glycoprotein
  - o Lipoproteins : Transport form of blood lipids. (lipids + apoproteins). Associated with α and β fractions.
    HDL – α, LDL –β, VLDL – β, Chylomicrons
  - o Coagulation proteins : Prothrombin, thromboplastin

•Some important Globulins are:

oTransferrin : Iron binding. Binds with 2 atom Fe

oHaptoglobulins : Mol wt 90000. Plasma level 0.12 g%. binds with free Hb and forms a stable complex which prevent undue loss in conditions of hemorrhage by blocking the renal tubules.

oCeruloplasmin :

-Cu binding protein.
-Binds 6-8 atoms per molecule
-Also called ferroxidase(an enzyme which binds
-Fe to transferrin)
-Carries 90% of the Cu
-Important antioxidant in plasma
-Conc is 25-50 mg/dl
-Deficiency :Wilson's disease
▪Concentration <20 mg/dl
▪Accumulation in liver leads to hepatocellular degeneration.
▪In basal ganglia it leads to lenticular degeneration
▪Golden ring around the cornea : Fleischer ring
▪In kidneys it leads to renal failure
▪In bone marrow it leads to haemolytic anemia

oFetwin :Growth promoting proteins in infants. Cell proliferation and growth of foetal tissue.

oImmunoglobulin: 5 classes IgG, M, E, D and A. Also called Gamma globulins. Concerned with immune mechanism.

oHaem agglutinin: antibodies against RBCs

oErythropoietin: Refer back

oAngiotensinogen

oCarrier proteins

oPlasma protease inhibitors.

- Anti-trypsin which inhibits trypsin, chymotrypsin, thrombin, elastase, cathepsin
- α_2 Macroglobulin
- Serine protease inhibitor

•Variations:

o Decrease in,
Hypoproteinaemia
Hemolytic Anaemia
Hypogammaglobulinaemia
Lymphatic Leukemia
Chronic Infections
Extensive tissue destruction

o Increase in,
Cirrhosis
Acute Hepatitis
Multiple Myeloma
Nephritis

Fibrinogen:

- Molecular weight 4 lakh
- Plasma level: 200 to 400 mg/dl
- Half life 4 days
- Function: Clotting

•Variations:

o Decrease in,
Congenital Conditions
Carcinoma Prostate
Extensive Cardiac and Pulmonary Surgeries
Increased Fibrinolysis
Intravascular Coagulation
Afibrinogenaemia

o Increase in,
Malaria
Acute and Chronic Infections
Tissue injury

Variations in A/G ratio:

Decreased A/G ratio is seen in Liver dysfunction and Nephrosis. Increased ratio is seen in Hypoglobulinaemia, intake of high carbohydrate and protein diet.

Functions of plasma proteins:

• Helps to maintain colloid osmotic pressure.

Cappillary wall impermeable to plasma proteins.So they exert pressure on cappillary wall.Maximum pressure exert by Albumin.This is responsible for the exchange of material between tissue and blood and help to regulate blood volume and water balance.

•Plasma proteins help to increase viscosity

By size and shape they contribute greatly to the viscosity thereby helps to increase peripheral resistance to the flow of blood and maintain blood pressure. Viscosity is maximum for Fibrinogen.

•Acid base balance

Plasma proteins act as buffers due to their capacity for H^+ ion acceptance and ionization to acids or bases due to presence of COOH and NH_2 groups. At a pH of 7.4, they exist as anions.15% of buffering capacity by plasma proteins and rest by 85% by Hb.

•Blood coagulation

Fibrinogen,Prothrombinand other proteins present in the plasma play an important role in coagulation, prevents blood loss.

•Gamma globulins play an important role in immunity.

•Transport function

Albumin is the primary carrier for bilirubin, fatty acid, drugs,minerals and secondary carrier for thyroid, ACTH and Gonadal Hormones.Pre-Albumin helps in T_3 and T_4 transport. The binding helps to prevent the filtration of the proteins through glomerulus.

•Reserve proteins

The bound form serves as the reservoir which can be mobilized in conditions like Malnutrition and Starvation.

•Triphones

Substances produced by WBCs from plasma proteins which are important for culture medium. They act as enzyme activators or inhibitors of certain reactions. Eg: Plasma Proteolytic system, Plasma Protease Inhibitor.

•Rouleaux Formation

Albumin decreases and Fibrinogen and Globulin increases Rouleaux formation, thereby affecting ESR.

7. Lymph:

Lymph is a modified tissue fluid.It represents an accessory route through which fluid can flow from interstitial space back to blood.

Lymph channels of the body

Lymph system actually starts peripherally as a network of delicate vessels called lymphatic capillaries which drain the tissue space.Large vessels are formed by the confluence of smaller ones.They receive tributaries along their course and form right lymphatic duct and thoracic duct which open to right and left subclavian veins respectively.Right lymphatic duct receives lymph from right side of head and neck,right arm and right thorax and drain at the junction of right internal jugular vein and right subclavian vein.Thoracic duct drains the lower part of the body,left side of head,neck and thorax and left arm.Small lymph nodes are interposed in the course of large lymph channels.Large lymph vessels on reaching the node breaks into fine channels and open into sinuses.Lymph flows through the node and gets collected at the other end of the node, which again forms a large trunk.Lymph nodes are commonly placed at elbow, axilla,groin, abdomen, thorax and neck.Lymphatics are present in all parts of the body except in superficial parts of skin, CNS, endomysium of muscle and bones.But they have minute channels called prelymphatics through which interstitial fluid can flow through this area.

Structure of lymphatic capillaries

Endothelial cells of lymphatic capillaries are attached by anchoring filaments to surrounding connective tissue.At the junction of adjacent endothelial cells the edge of one cell overlaps the other.The overlapping edge is free to flap inward thus forming a minute valve that opens to the interior of the capillary.The interstitial fluid along with its particles pushes the valves open to the interior of the capillary,but backflow does not happen as it closes the valve.

Formation of lymph

Lymph is derived from interstitial fluid that flows into the capillaries.It is a passive process.Pressure in the arterial end of the capillaries causes filtration of water, solutes and small amounts of protein into extra cellular space in the tissue.A large amount is returned to the venous end and some of this enters the lymph channels and form lymph.About 1/10th of fluid filtered at the arterial end of capillaries enters the lymphatic channels and returns to blood.Lymph in the terminal lymphatics has the same composition as ISF.

Mechanism and pressure involved are Starling's forces.The vol. of lymph drained from an area = the amount filtered from the capillaries at the arterial end – that reabsorbed at the venous end.The vol of lymph formed in 24 hrs is 2-3 L or 120 ml/hr.

Fluid movment=K((Pc-Pif)-(πc-πif))

K-capillary filtration co-efficient.It is propotional to capillary permeability and surface area for filtration.

Pc-Capillary hydrostatic pressure

Pif-Interstitial hydrostatic pressure

πc-Plasma colloid osmotic pressure

πif-interstitial fluid osmotic pressure

Factors influencing lymph formation & flow

- Interstitial fluid pressure

Factors which increase the ISF pressure increases the formation of lymph. They are

- Increased capillary hydrostatic pressure
- Decreased plasma colloid osmotic pressure
- Increased Interstitial fluid colloid osmotic pressure
- Increased capillary permeability and area

- Lymphatic pump

It increases lymph flow by 2 mechanisms.

1.Intrinsic mechanism; Each segment of the lymph vessel between successive valves functions as separate automatic pumps. Filling of a segment causes it to contract and the fluid passes to the next one. This continues all along the lymph vessel until the fluid is emptied in to the circulation. This lymphatic pumping is due to the automatic contraction of smooth muscle in the walls of the vessel when a fluid stretches it.

2.Extrinsic mechanism:Factors affecting are

- Contraction of the surrounding smooth muscle
- Pulsations of adjacent arteries
- Compression of tissues by external objects
- Negative intra thoracic pressure during inspiration

•Lymphagogues :They increase the flow by increasing the capillary permeability,eg:-histamine

Composition of lymph

As same as interstitial fluid in terminal lymphatics.Later composition varies as different interstitial fluids enters to the lymphatics.

- Proteins: They vary with the region from where the lymph is collected. The value is =always less than that in plasma.
- Lipids: contains cholesterol and lipoproteins.High in GIT due to absorption of fat by lacteals.
- All coagulation factors: Amount is high in hepatic lymph.
- Enzymes, hormones and antibodies present in plasma

- Electrolytes: conc similar to plasma except that cations are little lower and anions are higher
- Cells: lymphocytes are present in large no.RBC's if present indicates the degree of hemorrhage into the tissues. Granulocytes, if seen in large amounts, indicates infection.

Functions of lymph

- Keep the interstitial pressure normal by draining extra fluid and electrolyte to blood.
- Carry proteins & large particulate matter away from the tissue space.20-50% of protein return to blood.
- Absorb fat from intestine internal lymphatics/lacteals
- Transport of invading microorganisms to lymphnodes. Infection in the distant part of the body, regional lymph node gets inflamed as a result of localization of bacteria and toxins carried in lymph to the node.
- Lymph carries RBC's entering the tissues following hemorrhage
- Lymph nodes contain a very efficient filtrating mechanism in the cortical & medullary sinuses , lined with phagocytic cells that engulf bacteria, RBC's or other particulate material.
- Immunity by releasing Lymphocyte from lymphnode.

Oedema:

Excessive accumulation of fluid in the tissue spaces. Types-extracellular and intracellular,clinically pitting and non pitting.

•Clinical features

- o Swelling
- o Pitting;When sustained pressure is applied a depression is felt in skin for few seconds.

•Extra cellular-Fluid is accumulate in extra cellular spaces

Causes

- o Due to disturbances in the fluid exchange mechanism across the capillaries due to increased filtration or inadequate removal.
- o Abnormal leakage of fluid from plasma to the interstitial space across the capillaries
- o Failure of the lymphatics to return fluid from interstitium back to blood.

Factors increasing capillary filtration rate:

- o Increased capillary permeability and surface area :
  - Immune reactions due to release of histamine
  - Toxins
  - Bacterial infections
  - Prolonged ischemia
  - Burns
- o Increased capillary hydrostatic pressure
  - More fluid collected in the vessels when there is excessive retention of salt and water by the kidneys due to acute or chronic renal failure
  - High venous pressure and venous constriction due to cardiac failure, venous obstruction, failure of venous pumps etc
- o Decreased colloidal osmotic pressure: due to decreased plasma proteins
  - Nephrotic Syndrome : Characterized by proteinuria, facial oedema and size of glomerular sieve is enlarged
  - Burns : Loss of fluid from the burnt surface.There is oozing of plasma from the surface
  - Wounds : Loss of proteins from the denuded skin
  - Failure to produce proteins:cirrhosis of liver

Lymphatic blockage

When lymphatic blockage occurs severe oedema occurs because plasma proteins which lead to interstitium has no other way to be removed.So there is increased drainage of fluid out of capillaries It is seen in filariasis,surgery,malignancies, congenital absence of lymph vessels.

SHORT NOTES

1. Neutrophils:

- Abundance : 50-70%
- Diameter : 10-14 μm
- Nucleus: central or eccentric, 2-5 lobes connected by chromatin strands and stains purplish blue.
- Cytoplasm plenty,pale pink in coulor contain pink/ violet granules
- Motile
- Phagocytic property
- Granules are membrane bound lysosomes that contain enzymes. 3 types
  - o 1^0 or lysosomal :These granules contains several antimicrobial compounds and enzymes.Eg; hydrolase, myelo peroxidase, cationic protein, lysozyme, defensin, elastase,esterases and non specific granules.
  - o 2^0 or specific granules :More numerous.They contain apolactoferrin,vitamin B_{12} binding protein, lysozyme, alkaline phosphatase, phospholipase A2, plasminogen activator
  - o 3^0 or gelatinase granules:Contain many membrane proteins.Toxic granules may be seen during infection.
- Neutrophils are distributed in 3 main pools.
  1-marrow pool 90%
  2-blood pool 3%
  3-tissue pool 7%
- Functions:
  - o First line of defense
  - o Phagocytosis
- Increase in neutrophil count is known as neutrophilia/ polymorphonuclear leucocytosis. Seen in
  - o Acute pyogenic infections like boils, abcesses, tonsillitis, pneumonia
  - o Metabolic disorders like uremias, diabetic acidosis, gout etc
  - o Poisoning with drugs or chemicals like Pb, Hg, digitalis etc

- Post operative conditions and in tissue injuries like myocardial infarction
- Physiologically in newborn, during labour, after strenuous exercise etc

- Decrease in count is neutropenia. Seen in
  - Certain infections like typhoid, paratyphoid, influenza, measles, malaria, kala azar.
  - Hemopoeitic disorders like aplastic anemia, agranulocytosis etc.
- Arneth count;refer short note 2

2 .Arneth Count:

Arneth, a german physiologist pointed out that the number of lobes of neutrophils depends on the age of the cell. The oldest cells have the largest number of lobes. The count takes it's determinant by counting the number of lobes in 100 neutrophils and the cells in different stages are expressed as % of the total.

Stage 1: 5% (single nucleus without a lobe)
Stage 2: 30% (2 lobes)
Stage 3: 45% (3 lobes)
Stage 4: 18% (4 lobes)
Stage 5: 2% (5 lobes)

Count more in 1&2 = shift to left of Arneth count ie, increase in number of younger cells seen in conditions like TB, acute pyogenic infections and irradiation,, more in 4&5 = shift to right is seen in megaloblastic anemia.

3.T-Lymphocytes:

- Helper T-cells
  - Three fourth of the total T Cells
  - They are two subtypes T-Helper1 and T-Helper2
  - TH1 secrete IL-2 and stimulate suppressor and cytotoxic T cells,concentrated with cellular immunity.
  - TH2 secrete IL-4, 5,6 and stimulate B cells,concentrated with humoral immunity.
  - Help to regulate almost all immune functions through lymphokines.The important lymphokines secreated are IL-1,IL-2,IL-3,IL-4,IL-5,IL-6,GM-CSFand interferon γ.
  - Stimulate growth and proliferation of Cytotoxic and Suppressor T cells.IL-2 has the stimulatory effect.
  - Stimulate growth and differentiation of B cells.
  - Activate macrophage system.They accumulate at the site of infection and cause more efficient phagocytosis.
  - Direct feedbak stimulatory effect on helper cells themselves especially by IL-2.This amplifies helper cells response as well as immune response.
  - They have CD4 glycoprotein on the cell surface.
- Cytotoxic T-cells
  - Called Killer cells
  - CD8 glycoprotein on the cell surface
  - They bound tightly to the organism or cell that contain specific antigen.They secrete Perforins which punch large holes in the membrane of attacked cells.Fluid flows out and cell get dissolves.
  - Release cytotoxic substances and kill the microorganisms.
  - Destroy cancer cells, Transplanted cells,cells invaded with virus and foreign cells.
- Suppressor T-cells
  - They suppress the activity of cytotoxic and helper T-cells to prevent excessive immune reaction.
  - They play an important role in limiting the ability of the immune system to attack a person's own body tissue – self-tolerance
- Memory T-cells
  - After exposure to a given antigen a small number of B and T cells readily converted to Effector Cells on later encounter with the same antigen and produces an accelerated response.This ability may be longlasting or life long.

4.Properties of WBC:

-Margination
-Diapedesis
-Chemotaxis
-Opsonization
-Ameboid movement
-Phagocytosis

Invasion of body by bacteria triggers inflamatory response.There is vasodialation of especially cappillaries and veins.There is release of neutrophil from the BM and more neutrophils are triggered to enter the tissue.

- Margination:-neutrophils are attracted to endothelial surface by the cell adhesion molecule known as selectins.Selectins are glycoproteins expressed on neutrophils and endothelial cells.
- Diapedesis:-The neutrophils themselves insinuate through the walls of capillaries between endothelial cells.
- Chemotaxis:-The bacterial product interact with plasma factors or cells produce agents that attract neutrophils to the infected area.chemotaxis depends upon the conc gradient of the chemotactic agent and is effective up to 100 mm away from the inflamed area.
- Opsonization;-Plasma factors act on the bacteria to make them tasty to phagocytosis.The principle opsonins are IgG and complement proteins.The opsonin coat the bacteria and cause their binding to receptors on the phagocyte cell membrane.
- Ameboid movement:- Neutrophils and macrophages are move through the tissue by ameboid action.
- Phagocytosis:-Cell eating

5. Helper T cells: (Refer short note 3)

6.Cellular & humoral immunity:

Cell mediated immunity:

Specific immune response that does not involve antibodies. The major cells are T-cells. It is a major defense against infection by viruses, fungi and bacteria-like TB. It is responsible for delayed allergic reactions and rejection of transplant of foreign tissue and defense against tumors.

It involves antigen processing and presentation. When an antigen invasion occurs, it is taken up by antigen-presenting cell. e.g Macrophage and is partially digested. A peptide fragment of the antigen is presented to the T-cells along with MHC peptide. The T-cell possesses antigen recognition sites called T-cell receptors. They consist of two subunits, in 90% α and β and in 10% γ and δ. They have two regions, variable and constant. The T-cell receptor form heterodimers that recognize MHC proteins and antigen fragments with which they are combined. The receptor has a cleft on it for antigen binding. The receptor of one lymphocyte differ from another so that a particular antigen alone can bind to a particular receptor and cause activation and proliferation of a clone of T-Lymphocytes. The cytotoxic T-cells recognize the combination of foreign antigen and classII MHC. The cytotoxic T-cells after combining with foreign antigen and MHC I Complex are activated and differentiated. Two signals are required for T-cell activation. 1. Binding of digested antigen to the receptor 2. Formation of immunological synapse: Binding of adhesion molecules and proteins adjacent to the receptor to the complementary proteins in the antigen-presenting cells to form an immunological synapse. If the first signal occurs and second one does not the T-cell is inactivated and becomes irresponsive.

Helper T-cell before it contacts an antigen is called naive T-cell. When an immune synapse forms with it, it is activated to produce IL2. It acts in an autocrine fashion to cause the cells to multiply forming a clone. The activated CD4 helper cell may promote B cell activation and production of plasma cells or it may activate a cytotoxic T-cell. Cytotoxic T-cells can also be activated by forming a synapse with MHC 1 antigen-presenting cell. The cytotoxic T-cells and natural killer cells are responsible for the attack phase of cell-mediated immunity. The cytotoxic cells after binding with the target cell insert hole-forming proteins called perforins into the cell membrane. It also releases cytotoxic substances. This ultimately results in cell killing. Some cytotoxic cells become Memory cells.

Natural killer cells are large granular lymphocytes. They are called Null cells are they are neither T or B cells. They constitute 10 to 15% of the lymphocytes. They kill cells without prior sensitization and without involvement of MHC antigen. They destroy cells that have undergone malignant transformation. They are the first line of defense against viral infection because they are effective without antigen exposure. IL2 and Interferon cause their activation and proliferation. Normal cells are protected from natural killer cells by MHC class 1 molecule. They have receptors for IgG and they are able to kill antibody coated virus.

Natural killer cells help in cell lysis by releasing their granule contents which include perforins.

Humoral immunity:

- Immune responses that involve the formation of antibodies.
- It provides defense against most extracellular bacterial pathogens and viruses that inject through the respiratory and intestinal tract. It participates in the pathogenesis of immediate hypersensitivity reactions.

Types of immune response:

B cell can bind the antigen directly or by the macrophage presenting the antigen to B and T cells.But they must contact helper T cells for the activation and Ab formation.The activated B cells enlarges to form lymphoblast-plasmoblast-and finally B cell transform in to memmory B cell and plasma cells.1 plasmoblast give rise to 500 plasma cells in 4 days and mature plasma cells produce antibodies.These Abs circulate in the globin fraction of plasma and are called immunoglobins.Ig constitute about 20% of plasma proteins.There are 5 general classes IgM, IgG, IgD, IgA and IgE

- 1^0 immune response: Refers to the response of the body's immune system to an antigen which is introduced in the body for the first time. There is a latent period varying from 4 days to 4 weeks before the primary response in the form of increase in the antibody titre is detected
- 2^0 immune response: It refers to response of body's immune system to an antigen which is introduced into the body on a second occasion. Such response occurs more quickly and more abundantly. This is because the immune system retains the memory of prior antigen exposure for long periods. B cells can bind antigen directly.

Immunoglobulins:

IgG -constitute 70%,can pass through placenta(passive immunity),plasma conc.1000mg/dl, functions;-complement activation,neutralisation of toxins.

IgA -constitute 10-13%,plasma conc.200mg/dl, functions;- promote phagocytosis and intracellular killing of micro organisms,activate complement activation

IgM -5-8%,plasma conc.120mg/dl,Abs formed during 1^0 response are IgM type,
functions;-opsonization and complement fixation

IgD -plasma conc.3mg/dl,
functions;-act as Ag receptor on B lymphocytes.

IgE -plasma conc.0.05mg/dl,also called as reagin functions;-release histamine from basophil and mast cells, involved in hyper sensitivity reactions and in allergy.

7.Granules & Functions of eosinophil:

Eosinophils have diameter of 12-16μm with bilobed nucleus staining purplish blue.Cytoplasm contain large coarse granules or dense granules.Granules contain,

- o Eosinophil peroxidase:catalyse oxidation of many substances by Hydrogen peroxide.
- o Eosinophil major basic protein:important in defence against parasites.

o Eosinophilic cationic proteins:some of them bind to heparin and reduces the anticoagulant activity.

Functions of Eosinophil

- Antiparasitic action : Eosinophils migrate in large numbers to the tissues diseased by parasites. Eosinophils attach themselves to the parasites and kill them by releasing a hydrolytic enzymes from their granules which are modified lysosomes and by releasing highly reactive forms of O_2 which are lethal. Also by releasing from their granules highly larvicidal polypeptide called major basic protein.
- Allergic reaction: Eosinophils have special means to collect in tissues in which allergic reactions have occurred as in peribronchial tissues of lungs and people with asthma. Mast cells and basophils release an eosinophil chemotactic factor which causes eosinophil to migrate towards the inflamed tissue
- They have the phagocytic power to ingest the allergin antibody complex
- They detoxify inflammation inducing substances released by mast cells and basophils

8. Macrophages:

They are large actively phagocytic cells with irregular shape, motility and abundant cytoplasm. Cytoplasm has abundant coarse azure granules and vacuoles.The term macrophages means big eaters. Some of these mobile cells are capable of wandering through the tissue, but a larger portion of these cells become attached to the tissues for months or even years until they are called on to perform specific local protective functions. The total combination of monocytes, mobile macrophages, fixed tissue macrophages and a few specialized endothelial cells in the bone marrow, spleen and lymph nodes is called **Reticuloendothelial system** or Monocyte Macrophage cell system.They form the second line of defence. They can phagocytose large quantities of bacteria, virus, necrotic tissue, other foreign particles in the tissue or even RBCs and Malarial Parasites. Some end up as multi-nucleated giant cells, in inflammations like TB. All the macrophage cells are originate from Monocytic stem cells. Monocytes that enters the blood from the bone marrow become larger and devolope large quantities of lysosomes and take 8 hours to become macrophages. Macrophages are the end stage products of Monocytes that enter the tissues from blood.Tissue macrophages include Kuffer cells of liver,pulmonary alveolar macrophages,microglia in the brain,littoral cells of bone marrow,histiocytes in connective tissue,macrophages in spleen,lymphnode etc.

- Lung Macrophage: Interstitial and Alveolar Macrophages constitute the lung Macrophage pool. They are essential components of respiratory defense system. Alveolar Macrophages exist at tissue air interphase where they encounter inhaled pollutants and micro-organisms. They phagocytose particles that become entrapped in alveoli. If digestable, Macrophages digest them and release the products to lymph. If not macrophages form a giant cell capsule around the particle. Eg. TB bacilli , silica and carbon particle.These particles enters to the lymph and reach the lymph node where they trapped and phagocyted by tissue macrophages.
- Skin Macrophages: Called Langerhans cells. Make up 3-8% of the epidermal cells. Have some phagocytic activity but less than other Macrophages. Primary function is to serve as antigen-presenting cell. They are also involved in rejection of skin allograft. Also involved in various diseases like Allergic Contact Dermatitis, Histiocytosis X etc.
- Liver Macrophages: Called Kupffer cells. They line the sinusoids. They lie on the endothelial cells or are embedded in endothelial lining. They phagocytose particles like Carbon, bacteria, parasites, viruses and altered RBCs. They play an important role in liver injuries also. They produce Interleukin –I, TNF, Arachidonic Acid catabolites, Reactive oxygen species etc. which alter the function of hepatocytes which may lead to marked hepatocyte injury. They serve as accessory cells in presenting the antigen to and stimulating DNA synthesis in T-Lymphocytes.
- Brain Macrophages: Called Microglial cells. An injury or inflamation will lead to increase in their number. They internalize RBCs and carbon particles. Also phagocytose dying neurons and their processes, common debris and foreign material. They also prevent excessive inflamatory responses by controlling T-Lymphocyte responses in mediating anti-microbial and anti-tumour effects in the brain.
- Bone Macrophages: Osteoclasts. They are specialized multinucleated cells found in bone that mediate bone resorption.
- Splenic Macrophages: Present in both red and white pulp. Red pulp is composed of Macrophages involved in phagocytosis and destruction of blood cells. In the white pulp Macrophages are found in the germinal centers and they phaogcytose lymph cells. They are also involved in antigen processing and generation of immune responses
- Functions of Macrophages:
  - o Defence against invading organisms such as bacteria and viruses.
  - o They form second line of defense.
  - o They phagocytose i.e. digest the bacteria, secrete Cytokines including Pyrogens.
  - o They also help in lymphocyte-mediated immune response
  - o By acting as APC
  - o Secreting various Interleukins
  - o T and B cell proliferation
  - o Help the natural killer cells

- They act as scavengers by removing dead RBCs, foreign bodies etc.
- They secrete some Haematopoetic Factors.

9.Functions of RES:

The total combination of monocytes, mobile macrophages, fixed tissue macrophages and a few specialized endothelial cells in the bone marrow, spleen and lymph nodes is called Reticuloendothelial system or Monocyte Macrophage cell system.Their important functions are,

-Defence against invading organisms such as bacteria and viruses.

-It processes the antigen and stimulate the production of antibody.

-Dust cells of lung remove the foreign particles entering the lungs.

-RE cells help in repair process and they are called scavenger cells by removing dead RBCs, foreign bodies , cellular debris,fibrin,bacteria etc.,from inflamed area and promote healing.

-It can ingest and destroy old and fragmented RBC,WBC and platelets.

-Iron released from Hb is stored in RE cells.They also store excess lipid and mucoprotein.

also refer short note 8

10. Platelets: Properties and functions

Platelets –Properties

- Round or oval discs.
- Granulated
- Smallest blood cell, 2-4 µm in diameter
- Non nucleated
- When active they become spherical from the disc shape in inactive state
- Half life :8-12 days.eliminated by tissue macrophage system especially spleen.
- Normal Platelet count: 1.5 lakh to 4 lakh per mm^3
- Cell membrane :Outer glycoprotein contain receptor for VWF,collagen,fibrinogen,ADP etc.Inner lipoprotein contain phospholipids,cholesterol etc.The glycocalyx layer has glycoproteins that repels adherence to endothelium and yet causes adherence to exposed collagen in the injured vessel wall. The major glycoproteins are Ib, IIb and IIIa .
- Formed from megakaryocytes by pinching off cytoplasm & extruding them into circulation. 60% of the extruded platelets are in the general circulation and the remainder in spleen. So spleenectomy causes an increase in platelet count.
- Cytoplasm consists of organelles like mitochondria, ER, Golgi apparatus, Granules, Microvesicles, Microtubules, Contractile proteins like Actin, Myosin and Thrombasthenin, Fibrin stabilizing factor also consists of glycogen and lysosomes. VWF and PDGF are aiso present.
- Granules are of 2 types:
  - α granules: Around 50 are present. They contain secreted proteins including clotting factors (I and V), PDGF(Platelet derived growth factor.repair of damaged vessel wall). Other contents are PF4, VWF, Thrombospondin and β-Thromboglobulin.
  - Dense Granules: Bull's eye appearance. Around 5 per platelet. Contains serotonin, ADP, ATP and Calcium.
- Staining: Leishmann's stain is used. Platelets are seen in grooves as a small body with a small central part & a pale periphery. Cytoplasm stains blue and nucleus is absent, they have a ring of microtubules around periphery & extensively invaginated membrane forming an intricate canalicular system in contact with ECF.

Functions:

- Primary hemostasis(arrest of bleeding).
  vasoconstriction
  formation of temporary platelet plug
- Secondaryhemostasis.Release of procoagulants(Platelet Factor 4, help in clotting)
- Role in clot retraction- Actin, Myosin and Thrombasthenin
- Fixation of Fibrin
- Release of substances that oppose coagulation. E.g. Prostacycline
- Repair of wounds by PDGF,TGF(Transforming Growth Factor)
- Storage function
- Mild phagocytic function

11.Clotting factors: refer essay 3

12.Role of Calcium in coagulation

Except first 2 steps in intrinsic mechanism Ca^{2+} is required in all other steps of intrinsic and extrinsic mechanisms.Only minute amount of Ca^{2+} is required.In vivo, low plasma Ca^{2+} level is enough to affect coagulation and incompactible to life.In vitro coagulation can be prevented by chelating agents which remove Ca^{2+}.

13.Vitamin K deficiency:

Manifested as bleeding.Vitamin K is produced by the intestinal flora. Vitamin K is necessary for gamma carboxylation of Glutamic acid residues of the clotting factors 2, 7,9,10. Clotting time is prolonged and bleeding time is normal.

Causes

- Liver disease
- Obstructive jaundice since bile flow is obstructed
- Chronic diarrhea
- Excessive antibiotic therapy
- Hemorrhagic disease of newborn. Liver function is less than optimum and intestinal flora. Vitamin K is routinely given to the preterm babies

14. Why Circulating blood does not clot?

The tendancy of blood to clot is balanced in vivo by the limiting factors which prevent accedental intravascular clotting.There are several factors which prevent intravascular clotting are,

- Velocity of flow of blood
- Endothelial factors,
  - Smoothness of endothelial lining inhibits platelet adhesion
  - Layer of Glycocalyx adsorbed to the inner surface of endothelium being negatively charged repels the clotting factors.
  - Intact endothelium acts as a barrier between thrombogenic sub-endothelial collagenic tissue and blood.
- Circulating Anti-coagulants:
  - Heparin
  - Anti-thrombin III
  - Alpha 2 Macroglobulin
  - Protein C and S
- Fibrinolytic System:
- Balance between Thromboxane A2 and Prostacycline
- Clotting Factors in plasma are in inactive state.
- Removal of activated clotting factors by liver at the onset of spontaneous clot formation.

15. Anti coagulants

Substances used to prevent clotting.Used both in-vivo and in-vitro.

- Criteria:
  - Shouldn't change the shape of RBCs
  - Shouldn't cause hemolysis
  - Shouldn't destroy WBCs
  - Should be soluble in blood
- In-vitro:
  - EDTA(Ethylene Diamine Tetra Acetic acid): Sodium and Potassium salts of EDTA act by chelating Calcium and removing it from blood.Dose 1mg/ml
  - Double oxalate mixture: Ammonium oxalate and Potassium oxalate in the ratio 3:2. It acts by precipitating Calcium. Dose 2mg/ml. Used in determining PCV.
  - Sodium citrate: 3.8%.Citrate combine with Ca to form unionised Ca. Used in determining ESR
  - ACD,CPD and CPDA: For storing blood before transfusion(refer essay)
  - Siliconised container prevent the contact activation of platelets and factor XII.
- In-vivo:
  - **Heparin:** Naturally occurring anticoagulant used both in vivo and in vitro. Molecular weight 15,000 to 18,000. It is a mixture of sulphated polysaccharides produced from mast cell, lung, liver and intestinal mucosa.Its anticoagulant property is due to the electronegetive charge on sulphate group.Heparin itself has little or no anticoagulant activity but when it combine with Anti-thrombin III ,the effectiveness is increased100-1000 times.it activates anti-Thrombin III in plasma. It binds with Serine protease and blocks their activity. The clotting factors deactivated are IX, X, XI, XII, XIII,thrombin and Kalikrin. It is a lipemia clearing agent. i.e. infusion of heparin clears turbid postprandial lipemic plasma. Heparin realeases lipoprotein lipase from vessel wall and tissues which hydrolyses Triglycerides, Chylomicrons and VLDL to FFA. Injuction of very small amount of heparin 0.5-1mg/Kg of body weight causes clotting time to increase from normal to 6-30 minutes or more.If there is severe bleeding after heparin therapy Protamine which is a antidot of heparin can be given to recover clotting mechanism.It is a Anticoagulant of choice in pregnancy. Disadvantages are bleeding due to overdose, Alopecia, Osteoporosis and Thrombocytopenia.
  - Low Molecular weight Heparin: Molecular weight 5,000. Recently fractionated. Selectively inhibits FactorXa with little effect on Va. It has long half-life and more predictable effects.
  - Oral anticoagulants:Dicumarol and Warfarin: Vitamin K antagonists. Inhibitors of Factors II, VII, IX and X. Since Vitamin K is necessary for gamma carboxylation of Glutamic acid residues of these clotting factors.

16. Fibrinolytic system: refer essay 3

17. Bleeding disorders

Bleeding dissorders are due to,

Abnormalities of vessel wall

Abnormalities of platelet

Abnormalities of coagulation

This bleeding dissorders manifest as petiche,purpura,echymoses,hematoma.

Abnormalities of vessel wall:

- Scurvy ;collagen synthesis is impaired
- Senile purpura ;Due to atropy of perivascular tissue
- Hereditory hemorrhagic telengiectasia ;congenital defect in endothelium
- Dissorders of connective tissue matrix in Marfans syndrome.

Abnormalities of platelet:

- Thrombocytopenia ;Decreased production due to bone marrow aplasia,malignancies,hyper spleenism etc
- Idiopathic thrombocytopenic purpura: Autoantibodies formed against platelet glycoprotein IIb-IIIa complexes. Premature removal of platelets by monocytic macrophage system occurs in children and young adults. Follows viral infections in children.
- Platelet functional defect ;Bernard soulier syndrome(defect in Gp1b),Glanzmann'sthrombasthenia (defect in Gp2b/3a complex),.etc

Abnormalities of coagulation:

o Due to clotting factor deficiency Eg;Afibrinogenemia,hypoprothrombinemia,hemophilia,Stuart prower factor deficiency,.etc

o Hemophilia ;Sex linked recessive inheritance transmitted in X chromosome.Females are carriers but males manifest the disease.It is due to deficiency of factor VIII(Hemophilia A),factor IX (B), rarely due to factor XI(C). Carrier females will transmit the disease to half of her male offspring and carrier to half of her female offspring. In hemophilia platelet count and bleeding time are normal,but clotting time is prolonged.
Treatment;Fresh frozen plasma,administration of recombinant clotting factors.

18.Difference between hemophilia and purpura

Hemophilia is due to deficiency of clotting factor VIII(Hemophilia A),factor IX (B), rarely due to factor XI(C).In hemophilia platelet count and bleeding time are normal,but clotting time is prolonged.

Purpura is due to decreased platelet count.In purpura clotting time is normal but bleeding time is prolonged.

19.Tests for hemostasis :

- Platelet count:Normal 1.5 - 4 lacks/dl.
  If it is between 50,000 -1 lack/dl -mild bleeding
  <50,000 - easy bruisability
  <20,000 - spontaneous bleeding
- Bleeding time: The time interval between the onset of bleeding and arrest of bleeding by formation of temporary platelet plug. Time taken for bleeding to stop from a small subcutaneous vessel is noticed.
  - o Duke's method : 1-5 minutes
  - o Ivy's method : 5-11 minutes
  - o Prolonged in Thrombocytopenic purpura, thrombasthenia,and Normal in hemophilia, vitamin K deficiency
- Clotting time : Time interval between collection of blood and formation of definitive clot.
  - o Capillary tube method : 2-8 min
  - o Lee and White's method : 5-12 min
  - o Prolonged in hemophilia,clotting factor deficiencies, deficiency of vitamin K,liver diseases and hypocalcemia.
- Prothrombin time : It is an indication of total quantity of prothrombin in blood. Blood removed from patient is immediately oxalated so that none of the prothrombin can change into thrombin. Later a large excess of calcium & tissue factor is suddenly mixed with oxalated blood. Tissue factor activates the conversion of prothrombin to thrombin by means of extrinsic pathway. The time required for the coagulation to take place gives the prothrombin time. Normal value is 12-15 sec. The test is compared with that obtained from a normal control and the result expressed as a ratio of the control sample.The upper limit of this ratio is 1.2
  - o Prolonged in abnormalities of extrinsic pathway, liver diseases, oral anticoagulant therapy, hemorrhagic disease of the newborn,deficiency of Vit k.
- Partial Thromboplastin Time: Test for intrinsic and common pathway. Time for recalcified citrated plasma to clot in the presence of partial thromboplastin. Platelet phospholipid substitute cephalin is used. Plasma and partial thromboplastin are mixed in the test tube at 37°C and kept for 30 seconds.Calcium is added and time taken for the formation of clot is noted. Average time is 75 sec. Range is 67 to 85 sec.
  - o Prolonged in deficiency of clotting factors(I,II,VIII,IX,X,XI,XII), Anticoagulant therapy, Hepatic failure and intravascular coagulation,hemophilia.
- Activated Partial Thromboplastin Time: Also known as Kaolin-Cephalin Coagulation time. In the original time contact activation was provided by glass tube, but the addition of activators like Kaolin provides more optimal and standardized contact activation and represents a significant improvement over the original non-active state. Normally clot forms in 40 sec.
- Thrombin Time: Mixture of thrombin and calcium is added to citrated platelet poor plasma. Clot forms in 10sec. This measures the conversion of fibrinogen to fibrin.
  - o Prolonged in hypofibrinogenemia, dysfibrinogenemia,disseminated intravascular coagulation and heparin therapy.
- Clot retraction: Blood is collected in a glass tube and kept at 37°C to find out the time of clotting. On allowing standing the clot retracts and separates from the sides of the test tube. Normally occurs in 30-60 minutes.
  - o Prolonged in platelet deficiency and its dysfunction.
- Clot lysis time: Blood is collected in a glass tube and allowed to clot at 37°C in a water bath. This is then observed at 8 hrs, 24 hrs, 48 hrs and 72 hrs. Normally the complete lysis of clot occurs in 72 hrs. if it occurs early it indicates the increased presence of fibrinolytic system in blood.
- Clot solubility time:This test is usually done when activated PTT and PT are normal and bleeding is strong.here screening test for factor XIII.A small amount of clotted plasma is placed in a solution of urea.An identical clot is placed in a saline as control.An unstable clot due to factor XIII deficiency will dissolve in urea.

20. Reticulocytes: (Refer essay 1)

21. Rh factor : (refer essay 5)

22. Landsteiner's laws : (refer essay 5)

23.Cross matching : (refer essay 5)

24. Exchange transfusion : refer essay 5

25.Autologous transfusion:

Recently popular. Blood is withdrawn from a patient in advance of elective surgery and then transfused back, if required during surgery. Useful in patients with rare blood groups or with multiple allo-antibodies in whom cross-matched compatible blood is not available. Also it prevents the risk of transfusion transmitted infections like AIDS, and also eliminates the risk of transfusion disorders.

26. ABO incompatibility :

Hemolytic disease of the newborn rarely occurs if the mother is O and the fetus is A or B. Antibodies can enter the fetal blood leading to hemolytic anemia. Here the difference from Rh is that it commonly affects the first pregnancy and not so severe. Rh is confined to RBCs alone, but here ther are several target organs and is less severe. Requires mild or no treatment.

27.Erythroblastosis fetalis:

o Hemolytic disease of the newborn: Erythroblastosis Fetalis- disease of newborn or fetus which results from Rh incompatibility between mother and fetus.When Rh negative person is exposed to Rh positive blood, Anti-Rh antibodies develop slowly. Reaches the maximum concentration by 2 to 4 months. When he receives repeated transfusion of the same he can develop a severe transfusion reaction is called Rh incompatibility. It happens when an Rh negative mother carries an Rh positive fetus as the father is Rh positive. Normally the fetal blood doesn't come into contact with mother's blood.At the time of pragnancy small amounts of fetal blood containing Rh antigen leaks into maternal blood and mother develops significant titres of anti-Rh antibody. I.e. she gets sensitized to Rh antigen during postpartum period. Detectable antibodies develop after 6 months. So during the next pregnancy the antibodies cross the placenta to fetus.If the second foetus is Rh positive these antibodies cause agglutination and hemolysis of RBCs.The antibodies will not affect the Rh negative fetus.The anti-Rh antibodies cross the placenta to reach the fetus and cause hemolysis and various forms of hemolytic disease of the newborn called Erythroblastosis Fetalis. Degree of fetal damage depends upon magnitude of maternal anti-D response and the ability of maternal Rh antibodies to cross the placenta. If severe it will lead to hydrops fetalis. Infant is stillborn or may develp anemia, sever jaundice and edema. The hemolysis leads to anemia and tissue anoxemia. If the liver is damaged, there will be hypoproteinemia. Generalized edema, ascites and hydrothorax will be there. If the baby alive the condition is known as Icterus Gravis Neonatorum. Anemia is seen at birth. RBCs continue to be destroyed for 1-2 months. There will be enlargement of liver and spleen. Agglutinated cells gets hemolysed leading to jaundice.If the baby is born without jaundice,It will develops jaundice within 24 hours of birth. When the baby is in utero bilirubin will reach the maternal blood, but once the umbilical cord is clamped,level increases in fetus. The unconjugated bilirubin crosses the poorly developed blood brain barrier in fetus and gets into the basal ganglia leading to kernicterus. Bilirubin concentration will increase up to 18 to 20 mg/dl. Bllirubin rarely penetrates the BBB in adults but may do in fetus.

o Congenital Anemia of newborn: Mildest form, slow hemolysis, destruction of RBCs up to 6 weeks. Liver and spleen enlarged due to extramedullary hemopoeisis.

o Incidence: Rh negative mother with Rh positive fetus won't develop that much Anti Rh antibodies. So the first child is not affected. Hemolytic diseases occur in 3% of Rh positive fetuses born to Rh negative mother who have previously been pregnant with Rh positive babies.On third delivery 10% of Rh positive fetus are affected.The incidence progressively increases.

o Treatment:

-Curative: Exchange transfusion and phototherapy.

Exchange transfusion:Replace the Rh positive blood of fetus with Rh negative blood.A polythene catheter introduced into inferior venacava through the umbilical vein during the first 2 weeks to keep the bilirubin level decreased to prevent kernicterus. By about 6 weeks the tansfused Rh negative cells are replaced by Rh positive cells of the fetus and anti-Rh antibodies will be destroyed.

Phototherapy:The jaunticed baby is exposed to blue light. This degrades the bilirubin by photooxidation.

-Preventive: To prevent active immunization of mother, anti-D immunoglobulin of IgG type is administered via IM to mother during delivery and abortion. This antibody binds to the antigen sites on the fetal RBCs, thereby these cells cannot be recognized by mother's immune system and it can't elicit the response. It neutralizes the volume of red cells reaching maternal circulation. It should be administered within 72 hours following delivery or abortion. 300 micrograms should be given after delivery. 100 micrograms during abortion (>20 weeks), 50micrograms following abortion <20 weeks or in case of ectopic pregnancy.

28.Functions of lymph: (refer essay 7)

29.Relation of oedema with malnutrition

In malnutrition, protein content decreases and thereby colloid osmotic pressure decreases resulting in oedema. refer formation of lymph,essay 7

Physiological basis:

* **1.Bleeding time is prolonged but cloting time is normal in trombocytopenic purpura**

Refer shortnote-18(Bleeding time is determined by no of platelets and clotting time is determined by availability of clotting factors)

2.Blood clots are not formed in vascular sysem(in vivo)

Refer shortnote-14

3.Bleeding is manifested in deficiency of factor VIII & IX eventhough extrinsic mechanism is normal

Refer essay-3(During extrinsic mechanism whenever more Xa is formed tissue factor inhibitor inhibit VIIa and tissue thromboplastin and tissue factor inhibitor form a complex with VIIa and tissue thromboplastin which lacks enzymatic activity.)

4.Edema is manifested in malnutrition/ hypoproteinemia

Refer shortnote-21

5.Bleeding manifestations in liver disease

Refer clotting factors page no.5(synthesis of clotting factors by liver)

7.Polycythemia in high altitude

Refer regulation of erythropoiesis page no.4(high altitude-hypoxia-increased erythropoietin secreation-increased erythropoiesis-polycythemia)

RESPIRATORY SYSTEM

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ESSAYS

1. Regulation of respiration:

Rspiration is a automatic process that is constantly adjusted to meet the everyday requirement.Even though widely differing demand for O_2 uptake and CO_2 output is made by the body, the arterial pO_2 and pCO_2 are kept within normal limits. Respiration is produced by rhythmic discharge of the neuron that innervate the respiratory muscle .The discharge of this motor neuron in turn depend on impulse from brain. Respiration regulated by

1) Neural mechanism
2) Chemical mechanism

Neural mechanism

Two separate mechanisms:-

1)Automatic control
2)Voluntary control

Automatic control:-

It begins at birth.Controll is mainly through respiratory centers: Respiratory centers are group of neurons located bilaterally in pons and medulla.Its modification by input of information from higher centres and from systemic receptors.From these centres efferent neurons arise and are located in the white matter of spinal cord between anterior and lateral corticospinal tract. This efferents connect with anterior horn cell of the spinal cord from which phrenic nerve(C3,C4,C5)which supply diaphragm and the external intercostals nerve that supply the external intercostals muscles arise.When inspiratory neuron are active expiratory neuron inhibited. This is due to reciprocal innervation.

Respiratory centres are divided into medullary and pontine centres .

Medullary centres are 3 types :-

1)Dorsal Respiratory Group of neurons(DRG)
2)Ventral Respiratory Group of neurons(VRG)
3)PreBotzinger Complex(PreBOTC)

Pontine centres:-

1)Pneumotaxic centre
2)Apneustic centre

DRG:-DRG of neurons extends most of the length of the medulla.Located on dorsal portion of medulla in and near the Nucleus Tractus Solitarius(NTS).They contain neurons that active during quiet inspiration.It controls the rate and amplitude.Signals from this neuron is inspiratory ramp signal(signal that is transmitted to respiratory muscls in normal inspiration).It begins weakly and increase steadily in a ramp manner for about 2 seconds and it ceases abruptly for approximately next 3 seconds. This ramp signal causes contraction of inspiratory muscles.When ramp signal ceases inspiratory muscle relax and expiration occurs.Then inspiratory ramp signal for another cycle start. This is repeated again and again.

Advantage of ramp signal-It causes steady increase in lung volume during inspiration rather than inspiratory gap.Dorsal group of neuron receive afferent from chemoreceptors,baroreceptors,propioceptors,pulmonary mechanoreceptors and from higher brain centres(pons,cerebral cortex,hypothalamus,lymbic system).DRG emit repetitive burst of inspiratory action potential and the basic cause of repetitive discharge is unknown.

VRG:-are long columns of neuron located in each side of the medulla ,anterior and lateral to DRG in the nucleus ambiguous rostrally and the nucleus retro ambiguous centrally.The neurons of VRG remain almost totally inactive during normal respiration , but in forceful breathing as in exercise , it become active,i.e. respiratory signals spill over from DRG to VRG.It contain both I and E neurons. I neurons are situated in the midportion and are active during forceful inspiration where as E neurons at caudal and rostral end are important in providing the powerful respiratory signals.Then VRG also contributes to respiratory drive .They are especially important in providing powerful expiratory signal to abdominal muscle during heavy expiration.

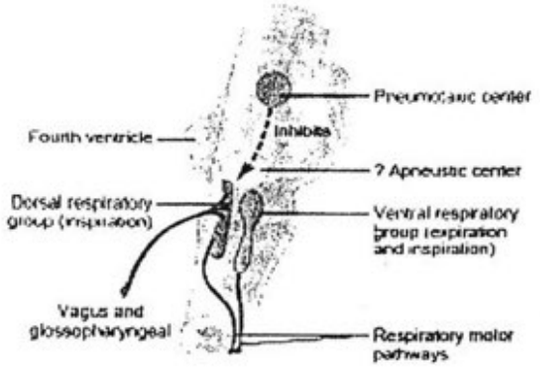
Pre-Botzinger complex:-It is now clear that rhythmic respiration is initiated by a small group of pacemaker cell in pre-botzinger complex on either side of medulla between nucleus ambiguous and lateral reticular nucleus.These neurons discharge rhythmically and the produced rhythmic discharge in phrenic motor neuron that are abolished by section between pre-botzinger complex and these motor neurons.DRG and VRG in medulla project into PreBOTC .However lesion of DRG and VRG don't abolish respiratory activity.

Pontine centres and vagal influences

Although the rhythmic discharge of medullary neurons is concerned with spontaneous respiration. It is modified by pontine neurons and afferent in the vagus from receptors in the airways and lungs.Pontine centres are pneumotaxic centre and apneustic centre.

Pnemotaxic centre:-Is in upper pons. It is located in the medial parabrachial and kolliker fuse nuclei of dorsal lateral pons.Normal function is unknown.Contain neurons active during inspiration and expiration(both I and E neurons are present) Main function of this centre is to switch off inspiration thus controlling the duration of inspiration and inspiratory volume. It limits inspiration. Strong signal from pneumotaxic centre increase the rate of respiration and decrease the filling of lung. When this area is damaged respiration become slower and tidal volume increases.

Apneustic centre:- This centre is situated in lower pons. Impulses from this area has an excitatory effect on DRG and may prolong inspiratory ramp signal. The exact role of this centre in normal respiration is unknown. This centre operate in association with pneumotaxic centre to control the depth of respiration There is controversy regarding its existence .In experimental animal section of brain just above this area will cause apneusis i.e. prolonged inspiratory gasp interrupted by transient expiratory effort.



Organization of the respiratory center.

✱ **Effect of lesion at various levels:**

1) Transection of brainstem above pons- Automatic respiration is normal. It shows that respiratory centres are located below this level.

2)Just below to pneumotaxic centre or midpontine section– Respiration become slower , tidal volume greater.When vagi are also cut there is prolonged inspiratory spasm that result on breath holding called apneusis.

3)Transection at inferior border of pons – spontaneous respiration continues,but somewhat irregular and gasping because there is no control from pneumotaxic centre.

4) Transection of brain stem below medulla – completely stop respiration.

Selective lesion of DRG or VRG reduces the amplitude of respiration but don't abolish respiration. So they are not obligatory part of impulse generation. Actual generator is PreBOTC.

✱ **Herring Breuer Reflex:(short note)**

In addition to neural respiratory central mechanism operating entirely within brain stem,sensory signals from lung also help to control respiration. Slowly adapting stretch receptors are located in the muscular wall of bronchi and bronchioles through out the lungs.

Overstretching of the lungs during inspiration stimulate the stretch receptor and impulses are carried through afferent pulmonary vagal fibres. These impulses are carried to DRG.When there is increase in tidal volume to more than 1 litres,the stretch receptors of lung are stimulated to greater extent and there is increase in the rate impulse discharge to DRG.It switch off inspiratory ramp signal and further inspiration just like signals from pneumotaxic centre. This reflex is called herring Breuer inflation reflex. This reflex also increase rate of respiration. It doesn't seem to have a role in control of normal respiration because,these stretch receptors are not activated until the tidal volume increases greater that 1.5L.So this appears to be a protective mechanism to prevent excess lung inflation.

Herring Breuer deflation reflex is a decrease of expiration produced by marked lung deflation.

Voluntary control of respiration.

Breathing can be voluntary control to considerable extent by cerebral cortex.Cortex can override the function of brain stem within limits .For voluntary control,nervous pathway pass directly from cerebral cortex and higher centres through corticospinal tract to the spinal neurons that innervate the respiratory muscles. These nervous pathways bypass the medullary respiration centre. Automatic and voluntary control of respiration are seperate and they can be affected seperately.Automatic control of respiration is sometimes disrupted without loss of voluntary control. This rare clinical condition is called 'Ondines curse'.

Although respiration can be inhibited for sometime the voluntary control is eventually over widened .The point at which breathing can no longer be voluntarily inhibited is called **breaking point**.The breaking point is due to rise in arterial pCO_2 and fall in pO_2 .In normal this ranges from 40-80seconds after a maximum inspiration.

✱ **Chemical regulation of respiration**

Chemical regulatory mechanism adjust ventilation in such a way that normal concentration of O_2,CO_2,H^+ ions are maintained in blood and tissue. Decreased O_2 tension, increased CO_2 , increased H^+ ions stimulate respiration and viceversa.These effects are mediated through spinal receptors called chemoreceptors.A chemoreceptor is a receptor which responds to changes in chemical components of blood and other fluid.

Two types of respiratory chemo receptors are there:-

1) Central chemoreceptor
2) Peripheral chemoreceptor

Central chemoreceptors

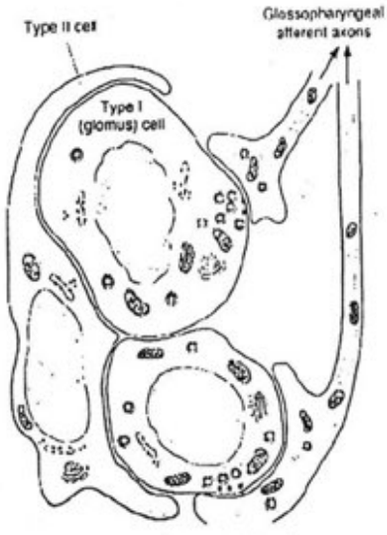
DRG , VRG and pneumotaxic centre are not affected with changes in blood CO_2 and H^+ ions. In addition there are additional neuronal area called central chemoreceptors located 0.2 mm beneath ventral surface of medulla. This area is highly sensitive to H^+ ion concentration of CSF and interstitial fluid.

But H^+ ions in blood does not pass through blood brain barrier or blood CSF barrier. For this reason change in H^+ ion in blood has considerably less effect.

When pCO_2 increases CO_2 cross the BBB easily and CO_2 immediately react with H_2O of CSF and interstitial fluid,to form H_2CO_3 which splits to H^+ and HCO_3^- .This H^+ ion stimulate central chemo receptors . Therefore CO_2 has potent indirect effect on central chemoreceptors.

Increased CO_2 in blood has acute effect that is the effect in first few hrs and gradually decrease in next 1 to 2 days .This is because H^+ ions adjusted back to normal by kidney by increasing HCO_3^- in blood and CSF.HCO_3^- crosses the BBB,it binds with H^+ and decrease their concentration.Therefore change in blood CO_2 has potent acute effect but only weak chronic effect.

Peripheral chemoreceptors:



Organization of the carotid body

They are carotid and aortic bodies discovered by Heymen for which he got Nobel. There is a carotid body near the carotid artery bifurcation on each side .There are usually 2 or more aortic bodies near arch of aorta.

Each carotid or aortic bodies (glomus) contain islands of two types of cells – Type 1 and type 2 cells surrounded by fenestrated capillaries .Type 1 cell is also called glomus cell which are closely associated with cuplike ending of afferent nerve .Type 1 cell resemble adrenal chromaffin cell and have a dense core granules containing catecholamine particularly dopamine.It is released on exposure to hypoxia.Type 1cell have O_2 sensitive K^+ channels.Type 2 cell surrounds 4-6 type 1 cells.They are glia like cells.

Afferent nerve from carotid body is carotid sinus nerve that is a branch of ninth cranial nerve. Aortic body's afferent nerve is aortic nerve i.e. a branch of vagus nerve.These nerves end on DRG. When exposed to hypoxia type I cell secrete catecholamine (dopamine) that stimulate the afferent nerve via D_2 receptors.

Mechanism of release of neurotransmitter by type 1 cell

Hypoxia ⟶ decrease activity of O_2 sensitive K^+ channel⟶ decrease in K^+ efflux ⟶ increased Ca^{2+} influx⟶ depolarization of cell membrane⟶ generation of AP⟶ dopamine release⟶ binds to O_2 receptor⟶ stimulation afferent nerve endings via D_2 receptors⟶ increase respiratory activity.

Blood flow in each carotid body weighing 2mg is approximately 0.04ml/min i.e. 2000ml/100gm/min. This blood flow is highest in body compared to brain(54ml/100mg/min), to kidney (420ml/100mg/min) and to heart (84ml/100mg/min).

Therefore O_2 need of this carotid body can be met largely by dissolved O_2 alone.The peripheral chemoreceptors are the only chemoreceptor that respond to change in pO_2 .An increase in either CO_2 conc or H^+ can also excite the PCR but the effect in central CR is 7 times greater.But the stimulatory effect of CO_2 via PCR occur 6 times as rapid as central CR.

Stimulants of peripheral chemoreceptors

1 – Hypoxic hypoxia – pO_2 is less

2 – Stagnant hypoxia – The amount of O_2 delivered to receptor per unit time is decreased.

3 – Histotoxic hypoxia – drugs like cyanide, nicotine, lobeline etc prevent O_2 utilization at tissue level .

4 – asphyxia – combination of O_2 lack with CO_2 excess. So CO_2 also stimulate peripheral chemoreceptors

5 – increased plasma K+ level – stimulate peripheral chemo receptor. For e.g.: in exercise there is increased plasma K+ level that cause exercise induced hyperpnoea.(either rate or depth of respiration)

Peripheral chemo receptors are not stimulated in anemia or CO poisoning. These receptors not stimulated because although the combined O_2 in the blood is markedly reduced the amount of dissolved O_2 reaching the chemoreceptor is normal and also in anemia there is increased blood flow.

Because of anatomical location of aortic body , they haven't been studied in detail as carotid body.Suppose in human both carotid bodies have been removed but aortic bodies left intact. The response is similar to denervation of both aortic and carotid body in animals i.e. there is little change in ventilation at rest but ventilatory response to hypoxia lost and 30% of reduction in ventilatory response of CO_2.

Ventilatory response to changes in acid base balance: - There are metabolic acidosis and alkalosis and respiratory acidosis and alkalosis.

Metabolic acidosis

One example is diabetic ketoacidosis .Increased ketone bodies – acidic pH - hyperventilation(kussmaul breathing) – CO_2 removed – pH back to normal.

Metabolic alkalosis

In vomiting – HCl lost – pH alkaline – decreased H^+ - so hypoventilation – CO_2 accumulated – pH decreases

Respiratory alkalosis

Eg:- In psychiatric patients – hyperventilation that is not secondary to increase H^+ ion in blood– so pH increases.

Respiratory acidosis

Hypoventilation if not secondary to decreased H^+ ion in blood produces respiratory acidosis.

Effect of CO_2 on ventilation

Under normal condition pCO_2 is the most important factor regulating ventilation.pCO_2 of arterial blood is 40 mm hg .When there is increased pCO_2 of blood (increased tissue metabolism) chemo receptors are stimulated,as a result which leads to hyperventilation and washing out CO_2 bring back pCO_2 to normal. Suppose if we inhale gas mixture containing CO_2, there is increased alveolar pCO_2 and increased arterial pCO_2 which stimulate chemo receptors – hyperventilation – bring CO_2 back to normal.

pCO_2 of inspired air – 0.03mmhg .If pCO_2 of inspired air increase up to 15mmhg it produces a slight increment in alveolar pCO_2(3 mm hg).This pCO_2 doesn't drop to normal level and a new equilibrium is reached at which the alveolar pCO_2 is slightly elevated and hyperventilation persist as long as CO_2 is inhaled .This is essentially a linear relationship between respiratory minute volume and alveolar pCO_2 but there is an upper limit to this linearity of relationship between alveolar pCO_2 and respiratory minute volume.

When pCO_2 of inspired air close to alveolar pCO_2 elimination of CO_2 become difficult and when CO_2 content is more that 7%,alveolar and arterial pCO_2 begin to rise abruptly in spite of hyperventilation. The resultant accumulations of CO_2 in the body depresses the CNS increasing respiratory centre and produces headache confusion and eventually coma .This is **CO_2 narcosis.**

If a normal man makes violent voluntary hyperventilation the alveolar pCO_2 decreases this finally leads to temporary apnea. This is because drive for respiration disappears due to elimination CO_2.CO_2 exerts 70-80% of its effect though central chemoreceptors .Of this direct effect is little but it has potent indirect effect. H+ ion has potent stimulatory effect on respiratory centre. H+ ion can also act on peripheral chemoreceptor. Effect of CO_2 on peripheral chemoreceptor is slight but it occurs 5 times as rapidly as central chemoreceptors. Ventilatory response to CO_2 is decreased in sleep,oldage,genetic and racial factors .Trained athletes and divers have low CO_2 sensitivity.

Ventilatory response to hypoxia

When arterial pO_2 below normal it causes stimulation of chemoreceptors and there is increased ventilation. This stimulation is slight when pO_2 is more than 60mmhg.Marked stimulation of chemoreceptor occurs when the pO_2 of arterial blood falls below 60mmhg.The reason is the hypoxia causes formation of reduced Hb, which is a weaker acid than oxy Hb .So it can act as a buffer and binds with H^+ ion readily. The fall in H^+ ion inhibit the respiration.

If any increase in ventilation due to hypoxia from 100mm Hg to 60mm Hg,it washes off CO_2 which tend to inhibit respiration .But pO_2 below 60mmhg there is a strong stimulation of peripheral chemoreceptors it override the inhibitory effect and produces marked increase in pulmonary ventilation .

Effect of hypoxia on CO_2-response curve:-

When alveolar pO_2 kept constant response to various inspired CO_2 show linear relationship. But response of CO_2 at different fixed pO_2 the slope of response curve changes, .The slope increased when alveolar pCO_2 decreases .In other words hypoxia makes the person more sensitive to arterial pCO_2.

Effect of CO_2 on O_2 response curve:

When pCO_2 held constant level above normal value there is stimulation of respiration even at 90-110 mm Hg range of pO_2.When pCO_2 fixed below normal there is no stimulation until pO_2 falls below 60mm Hg.

Effect of H+ ion on co_2 response curve:

An increase in arterial H^+ ion concentration stimulate the respiration.Stimulatory effect of H+ ion and CO_2 on respiration appear to be additive. At higher pH the curve shifted to right and vice versa.

2. Transport of O_2

The diffusing capacity of O_2 across respiration membrane is 21ml/ml/mmHg.So total 230-250 ml of O_2 is diffused across the respiratory membrane per minute.O_2 is transported into tissue through blood in two forms.

1) Dissolved state i.e. about (3%)
2) Combination with hemoglobin (97%)

Dissloved State:

The amount of dissolved O_2 is directly proportional to pO_2 .For each mm of Hg of pO_2 there is 0.003ml of O_2 per 100ml.pO_2 of arterial blood is 100mmHg ,so 100ml of arterial blood can hold only 0.3 ml of O_2 in solution.pO_2 of venous blood is 40mmhg, dissolved o_2 in venous blood = 40 × 0.003 = 0.12ml/100ml.Therefore 0.18ml (0.3-0.12) of oxygen is taken into tissue in dissolved state. Although the dissolved form is very small it is functionally very important , because it is the gas in solution that exert partial pressure. It is the pO_2 in the blood which determine the quantity of O_2 that will combine with hemoglobin.

Combination with hemoglobin:

97% of oxygen transport is by combination with Hb.

Presence of hemoglobin increase O_2 carrying capacity 70 fold .Binding of O_2 with Hb depend on po_2.When pO_2 is high,O_2 binds loosely and reversibly with Hb as in pulmonary capillary. In tissue po_2 is low so O_2 releases from Hb to tissue.

When blood is equillibrated with 100% O_2 (pO_2 760mmHg),the normal Hb become 100% saturated.At this stage 1gm of Hb can bind with 1.39ml O_2 .Due to small inactive Hb derivatives it can bind maximum 1.34ml O_2.Average Hb conc is 15gm%.Therefore 15gm can bind 15 × 1.34 = 20.1ml of O_2 per 100ml.But arterial blood it is only 97% saturated because of the admixture of venous blood (physiological shunt).Therefore it can bind only 19.5ml of O_2 .Arterial blood contain 19.8ml of O_2 (dissolved state + combination of Hb) ie = 19.5ml + 0.3ml = 19.8ml. In venous blood Hb is 75% saturated with O_2 .Therefore 15.1ml of O_2 in combination with Hb. Dissolved state is

0.12ml .Therefore total O_2 carried by venous blood = 0.12 + 15.1 = 15.2ml

Total O_2 in arterial blood = 19.8ml

Total O_2 in venous blood = 15.2ml

Differance= 4.6ml i.e. 4.6ml of O_2 is taken into the tissue from each deciliter of blood passing through them. Thus 250ml of O_2 is transported from blood into tissue at rest.

Reaction of Hb with O_2

Hb is a protein made up of four subunit .Each subunit contain a heme and globin (4 polypeptide chains).

Heme is iron containing porphyrin .Iron is in ferrous state. Each iron bind with one molecule of O_2 .Since Hb containing four iron atoms it can bind with four molecules of O_2 .The reaction is oxygenation not oxidation because after binding with O_2 the iron is still in ferrous state.The reaction is reversible.

Heme-heme interaction

$Hb_4 + O_2 \longrightarrow Hb_4O_2$
$Hb_4 + O_4 \longrightarrow Hb_4O_4$
$Hb_4 + O_6 \longrightarrow Hb_4O_6$
$Hb_4 + O_8 \longrightarrow Hb_4O_8$

Combination of first heme in hemoglobin molecule with O_2 increase the affinity of second heme for O_2 and O_2 cation of second heme increases affinity of third heme and so on. This is called heme – heme interaction. In deoxy hemoglobin the globin units are tightly bound,it is called **T configuration** or tense configuration which decreases the affinity of molecule for O_2 .When O_2 is first bound the bonds holding the globin units are relaxed producing a relaxed configuration of **R configuration.** It exposes more O_2 binding site .This oxygenation is very rapid .It takes less than 0.01seconds.

In the tissue, the reaction are reversed releasing O_2 into the tissue and deoxygenation also very rapid.

Oxygen content – is the total volume of oxygen in 100ml of whole blood i.e. 19.8ml/100ml.

Oxygen carrying capacity – maximum amount of O_2 that can combine with Hb in 100ml of blood when the Hb is 100% saturated. i.e. 20.1ml/100ml.

Oxygen saturation of Hb = (oxygen combined with hemoglobin /oxygen capacity) × 100

=(19.5/20.1) × 100

= 97.5%

Coefficient of O_2 utilization (utilization coefficient)

It is the % of oxygenated Hb that gives its O_2 as it passes through tissue capillaries.

Normal value – 25%.During strenuous exercise the utilization coefficient increases up to 75-80%.In some area where blood flow is very slow,so utilization coefficient is approximately even 100%.

O_2– Hb dissociation curve

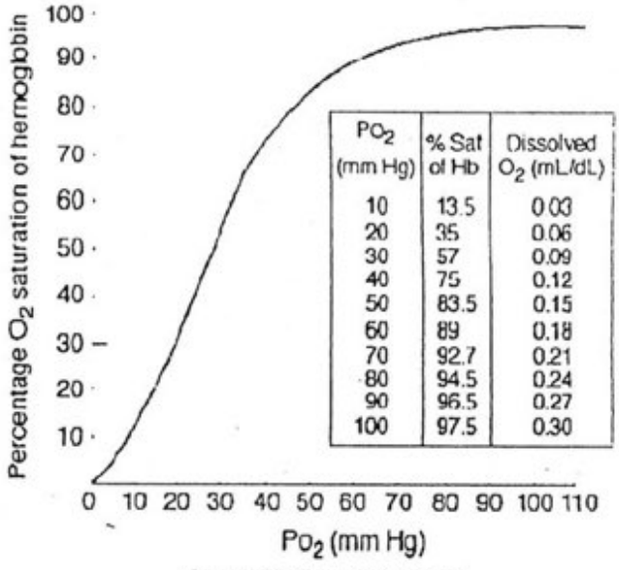
This is the curve relating % of O_2 saturation of Hb to pO_2.Here pO_2 is in X axis and % saturation of Hb is in Y axis. Shape of the curve is sigmoid. It has steep lower part and relatively flat upperpart.The sigmoid shape is due to heme interaction or TR interconversion.When systemic arterial pO_2 – 95mmhg, the percentage of saturation of Hb is 97%.

In 95mmhg – 97%
90mm Hg -95%
70mm Hg–93%
60mm Hg - 89 %
40mm Hg - 75%
26mm Hg - 50% saturated (p50)

Significances of sigmoid shape of the curve

Fall in pO_2 from 95 to 60mmHg in alveolar air doesn't cause a large reduction in %saturation of Hb and thus oxygen is available to tissue. Because of the above reason the relatively upper part is called margin of safety.

But when pO_2 below 60mmhg small fall in pO_2 causes significant reduction in percentage saturation of Hb. This means that peripheral tissue can withdraw large mount of oxygen for a small drop in tissue capillary pO_2 .This behavior of Hb enables uptake of O_2 in lung where pO_2 is high and release of O_2 into the tissue where pO_2 is low.



Oxygen-Hb dissociation curve

p50

p50 is the pO_2 at which Hb is half saturated (50%) with O_2 .So p50 is 26mmHg(at pCO_2 – 40mmhg , pH = 7.4 and temp = 37 degree Celsius).It is a useful measure of ODC.

Significance of p50

1)Higher the p50 lower the affinity of Hb for O_2 (O_2 dissociation curve shift to right)

2)O_2 affinity of different Hb or different red cells can be compared by determining p50.

3)pH, temperature and 2,3-BPG are factors that shift the curve .

Factors that shift the oxygen dissociation curve(ODC) to right:-

ODC shifted to right means decreased affinity of Hb for O_2 and it occurs in tissue.p50 is increased.A higher pO_2

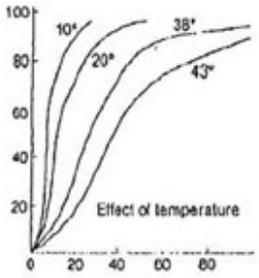
is needed for Hb to bind to a given amount of O_2.This favour dissociation.The factors are:-

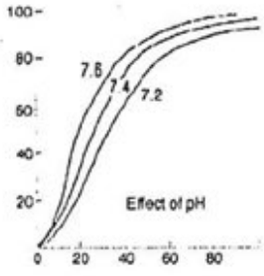
-increased pCO_2
-decreased pH
-increased temperature
-increased 2,3-BPG

Factors that shift ODC to left :-

Increased affinity of Hb for O_2 and it occurs in lung.p50 is decreased.Factors are:-

-decreased CO_2
-increased pH
-decreased temperature
-decreased 2,3-bpg
-increased fetal Hb





3. CO_2 transport:

CO_2 is carried though blood in following ways:

1) Dissolved state – both plasma and RBC (7%)
2) In the form of carbamino compounds (23%)
3)In the form of bicarbonate (70%)

Dissolved form

Solubility of CO_2 in blood is 20 times that of O_2 .Therefore 0.06 ml of CO_2 dissolved in100ml of blood/mmHg.Amount of CO_2 dissolved in venous blood = 0.06 × 46=2.8ml/ 100ml and in arterial blood = 0.06 × 40 = 2.4ml/100ml.

In the form of carbamino compounds

In the plasma CO_2 reacts with plasma proteins to form small amount of carbamino compound. In the RBC some of the CO_2 react directly with amino group of protein principally globin of Hb to form carbamino hemoglobin .It occurs with a loose bond and is a reversible reaction .So that CO_2 is easily released into the alveoli where pCO_2 is lower than in tissue capillaries.A small amount of CO_2 also react with the plasma proteins to form carbamino compounds.

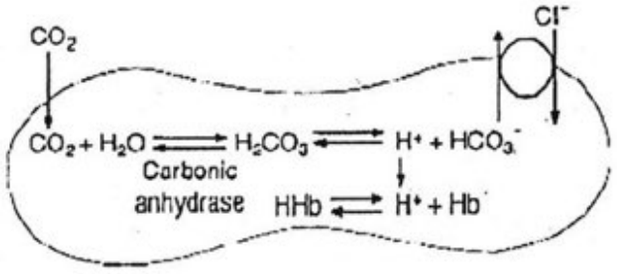
As bicarbonate

The dissolved CO_2 reacts with water to form carbonic acid.

$CO_2 + H_2O \longrightarrow H_2CO_3$ in the presence of carbonic anhydrase(CA).

Immediately carbonic acid splits to H^+ and HCO_3^-.CA accelerates the reaction 5000 folds .This enzyme is present in the RBC .So reaction is slow in plasma but very rapid within RBC.

Carbonic acid splits into H^+ and HCO_3^- .H^+ ion cant move easily out of RBC because RBC cell membrane is relatively impermeable to cation .So H^+ combine with Hb in RBC.70% of HCO_3^- diffuses from RBC into plasma in exchange of Cl^- .This is brought about by special protein in RBC cell membrane called Band 3 or anion exchanger1.This phenomenon is called **Chloride Shift or Hamburger phenomenon.**(Hamburger 1918).

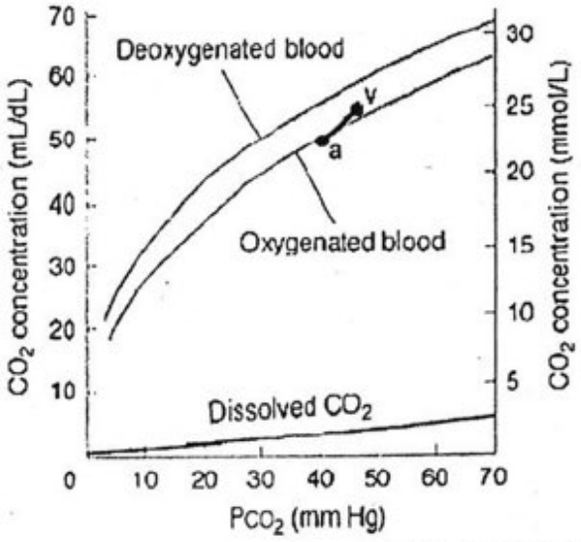


For each CO_2 molecule added to an RBC there is an increase of one osmotically active particle either HCO_3^- or Cl^- in RBC. So RBC take up more water and the size of RBC increases.So the hematocrit of venous blood is normally 3% higher than that of arterial blood.In the lung there is reversal of all these steps.

70% of CO_2 is transported from tissue to lung in this form .In lungs reverse chloride shift occurs. So HCO_3^- migrate from plasma to RBC and Cl^- from RBC to plasma .Within the RBC , HCO_3^- forms CO_2 which enters the plasma diffuses into alveoli , then to outside.CO_2 is given out and Cl moves out of the RBC - reverse chloride shift.

CO_2 dissociation curve

CDC shows the relation between pCO_2 and total CO_2 content.CDC is more linear and steaper than ODC.



CO_2 dissociation Curve.The arterial point (a) and the venous point (v) indicate the total CO_2 content found in arterial blood and venous blood of normal resting humans.

Total quantity of CO_2 combined with blood depend on pCO_2.The relationship between pCO_2 and CO_2 content is

depicted in CO_2 dissociation curve.The range of pCO_2 between arterial(40mmHg) and venous blood(46mmHg) is narrow. Binding of O_2 to Hb reduces its affinity for CO_2 and tend to displace CO_2 from blood .This effect is called **Haldane effect**. That means deoxygenated hemoglobin can bind more H^+ ion than oxyhemoglobin and forms carbamino compound.

When we compare CO_2 dissociation curve for oxygenated and reduced blood at any given pCO_2 reduced Hb contains more CO_2 than oxygenated blood. In tissue capillaries , Haldane effect causes increase picking up of CO_2 because O_2 is removed from hemoglobin .In the lung it caused increase release of CO_2 because O_2 picked up by Hb.

Change in blood pH during CO_2 transport

From the tissue, CO_2 enters the venous blood.So large change in pH is prevented by acid base buffers in blood, Cl^- shift mechanism and presence of carbonic anhydrase -enzymes .pH of arterial blood is 7.4 and venous blood is 7.36.

4. Hypoxia:

It is the deficiency of oxygen at tissue level. Oxygen available to the cells is insufficient to carry out the normal cellular activities.

Causes:

i)Inadequate oxygenation of blood due to extrinsic reasons.
- 1 reduced O_2 tension in atmosphere.
- 2 Hypoventilation as seen in neuromuscular disease.

ii)Pulmonary diseases causing inadequate oxygenation.
- 1 Hypoventilation caused by increased airway resistance.
- 2 Abnormal alveolar ventilation perfusion ratio.
- 3 decreased diffusion across respiratory membrane.

iii)Venous to arterial shunts (right to left cardiac shunts).

iv)Inadequate oxygen transport to tissues.
- 1 Anemia / abnormal hemoglobin.
- 2 Circulatory defect.

v)Inadequate tissue capability of utilizing oxygen.
- Occur in poisoning.
- 1cyanide poisoning

Classification of hypoxia:

Hypoxia is classified into 4 types depending on the following factors:-

a. pO_2 of arterial blood
b. O_2 carrying capacity
c. Rate of blood flow to the tissues
d. Utilisation of O_2 by the tissues(arterio-venous O_2 conc.difference)

4 types are,

1.Hypoxic hypoxia.
2.Anemic hypoxia.
3.Stagnant hypoxia.
4.Histotoxic hypoxia.

1. Hypoxic hypoxia: Most common type of hypoxia seen clinically. Can occur in normal individuals at high altitude or as a complication of respiratory diseases or heart disease causing right to left shunt. Large amount of venous blood is shunted to arterial side.

In hypoxic hypoxia,

1.Partial pressure of oxygen in arterial blood is low.
2.Hemoglobin is normal.
3.Oxygen carrying capacity is normal.
4.Hemoglobin is not saturated with oxygen and so the oxygen content is low.
5 .Arteriovenous oxygen concentration difference is normal.

2.Anemic hypoxia: The cause can be grouped into qualitative and quantitative.

In qualitative type: Total hemoglobin concentration is normal but hemoglobin is not available for binding oxygen and hence adequate oxygen cannot be transported to tissues.

This type of deficiency is seen in carbon monoxide poisoning and in altered hemoglobin (met hemoglobin and sulfated hemoglobin)

In quantitative type: There is decrease in the hemoglobin concentration i.e. amount of hemoglobin available for transport is less.

In anemic hypoxia,

1. Partial pressure of oxygen of arterial blood is normal.
2. Hemoglobin available to carry oxygen is less.
3. Oxygen carrying capacity is decreased.
4.Oxygen content is also low.

Hypoxia due to anemia is not severe at rest because here red cell 2, 3-BPG is increased, cardiac output is increased and there is redistribution of blood flow.

But anemic patients have considerable difficulty during exercise because of limited ability to increase oxygen delivery to the tissues.

3. Stagnant hypoxia: Seen when great reduction in velocity of blood flow i.e. due to slow circulation. Blood stays in capillary for long time, so maximum oxygen is extracted by tissues from the blood and oxygen in the blood is nearly exhausted.

In stagnant hypoxia,

1. Partial pressure of oxygen of arterial blood is normal.
2. Hemoglobin concentration is normal.
3. Arterio-venous oxygen concentration difference is high.

Causes:-

It can be due to general circulatory defect as in circulatory or cardiac shocks or failure.

Localized circulatory defect as in block or spasm of peripheral, coronary or cerebral vessels.

Kidneys and heart are commonly affected by stagnant hypoxia due to shock, liver and brain due to cardiac failure and lungs are less commonly affected because of its large blood supply. It takes prolonged hypotension to produce a significant damage. When this occurs, it produces adult respiratory distress syndrome (ARDS). This is a late complication of shock and it produces damage to capillary endothelial cells and alveolar epithelial cells with release of cytokines, causes pulmonary damage and acute respiratory failure.

4. Histotoxic hypoxia: Inhibition of tissue oxidative processes and as a result tissue cannot utilize oxygen even though adequate oxygen is delivered.

1. The partial pressure of oxygen in arterial blood is normal.
2. Hemoglobin is normal.
3. Oxygen carrying capacity and oxygen content normal.
4. Arterio-venous oxygen concentration difference is less.

Causes:-

Inhibition of cytochrome oxidase which is necessary for tissue oxidative processes. This occurs in cyanide poisoning.

Deficiency of tissue cellular oxygenating enzymes, seen in vit.B_{12} deficiency.

Clinical features of hypoxia:-

Effects of hypoxia depend on the rapidity, severity and duration. The organs most susceptible are brain and heart.

- Severe hypoxia of sudden onset:-

-Loss of consciousness in 10-20 sec and death in 4-5min

- Hypoxia of gradual onset:-

- Drowsiness
- Headache
- Disorientation
- Anorexia
- Nausea and vomiting
- Tachycardia
- Pulmonary and systemic hypertension

Effects of hypoxia on different systems

Effects on cells: - It causes production of transcription factors known as hypoxia inducible factors (HIFs)

These are made up of α and β subunits in hypoxic individuals. The α subunits dimerise with β subunits and the dimers activate genes that produce angiogenic factors and erythropoietin.

Effects on nervous system: - Depending on rapidity and severity of onset, the symptoms vary.

- Rapid sever hypoxia: - Causes sudden loss of consciousness. Sudden drop in inspired pO_2 to less than 20mm Hg as occurring when cabin pressure is suddenly lost in a plane flying above 16000m. There is loss of consciousness in 10-20 seconds and death in 4-5 minutes.
- Less severe hypoxia: - Produce symptoms similar to alcohol intoxication. Include impaired judgment, excitement and a false sense of well being.

Depressed or apathetic, disorientation and loss of time sense. Dulled pain sensitivity. Decreased visual and auditory acuity. Retinal hemorrhage.

- When hypoxia is very rapid and severe, there is a brief period of initial hyperventilation followed by inhibition of respiratory centre.
- Gradual deprivation of oxygen – here oxygen content is decreased gradually and progressively. When the partial pressure of oxygen goes below 60mm Hg, there is hyperventilation. Further decrease in partial pressure of oxygen causes respiration to assume periodic character. When PO_2 decreases again, there is depression of respiration followed by loss of consciousness and failure of respiration.
- Very gradual deprivation of oxygen – when oxygen deprivation is gradual onset as seen in association with increase in altitude, sufficient time is available for compensatory mechanisms to operate. There is stimulation of respiration and ventilation is maintained at adequate levels up to a certain limit of hypoxia.

Effects on CVS: - Initially, there is increase in rate and force of contraction. Increase in cardiac output and increase in B.P. Coronary and cerebral circulation is increased. Cutaneous and splanchnic circulation is decreased. Later, the force of contraction decreases and BP falls.

Effects on digestive system: - Loss of appetite, dryness of mouth and increased thirst, nausea, vomiting. Effects of hypoxia persist even after restoration of oxygen supply. Prolonged and severe hypoxia will cause irreversible brain damage even if oxygen is restored.

Treatment: -

1. Treatment of underlying cause.
2. Oxygen therapy.

Before Oxygen therapy,the physiological basis of hypoxia shoud be considered.Administration of O_2 -rich gas mixture is of limited value in stagnant hypoxia,anemic hypoxia and hypoxia due to heart disease with right to left shunt.In other forms of hypoxic hypoxia O_2 therapy is of great benefit.

In hypoxia, due to hyperventilation, breathing 100% oxygen can move more oxygen to alveoli than breathing normal air. In case of hypoxia caused by impaired alveolar membrane diffusibility, oxygen therapy will increase the partial pressure of alveolar oxygen and oxygen gradient. In hypoxia occurring at high altitude, oxygen therapy can completely correct the decrease in oxygen level in the inspired gases and therefore is very effective.

In anemic, stagnant and Histotoxic hypoxia, oxygen therapy is of lesser value because here normal oxygen is available in the alveoli and so in these patients, by giving

oxygen, the amount of dissolved oxygen can be increased and so this may be of some benefit.

5. Respiratory Changes During Exercise:

Exercise is associated with extensive alteration of respiratory system. During exercise, O_2 demand of the active tissues is greatly increased. So, in order to meet the changing demands of the tissues the respiratory and circulatory mechanisms operate in an integrated manner.

Exercise can be divided into 2 types.

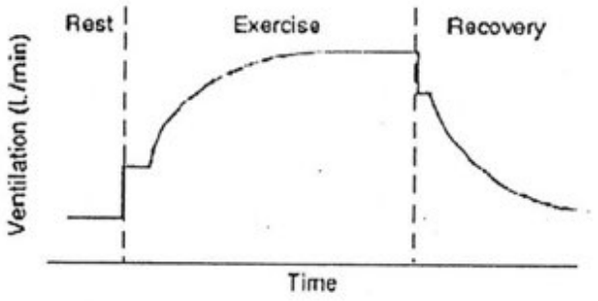
1) Moderate exercise- where all the tissue O_2 demands are met during the activity.

2) Severe muscular exercise- where the muscles do not get all O_2 required during exercise and O_2 debt is incurred.

So, the changes during these exercises are discussed separately. In general, there is increased ventilation during exercise.Circulatory adjustments include increase blood flow and there is increased extraction of O_2 by the muscles and more CO_2 enter the blood.Cardiac output increase from 5L/min to as much as 20-35l/min.Respiratory changes providesextra O_2 and eliminate more CO_2 and some of the heat.

I:Ventillatory Changes:-

A) In moderate exercise:-



Initially there is an abrupt increase in ventilation followed by a brief pause and then there is a gradual increase in the ventilatory response reaching a peak. Later during cessation of exercise there is a sudden fall followed by a brief pause and then a more gradual decline to pre-exercise levels.

Causes for abrupt increase:-

(i) Psychic stimuli – due to stimulatory impulses coming from the cerebral cortex to respiratory muscle.

(ii) Afferent impulses from proprioceptors in the muscle tendons and joints which stimulate the inspiratory centre causing an increase in ventilation.

Causes for gradual increase:-

1.Humoral stimuli - pO_2 ,pCO_2 and pH maintained. So actual respiratory mechanism not known.

May be due to-

(i) Increased sensitivity of respiratory centre to CO_2 due to increased production of CO_2 by increased metabolism

(ii) Decreased pO_2 due to increased utilisation of O_2

(iii)Increase in body temperature,

(iv) Increase in plasma potassium (K^+) levels – stimulate peripheral chemo receptors.

(v) Hypoxia in muscles also plays a role. – breathing 100% O_2 decreases the ventilatory response.

The chemical factors play a significant role in bringing about the final adjustment in respiration to keep the CO_2 and H^+ concentration normal.

At the beginning of exercise, there is dyspnoea which passes off after sometime and breathing becomes more comfortable. This is called **SECOND WIND.**

Recovery phase

When exercise is stopped, there is an abrupt decrease in ventilation followed by a pause and then a gradual decline to pre-exercise levels.

B) In Severe Exercise :-

1.In moderate exercise,there is an increase in depth of breathing,in severe exercise ,there is an increases in the depth as well as rate of respiration.

2.Oxygen consumption increases proportional to the energy expended and all the energy needs are met aerobically up to a point. But, when the muscular exertion is very great, increase in ventilation is inadequate to meet the oxygen requirement. So, energy is generated by anaerobic process by breakdown of glucose to lactate. So, the muscles contract anaerobically and oxygen debt is incurred.

Lactate accumulates in the muscle and H^+ concentration and the pH is decreased.

Lactic acid is that is produced is buffered with liberation of carbon dioxide. As more lactic acid is produced, more of carbon dioxide is liberated. This again causes a decrease in pH and has got an additive effect to increase the ventilation.

Increase in the ventilation is proportional to the increase in CO_2 produced. This is called Isocapnic buffering. As a result of this alveolar and arterial carbon dioxide changes are only little. With further accumulation of lactic acid, the increase in ventilation outstrips CO_2 production. The alveolar and arterial pCO_2 falls. This causes respiratory compensation for the metabolic acidosis produced by lactic acid.

After exercise, respiration rate continues to be increased and it may take as long as 90 minutes for respiration to come to basal levels. This is because oxygen debt has to be repaid and the stimulation to ventilation after exercise is the raised H^+ concentration due to lactic acidemia.

During repayment of O_2 debt, the oxygen concentration in myoglobin is slightly increased. ATP and phosphoryl creatinine are resynthesised. Lactic acid is removed.

*Magnitude of oxygen debt is the amount by which oxygen consumption exceeds basal consumption from the end of exertion until it has reached back to pre exercise levels.

II: Changes in tissues: -

During exercise, the contracting muscles use more oxygen. Tissue pO_2 and pO_2 in the venous blood from exercising muscles nears zero. More oxygen diffuses from the blood to the tissues. Previously closed capillaries open up. Capillary bed of the contracting muscles is dilated. So, the mean distance from blood to the tissues is decreased and this facilitates movement of oxygen from blood to tissue.

1.When PO_2 is less then 60mm Hg, oxygen dissociation curve is steep. So, a large amount of oxygen is supplied to the tissues.

2. Accumulation of CO_2 in the blood, rise in temperature in active tissues also increase in 2, 3-DPG shift ODC to right. This favors more oxygen delivery to the tissues.

3.Net effect is a 3 fold increase in extraction of oxygen from each unit of blood. This increase is accompanied by a 30fold increase in blood flow and it permits the metabolic rate of muscles to rise as much as 100 fold during exercise.

SHORT NOTES

1.Non respiratory functions of lungs:

- Defense:

o Respiratory passage humidify and cool or warm the inspired air.

o Hairs in the nostrils prevent the entry of many particles.

o The mucociliary clearance system remove inhaled pathogens of size 2-10μm.

o The pulmonary alveolar macrophages actively phagocytes the small particles, <2 μm that escape from the mucociliary escalator.

o Airway epithelial cells secrete a variety of substances that aid in lung diseases.eg;-IgA,collectins, defensins,peptides,proteases,reactive Oxygen and Nitrogen species.These act as antimicrobials.

o Lung is a part of body's mucosal immune system.

-Metabolic functions:

o Synthesis surfactants.

o Synthesise a variety of substances and they are used in the lung eg;-surfactants

o Synthesise substances and are released in to blood.eg;-prostaglandin,histamine,kalikrein

o Partial removal of substances from blood.eg;-prostaglandin,bradykinin,serotonin,adrenalin neuclotides,acetyl choline,nor epinephrine

o Convert Angiotensin I to Angiotensin II

2.Breath sounds:

Breath sounds are produced due to passage of air in the respiratory tract and alveoli.It can be heard on auscultation with a stethescope.There are 2 types - vesicular and bronchial.

vesicular breath sound;-Normally heard all over the chest.This sounds probably originate in the larger airway and it is of low pitched one.There is no pause between inspiration and expiration and inspiratory phase predominates over the expiratory phase(3:1).In bronchial asthma expiratory phase extented.

Bronchial breath sound ;-They also probably originate from the same airway but the sounds are heard with relatively little loss by filtration and attenuation.There is a gap between inspiration and expiration.Inspiratory phase and expiratory phase are equal.Normally heard over trachea.When heard over other areas of lung indicate that the lung tissue between airway and chest wall is not normal due to consolidation,fibrosis, and collapse.

Adventitious sounds:

Wheeze or rhonchi;Caused by airway narrowing,heard in contitions like asthma.

Crackles/crepitations;Short discontinous bubbling sounds heard in respiratory infections,pulmonary edema.

Pleural rub;Friction sound caused by inflamed pleural surface.

3. Pressure changes during respiration

During inspiration and expiration there is pressure changes in lung and pleural cavity.Pressure changes include Intrapleural,Intra pulmonary and trans pulmonary pressures.

1.Intra pulmonary pressure / Intra alveolar pressure. It is the pressure within the alveoli.The air passage and alveoli are in connection with atmosphere. Hence at ends of inspiration and expiration pressure is equal to atmospheric pressure. This is referred as zero reference pressure.

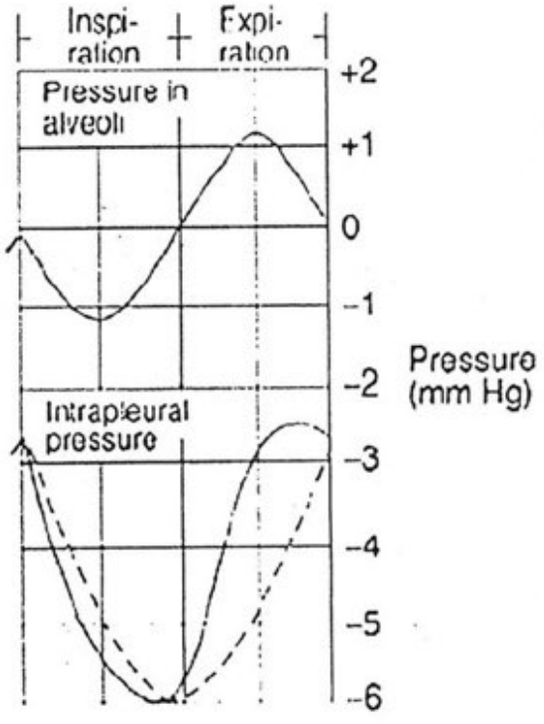
During inspiration lungs are pulled into more expanded position and intra pulmonary pressure become slightly negative and fall to -1mmHg and air flows into the lung. As air enters the lung the negativity decreases and at the end of inspiration it is again reaches to zero.

During expiration opposite changes occur, lung recoil and volume decreases and pressure raised to about +1mmhg and this forces air out of the lungs. At the end of expiration the pressure become zero .Therefore during quiet breathing /normal breathing intrapulmonary pressure varies from -1 to +1 .

During forced breathing, intra pulmonary pressure varies from -40 - +40 .Strong expiratory efforts are made with glottis closed by valsalva's maneuver as in coughing and spraining to defecate, the intrapulmonary pressure may rise to about +100 mmHg and can be reduced to -100 mmHg by strong inspiratory effort by muller'-s manever against clossed glottis.

2.**Intra pleural pressure / intra thoracic pressure** is the pressure inside the pleural cavity.This is the pressure throughout thoracic cavity outside the lung. Normally it is always -ve with respect to atmospheric pressure both

during inspiration and expiration. It is more negative at the apex than base.It is due to the effect of gravity.The intra pleural pressure at base of lung at start of inspiration is -2.5mmHg and decreases to -6mmHg at the end of inspiration and lung is pulled to the more expanded position .At the end of inspiration the lungs recoil and pull the chest wall to the expiratory position where the recoiled pressure of lung and chest wall balance and pressure return to the pre inspiratory level i.e. -2.5mmHg at the end of expiration.During forced inspiration IPP can become -30 mmHg and during forced expiration can become +25mHg. Involuntary inspiratory efforts as in muller's maneuver the intra pleural pressure reach to -80mmHg and in valsalva's maneuver IPP raise to +80 mmHg.



Dashed line indicate what wound be the IPP in the absence of airway and tissue resistance.

3.Trans pulmonary pressure: It is the pressure difference between the alveolar and IPP.It is the measure of elastic forces that tend to collapse the lung at the end of each respiration.At the end of inspiration and expiration it is equal to IPP as the alveolar pressure is zero

4. Cause of negativity of intra pleural pressure

In the fetus lungs are unexpanded and intra pleural pressure is equal to the atmospheric pressure. With the first breath at birth the thoracic cage enlarges and lungs expand and fill with air. After this lungs are never again completely empty of air.Normally chest wall has a tendency to expand and increase volume. But lung have a natural tendancy to recoil away from the chest wall due to abundant elastic tissue and surface tension ofa the fluid lining the alveoli.The recoiling forces trying to seperate 2 layers of the pleura produces the -ve IPP.But they can't be separated due to the surface tension of pleural fluid. The -ve IPP is also produced by continous suction of pleural fluid in to lymphatics and capillaries.

Significance of -ve IPP

-Prevent the collapse of lung and keeps them expanded

-Maintain alveolar stability

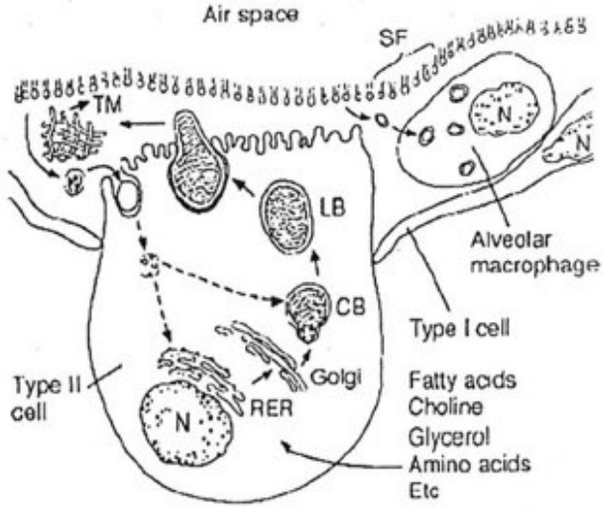
-Increases venous return to the heart

5. Surfactant:

It is a lipid surface tension lowering agent which lines alveoli and it was described by Pattle in 1955. It is a mixture of dipalmityl phosphatidyl choline,other phosopho lipids, protein and few amount of carbohydrate.

Composition

Dipalmityl phosphatidyl choline – 62%
Phosphatidyl glycerol – 5%
Other phospholipids – 10%
Neutral lipid – 13%
Protein – 8%
Carbohydrate – 2%



Surfactant are produced,secreted and recycled by type-2 alveolar epithelial cells. They are called granular pneumocytes.Typical lamellar bodies which are membrane bound organelle containing whorls of phospholipid.Phospholipids are formed in these cells and secreted into alveolar lumen by exocytosis. Tubes of lipid called tubular myelin formed from extruded lamellar bodies and tubular myelin inturn forms the phospholipids film .The surfactants are taken by alveolar macrophages. Formation of phospholipid film is greatly facilitated by proteins in surfactant. Main proteins are SPA,SPB,SPC and SPD.SPA regulate the feedback uptake of surfactant by type-2 cells and SPB and SPC facilitate the formation of phospholipids film. Phospholipids of surfactants line up

the alveoli with their hydrophobic fatty acid tail facing the lumen forming a monomolecular layer.

Surface tension is inversely proportional to surfactant concentration per unit area. During inspiration the lung expand and the surfactant molecule move apart and surfactant concentration per unit area decreases,hence surface tension increases.During expiration the lung shrink and concentration of surfactant per unit area increases,hence ST decreases. Surfactant normally appears at about 28th week of gestation and mature just before 36th week.So premature infants have deficiency of surfactant in their alveoli and there is increased surface tension .

Factors that influence surfactant production :-

-Insulin inhibit synthesis of surfactant

-Thyroid hormone increases the production of surfactant

-Maturation of surface is accelerated by glucocorticoid.

-Insulin inhibit synthesis of surfactant

- In diabetic mother there is hyperinsulinemia sothere is increased chance of infant respiratory distress syndrome(IRDS) or hyaline membrane disease.

-Cigarette smoking decreases the surfactant .There is decreased surfactant in person undergoing cardiac surgery involving pump oxygenator and interference of pulmonary circulation.

Function of surfactant:-

- It decreases the surface tension.Decrease in ST will increases the compliance of lung and decreases the work of breathing.Decrease in ST also prevent fluid from accumulating in the alveoli and keep the alveoli dry.

- Maintain the stability of alveoli and prevent collapse of small alveoli and lung,

- It lowers the elastic recoil at lowering volume and prevent collapse

- It keeps alveoli dry and prevent pulmonary edema

6.Infant respiratory distress syndrome

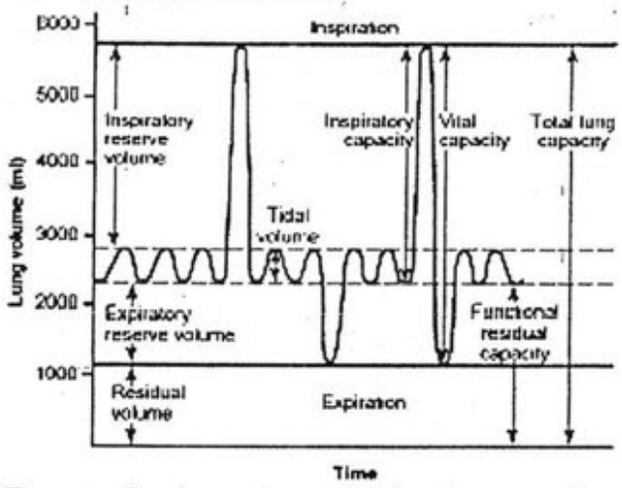
Due to deficiency of surfactant in newborn , usually in premature infants who have deficiency of surfactant in alveoli and surface tension in lung is high.Alveoli are collapsed in many lung areas (atelectasis). Here there is decreased O_2 , increased CO_2 and increased work of breathing. There is retension fluid in alveoli .During foetal life Cl- is secreted with fluid by pulmonary epithelial cells. At birth there is shift to Na absorption by these cells along with fluid vis epithelial sodium channel(ENaC) and fluid is absorbed with Na. Prolonged immaturity of ENaC contribute to pulmonary abnormality in IRDS.

Treatment:-

- Correction of hypoxia by giving continous positive pulmonary ventilation
- By giving inhalations of bovine surfactants

7. Lung volume and capacities:

The volume of respired gas can be measured using an instrument called spirometer or spirograph. The recording is called spirogram .Process is called spirometry.A wet or water type spirometer consists of a drum , inverted over a chamber of water and the drum is counterbalanced by a weight within the drum there is breathing gas or oxygen. A tube connects the mouth piece to the drum. During expiration the drum move upward. So the writing lever move downward. During inspiration, air is withdrawn from the chamber and drum falls down .So the attached writing lever move up.



There are four lung volumes and four lung capacities. Capacities ate combination of 2 or more volumes.RV cannot be measured by spirometer as RV cannot be exhaled out.FRC,TLC also cannot be measured as it involves RV.

Static Lung volumes

1.Tidal volume(TV) : It is the volume of air inspired or expired during each breath in quiet normal respiration. About 500ml

2.Inspiratory reserve volume(IRV) : It is the volume of air that can be inspired with maximum inspiratory effort in excess of TV.Normal value=3L

3.Expiratory reserve volume(ERV) : It is the volume of air that can be expired with maximum expiratory effort in excess of TV.Normal value=1.2L

4.Residual volume(RV) : Volume of air that remains in the lungs after a maximal expiratory effort.It can be expelled only by opening of chest wall causing collapse of lung.Normal male=1.2L

Significance of RV

-Keeps the lungs inflated between breaths.

-Helps to airate the lung between breaths thus preventing marked variation in alveolar PO_2 &PCO_2 .

-Medico legal importance;To detect whether the dead baby was still born or was born alive.If still born-lung will

be solid with no air and will sink in water.If born alive-RV will be there in lung and will float on water.

Lung capacities

1.Inspiratory capacity (IC):Volume of air can be inspired by a maximal inspiratory effort after a normal expiration. IC = TV + IRV.Normal value=3.5L

2.Functional residual capacity(FRC):Volume of air remaining after a normal expiration .FRC= ERV+RV Normal value=2.4L

3.Vital capacity(VC).Maximum volume of air that can be expired by a maximal expiratory effort after a maximal inspiration.VC = TV+ IRV + ERV

Normal value in male=4.7L,in female=3.1L

Significance of VC

-It asses the physiological fitness of a person
-Gives an index of pulmonary function .To asses the gross abnormalities of respiratory system.
-Useful in prognosis of respiratory diseases

Variations :-

Physiological variations–

-VC increases progressively from childhood to adolescence and is maximum in young adult and decreases in old ages.
-Built – height weight and body surface area have direct relation with VC.
-Higher in male than female
-Physical training – athletes have high VC
-Race – VC of black less than whites
-Posture – VC more in erect posture.In lying position,the abdominal contents are pressed against diaphragm
-In pregnancy VC decreases.

Pathological variations–

Decrease in,

-Disease of respiratory system like emphysema , fibrosis ,pneumothorax and pleural effusion
-CVS diseases like – pericardial effusion and congestive cardiac failure.
-Chest wall abnormalities lie kyphosis
-Acitis – fluid in the abdominal cavity

4.Total lung capacity(TLC) Maximum amount of air inside the lung after forceful inspiration.TLC= IRV+TV+ERV+RV Normal male= 5.9L

8. Timed vital capacity

Forced vital capacity(FVC);It is measured by a maximum inspiration followed by a rapid,forceful expiration in to a spirometer.It is either equal to or slightly lower than VC.

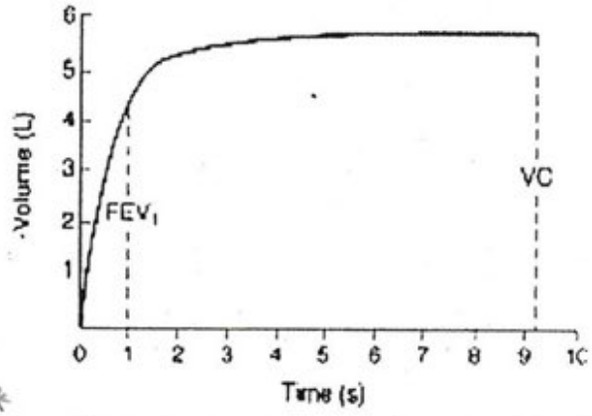
Timed vital capacity/ Forced expiratory volume(FEV) is the volume of air expelled in a specific time and is expressed in % .FEV is expressed as the % of FVC expelled in 1,2,3sec etc. FEV_1 Is the fraction of FVC expired at the end of first second i.e. 83%.Simillarly,

FEV_2 – 94%
FEV_3 – 97

It is important because it is a reliable index of pulmonary function. Helps to distinguish restrictive and obstructive lung diseases.

Restrictive lung diseases –Here there is limited expansion of lung and thorasic cage as in diseases like fibrosis of lung,kyphoscoliosis etc.Here FVC decrease much , but FEV1 decrease not much. So FEV1/FVC is normal or increases.

Obstructive lung diseases –Here there is airway obstruction as in diseases like asthma,emphysema.Here FVC decreases but FEV decrease more .So FEV1/FVC ratio is either normal or decreases



9. Dead space air and its measurment:

Normal tidal volume is 500ml .Of these 350ml occupies in the respiratory zone (from respiratory bronchiole onward) where the exchange of gas occurs. Rest 150ml occupies in the conducting zone(up to terminal bronchiole) where no gas exchange occurs with the pulmonary capillary blood. This part is called dead space air. Two types of dead space – Anatomical and physiological

Anatomical DS is the volume of air in conduction zone that does not take part in gaseous exchange .

Physiological DS is the volume of air not equilibrating with blood i.e. wasted ventilation.It include anatomical DS and alveolar DS(The air in the alveoli that is not equillibrating with blood)

Normally PDS=ADS,when all alveoli function normally.When there is under perfused or over ventilated alveoli, PDS > ADS.

PDS = ADS + alveoli under perfusion or over ventilation

Measurement

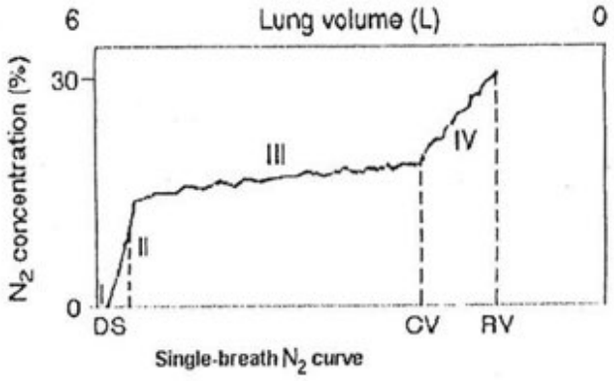
By single breath nitrogen curve analysis or Fowlers method.

Procedure

-Ask the subject to take deep single breath of pure O_2 after a forceful expiration.

-Expire into spirometer. Nitrogen content of expired air is continuously measured using nitrogen meter at the lips.

-Expired volume and N_2 conc. are plotted on a graph.



Single-breath N_2 curve

Phase 1 – No N_2.becouse air from conducting zone where the air has been completely replaced by O_2.

Phase 2 – Contains N_2 and N_2 concentration rises rapidly as alveolar emptying occurs and reaches a peak.It contains both dead space air + alveolar air.

Phase 3 –N_2 concentration reaches a plateau since the dead space air has been washed out and only alveolar air remains.

Phase 4 – increased N_2 from upper alveoli

The volume of DS is the volume of gas expired from peak inspiration to the mid portion of phase 2 .DS is calculated by drawing a vertical line that divide the phase 2 in equal part. Actually this measures the volume of conducting airways down to midpoint of transition from dead space to alveolar air.

Variations in dead space:

-ADS males>females due to increase in body weight.

- ADS increases in old age due to loss of elasticity.

-Increases during inspiration and decreases during expiration.

-Decreases when the neck is flexed and chin depressed.

-ADS decreases in bronchoconstriction.

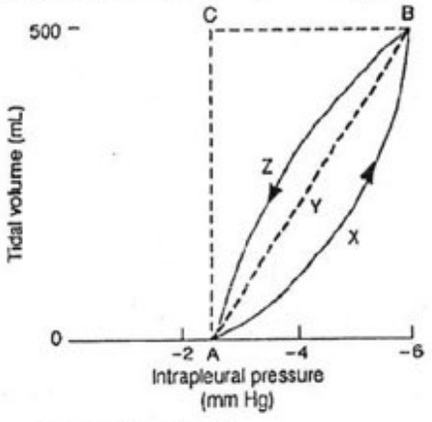
-PDS increases in emphysema.

10. Compliance of lung:

Compliance is the distensibility / expansibility of lung and chest wall.It is the change in lung volume per unit change in pressure. So compliance = ÄV/ÄP. It is the inverse of elasticity.Compliance reflects the ease with which an object can be deformed and elastance is the opposition of object to deformity by external force. Both lung and thorax are viscoelastic structures. Elastic property of lung is due to surface tension and elastic fibres of lung.Elastic property of thorax is due to natural elasticity of muscle tendon and connective tissue.

Compliance of the lung(both) is 0.2L/cmH_2O and chest wall compliance is 0.2L/cmH_2O , where as compliance of lung and thorax together is 0.1lL/cmH_2O due to counter balancing forces of lung and chest wall.

Measurement – The subject inhale or exhale small amount of air in successive step .At end of each breath intrapleural pressure is recorded. These observation are plotted in a graph .The curve obtained by plotting inspiratory volume is inspiratory compliance curve(AXB) and that by expiratory volume is expiratory compliance curve(AZB). The expiratory curve fails to follow the inspiratory curve fproducing hysteresis.The line AYD is the compliance line.Slope of the line at any point of this curve is compliance of lung i.e. ÄV/ÄP .Compliance is greater when measure during deflation than during inflation.This disparity is due to the difference in surface tension during inspiration and expiration which is regulated by surfactant conc.



Compliance depends on

-Volume of lung – larger the size of the lung higher the compliance .Less in patients with one lung removed i.e. half the ÄV/ÄP.

-Phase of respiration – it is more during deflation because surface tension is more during inflation.

Variations in compliance

-It is lower in children and in female.

-Lower in lying position and sitting position.

-Increased resistance in chest wall leads to decreased compliance e.g.: obesity ,kyphoscoliosis , weakness of respiratory muscle

-Compliance is decreased in following condition – fibrosis, pulmonary edema , collapse , deficiency of surfactant , pleural and pericardial effusion , acitis.

-Compliance is increased in emphysema .

11. Factors that maintain the stability of lung alveoli and importance: refer short note 4 & 5

12. Respiratory centres in brain stem & effects of vagotomy: (Refer essay 1)

13. Chemoreceptors & effects on ventilation: (Refer essay 1)

14. Herring bruer reflex: (Refer essay 1)

*15. Features of pulmonary circulation:

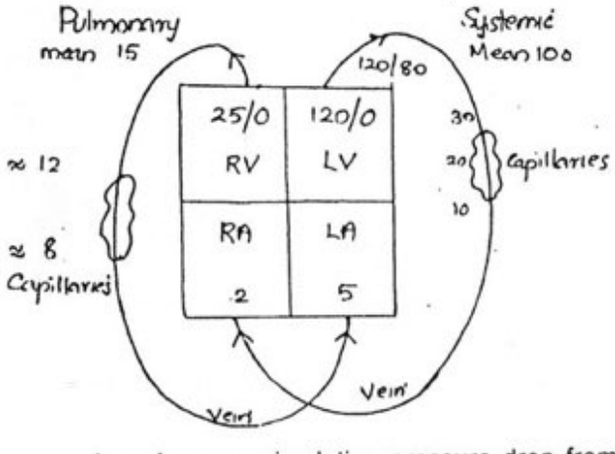
o Pulmonary artery is thin and carries deoxygenated blood. Wall thickness is twice of venacava and one third of aorta .Pulmonary arterial branches are short having larger diameter than the systemic counterpart .Vessels are thin with large compliance .Due to this pulmonary artery can accommodate two third of stroke volume.It is a low pressure and a low resistance system

o Reservoir of blood – because of distensibility and compliance pulmonary artery can accommodate large volume of blood and can function as a blood reservoir .When a person blows with force 250ml of blood can be expelled into systemic circulation. Also loss of blood by hemorrhage can partly be compensated by automatic shift of blood from lung into systemic circulation.

Pulmonary blood volume is higher in lying posture .During standing it decreases and some of the pulmonary reservoir is used to compensate the postural reduction of systemic venous return.

o pressure changes in pulmonary circulation – The right ventricular pressure is 25/0 mmHg and left ventricular pressure is 120/0 mmHg. During ejection aorta 120/80mmHg and pulmonary artery 24/9mmHg.Mean arterial pressure = diastolic pressure + 1/3 of pulse pressure i.e. average pressure during whole cardiac cycle .Mean arterial pressure = 100mmHg

Right arterial pr = 2mmHg andLeft arterial pr = 8mmHg.



In pulmonary circulation pressure drop from pulmonary artery to capillary is relatively small. Much pressure drop occurs in capillary bed itself and veins. In systemic circulation most of the pressure drop occurs just upstream of capillary. In addition pulmonary capillary pressure varies throughout the lung because of the hydrostatic effect.

o Pulmonary vascular resistance – it is very small when compared to systemic circulation .It becomes even smaller when pressure within it rises. This is because normally some pulmonary capillaries are either closed or open with no blood flow. As pressure rises they begin to conduct blood. This is termed as recruitment and also when pressure increases the vessels are more distended.

o Flow of blood – Right ventricular output is more or less equal to left ventricular output. It is 5L per minute. Velocity of flow is 40cm/s .It is same as that of aorta. Blood passes through pulmonary capillaries within 0.7seconds and decreases to 0.35 seconds when cardiac output increases as in exercise.

o Distribution of blood flow (effect of gravity and hydrostatic pressure) .In standing person pressure in foot is more than pressure at heart level. This is caused by hydrostatic pressure i.e. the weight of blood itself in the blood vessel. The same effect but to a lesser degree occurs in lung.

The pulmonary arterial pressure at the level of heart is 24/9 mmHg.In apices of lung in standing position it is about 15mmHg lower than at the heart level.In the base of the lung it is about 8mmHg more than at the heart level.So ther is a gradient of 23mmHg in pulmonary artery from top to bottom.Such pressure difference has profound effect on blood flow through difference areas of lung.

Lung divided to 3 zones according to pattern of blood flow .It depends on pulmonary capillary pressure and alveolar air pressure.

Zone 1 – no blood flow during any part of cardiac cycle; Pr.alveoli > Pr.cap

When alveolar pressure is more vessels are compressed so no blood flow.

Zone 2 – intermittent blood flow – Blood flow during systolic phase of cardiac cycle. Here systolic pressure > alveolar air pressure (Pr.alveoli < Pr.cap) .Pulmonary venous pressure is always less so they are collapsed.Blood falls into pulmonary vein this is called **waterfall effect.**

Zone 3 – here continuous flow - Pr.alveoli < Pr.cap

Normally lungs have only zone 2 and 3 in upright posture.Zone 2 at apex and zone 3 at lower part.In supine position zone 3 in all areas,

Under abnormal condition zone 1 occurs that means when alveolar air pressure is increased or pulmonary capillary pressure is very much decreased. It is called over ventilated or under perfused lung. This contribute to physiological dead space.

o Decreased alveolar pO_2 caused constriction of adjacent blood vessel .It produce vasoconstriction substance. In systemic circulation hypoxia cause vasodilatation , as result of vasoconstriction there is distribution of blood to better aerated area.

o Pressure around pulmonary blood vessel – when alveolar pressure more than pulmonary capillary pressure , pulmonary vessels constrict.The diameter of extra pulmonary Bessel influenced by lung volume .When lung volume increases the diameter increases due to stretching of wall of that vessel.

16. Alveolar air composition:

pO_2 = 100mmhg
pCO_2 = 40mmhg
pN_2 = 573mmhg
pH_2O = 47mmhg

pO2 decrease from 149mmhg(inspired air) to 100mm Hg(alveolar air) due to dilution with functional residual capacity. Alveolar air is only partially replaced by atmospheric air. At the end of each normal expiration 2.2L of air present in the lung.In each breath 350ml of inspired air reaching the lung and 350ml of alveolar air expired out. So only 1/7th of total alveolar air is replaced by new atmospheric air. So, pO_2 decreases to 100mmhg.

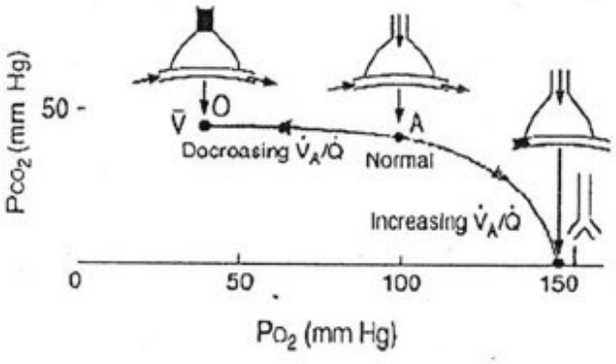
17. Ventilation perfusion ratio

It is the ratio of pulmonary ventilation to pulmonary blood flow.It determines the gas exchange in the lung unit.The VP ratio for the whole lung ispulmonary ventilation / pulmonary blood flow = 4.2L/min / 5L/min = 0.3.

There is some difference in VP ratio in various part of lung due to effect of gravity.

Both ventilation and perfusion decrease in a linear fashion from base to apex of lung.But blood flow decreases considerably more than that of ventilation.The decrease in perfusion is 3 times more faster than ventilation.So the V/p ratio is high in the apex.VP ratio is 3 at apex , 1 at midzone and 0.6 at base.In a normal lung the average V/P is only 0.8.

Ventilation gradient is due to high intra pleural pressure



Applied physiology

-During exercise, blood flow to the upper part of lung increases markedly.

-In the apex due to high VP ratio there is high alveolar pO_2 which favor the growth of tuberculum bacilli.**So TB affect mostly the apical part of lung.** VP ratio is 3 at apex , 1 at midzone and 0.6 at base.The poor perfusion of apex weakens the host defense and favours bacterial growth.

Variations in VP ratio

-VP ratio can varry from zero to infinity

-V/P=1 indicates well ventilated and well perfused alveoli

-V/P=0 indicate there is no ventilation as in obstruction of bronchiole

-When there is obstruction of blood vessel v/p ratio is infinite.

-Uneven pulmonary ventilation seen in obstructive airway disease and interstitial lung disease .

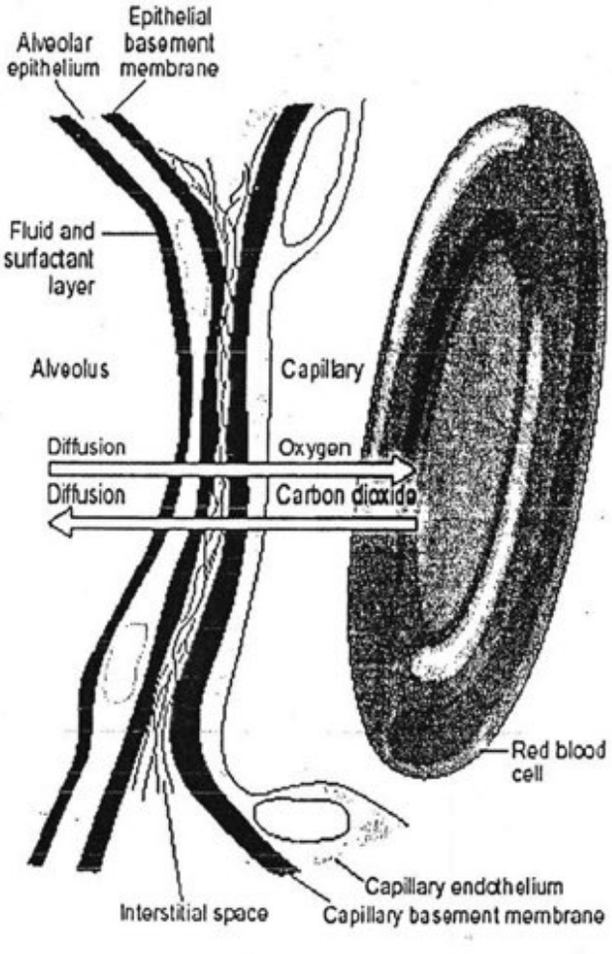
-Abnormality of blood flow is seen in pulmonary embolism or thrombosis (which occlude the pulmonary capillaries),pulmonary congestion and increases pulmonary vascular resistance.

18. TB affects lung apex first.Why?

refer short note 17

19.Respiratory membrane and factors affecting diffusion:

1.Layer of fluid lining the alveolus containing surfactant
2.Alveolar epithelial cells
3.Epithelial basement membrane
4.Thin interstitial space between alveolar epithelium and capillary membrane
5.Capillary basement membrane which fuses with alveolar epithelial cells in many places
6.Capillary endothelium



Ultrastructure of the alveolar respiratory membrane, shown in cross section.

Total surface area of membrane is 70metre square .Average thickness = 0.6im

Total quantity of blood in pulmonary capillary at any instant is 100ml (60 – 140ml).This small amount of blood spreads over a wide area.

The average diameter of pulmonary capillary is 5im.Diameter of RBC is 7im.So RBC need to squeeze through the pulmonary capillary.RBC membrane usually touches the capillary wall so that O_2 and CO_2 need not pass though significant distance through plasma. This increases the rapidity of diffusion.

Diffusion of gases across respiratory membrane

Diffusion of O_2 and CO_2 across the respiratory membrane obeys Fick's law. This law states that volume of gas diffusing through a membrane per unit time is directly proportional to the surface area of the membrane and pressure gradient of gas across the membrane and inversely proportional to thickness of the membrane.

FICKS

Volume of gas across the membrane = $(A \times D \times \Delta P) / T$

A = surface area of membrane

ΔP =pressure gradient

T= thickness of membrane

D = diffusion coefficient

Diffusion co-efficient is directly proportional to the solubility of the gas and inversely proportional to square root of molecular weight.

Factors affecting rate of diffusion:

1) Thickness of membrane- Rate of diffusion inversely proportional to thickness of membrane.In pulmonary fibrosis and edema thickness increases.

2) Surface area –Directly proportional to surface area, surface area decreases when

1) one lung is removed

2) emphysema – many alveoli coalesce to form a large alveolus and diameter is more than normal .But surface area decreases.

In exercise, lung expands - surface area increases - rate of diffusion increases.

3) Diffusion coefficient(DC) – it directly depends on gas solubility in membrane and inversely proportional to square root of mol.wt

Diff.coeff. = gas solubility in membrane / mol.wt

DC of O_2 is considered to 1 , CO_2 – 20.3 and N_2 is 0.53 i.e. for a given pressure difference CO_2 diffuses 20 times more than that of O_2 , where as O_2 diffuses twice that of N_2.

4) Pressure gradient – It is the measure of net movement. pO_2 is more in alveoli(100mmHg) than pulmonary capillary(40mmHg).So it diffuses from alvoali to capillary.pCO_2 more in pulmonary capillary (46mmHg) than that of alveoli(40mmHg) .So it diffuses from pulmonary capillary to alveoli.

Diffusing capacity:

It is defined as the volume of gas that will diffuse through the membrane in each minute for a pressure gradient of 1mmHg.

Diffusing capacity of O_2,

at rest:21ml/min/mmHg, exercise:up to 65ml/min/mmHg

Diffusing capacity of CO_2

rest:400-450ml/min/mmHg, exercise :1200-1300ml/min/mmHg

20. Oxygen dissociation curve: (refer essay 2)

21. Bohr effect

At the tissue leval, CO_2 diffuse from tissue into tissue capillaries. This increases the CO_2 content in tissue capillary which causes decreas of pH. This decreases the affinity of Hb for O_2 and deliver O_2 to tissue (ODC shifted to the right).H^+ concentration alter the configuration of Hb and decrease the accessibility of O_2 to heme group. This causes unloading of O_2 in tissue. The decrease in O_2 affinity of Hb when pH of blood falls due to increase in CO_2 concentration is called Bohr effect.

Double Bohr effect – ODC shift to right in maternal blood and shift to left in fetal blood at the same time is called Double Bhor effect.This favor the oxygenation of fetus by delivering O_2 from maternal blood to fetal blood and favors removal of CO_2 from fetal blood.

22. Chloride shift: (Refer essay 3)

23. Haldane Effect:

Whenever Hb is oxygenated,it displaces CO_2 from its combination and ODC shifts to right.This is known as Haldane effect.It is caused by,

-DeoxyHb has more affinity for CO_2 and so there is increased pick up of CO_2 from tissues.

-OxyHb has less affinity for CO_2 and so CO_2 is released from blood to alveoli in lungs.

-Reduced Hb is aweaker scid and a strong buffer and binds more at H ion tissue level.

-OxyHb is a stronger acid and releases h ion at lung level.

Importance of Haldane effect,

-Doubles the amount of CO_2 released from blood in to the lungs and doubles the pick up of CO_2 from the tissue.If Haldane effect was not there,at the lung level the CO_2 content of blood would have fallen only to 50 volume%.But due to Haldane effect CO_2 content falls to 48%.Thus 4 ml of CO_2 is removed by lungs when 100 ml of blood passes through the lungs.

-Haldane effect increases the uptake of O_2 by blood in the lung.

(also refer essay 3)

24. 2,3 – BPG:

It is formed from 3-phosphoglyceraldehyde which is a product of glycolysis via Embden Meyerhoff Pathway .It is plenty in RBC . Increased 2,3 BPG shift ODC to right.2,3 BPG binds to beta chain of deoxy Hb and O_2 is liberated.

$HbO_2 + 2,3\text{–}BPG \longrightarrow Hb2,3\text{-}BPG + O_2$

o Factors that increase 2,3 – BPG in red cells (ODC curve shift to the right)

-Exercise

-Thyroid hormone , growth hormone , androgen etc

-Hypoxic conditions as in chronic lung disease,anemia,at high altitude etc.Hypoxia increases glycolisis in RBC.

-Alkalosis stimulates glycolisis in RBC

o Factors that decrease 2,3 – BPG and Hb2,3-BPG formation

-Acidosis

-cyanosis inhibit red cell glycolysis and decrease 2,3 – BPG concentration.

-Stored blood

-Fetal Hb has high affinity to O_2. Higher affinity due to poor binding of 2,3 – BPG to gamma chain that replace beta chain.

-Abnormal Hb in adult have high O_2 affinity .So tissue hypoxia occurs .This may be due to reason that abnormal Hb can't bind with 2,3 – BPG.

25. Hypercapnia:

It is due to retention of CO_2 in the body and thus the partial pressure of CO_2 will be elevated.

Mechanism is inadequacy of ventilation with respect to the CO_2 produced.Hypercapnia initially stimulates respiration,but retention of larger amounts of CO_2 produces depression of CNS and leads to **CO_2 narcosis**. It is characterised by confusion, paresthesia (altered sensation), come with respiratory decline and finally death.

There will be Respiratory acidosis and urine become acidic.

Causes of hypercapnia: -

1.Ventilation perfusion inequivalent.

2. Hypoventilation as in fatigue,respiratory centre depression,paralysis of respiratory muscle etc.

3. Increased CO_2 production as seen in febrile patients. (1 degree rise in temperature leads to 13%increase in CO_2 production)

26. Asphyxia:

Condition where there is O_2 lack (hypoxia) combined with CO_2 excess (hypercapnia) generally produced by occlusion of airways.

Causes: -It is caused by obstruction to respiratory passage as in,

1. Strangulation.
2. Drowning.
3. Foreign body in trachea.
4. hypocalcemic tetany with severe laryngospasm

Effects of hypoxia produced in asphyxia can be divided into 3 stages.

1)Stage of exaggerated breathing.
2)Stage of convulsion.
3)Stage of collapse.

Stage I: -

1.Respiration becomes deep and rapid.
2.Dyspnea and cyanosis occurs.
3. Eyes become prominent and expression is intensely anxious.

Stage II: -

1. Respiratory efforts become violent here.
2. Generalized convulsion appears.
3. BP and heart rate rises steeply.
4.Catecholamine secretion is increased.Loss of conciousness within 1 minute.

Stage III: -

1. In this stage, convulsions cause abruptly, respiratory efforts causes and respiration becomes gasping in nature.
2. BP and heart rate decreases.
3. Pupils are widely dilated.
4. Reflexes are abolished.
5.Death occur due to respiratory centre depression and cardiac arrest occurs in 4-5 minutes.

27. Cyanosis: -

Cyanosis is bluish discoloration of skin and mucous membrane when the amount of reduced hemoglobin in the capillary blood is greater than 5g/dl.

Its occurrence depends upon

1. The total amount of hemoglobin in blood.
2.The degree of hemoglobin unsaturated.
3. The state of capillary circulation.

It is easily visible in the tongue, lips, nail beds, fingers, ear lobes etc.

Clinically 2 types of cyanosis

(i) Central cyanosis: -

•Results from imperfect oxygenation of blood at the level of lung or heart as occurring in lung diseases like pneumonia,lung collapse,pulmonary edema and can be also due to mixing of arterial and venous blood as in congenital cyanotic heart disease.

•Central cyanosis is looked for at tongue.

•Extremities are warm due to peripheral vasodialation.

(ii) Peripheral cyanosis: -

•It is due to stagnation of blood in the peripheral capillaries leading to excessive extraction of oxygen from Hb.It is seen in conditions like circulatory failure; extreme cold and venous obstruction.

•Peripheral cyanosis looked for at fingertips.

•Extremities are cold.

Both central and peripheral cyanosis occur in heart failure

Cyanosis does not occur in: -

(i)Anemic hypoxia

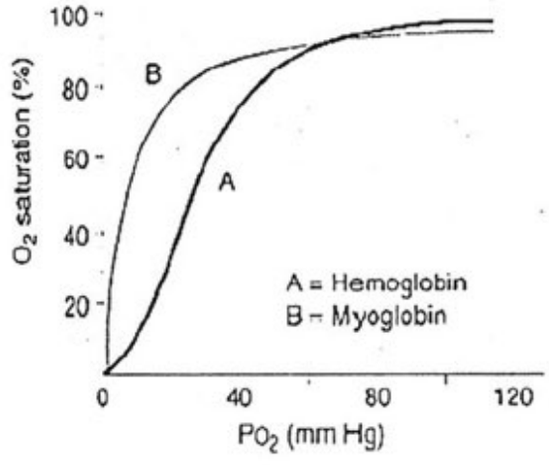
(ii)Carbon monoxide poisoning because the cherry red discoloration produced by carboxy hemoglobin obscures the color of reduced hemoglobin.

28.Cyanosis is difficult to manifest in anemia,why?

This is because Hb concentration is already less in anemia and hence the amount of reduced Hb will be less than 5 gm/dl.For cyanosis to occur it should be >5gm/dl.

29. Myoglobin

It s an iron containing pigment found in skeletal muscle.It resembles hemoglobin but only one heme unit is present in myoglobin and so one molecule of myoglobin can binds with only 1 molecule of oxygen.Its dissociation curve is rectangular hyperbola and is to the left of the hemoglobin curve.So it takes up O_2 from hemoglobin in the blood and releases O_2 only at low pO_2 values ie.,below 5mmHg, In exercise when there is sustained muscle contraction, due to compression of blood vessels blood flow is cut off and pO_2 in the muscle become zero or very low and muscle utilises O_2 from myoglobin.Thus myoglobin act as temporary store house of O_2 in the muscle.Evidence also suggests that myoglobin facilitates the diffusion of O_2 from the blood to the mitochondria where the oxidative reaction occur.



* 30. Acclimatization:

Acclimatization refers to a number of compensatory mechanisms that operate a period of time to increase the altitude tolerance.

Changes occurring in the body during acclimatization: -

(i) Increase in the pulmonary ventilation.

Immediate exposure to hypoxia produces a decrease in partial pressure of arterial blood causing stimulation of peripheral chemoreceptors. This causes an increase in alveolar ventilation and this increase in ventilation blows out the CO_2, thus decreasing the PO_2 as a result, the pH increases and this produces Respiratory alkalosis. Alkalosis, actually causes depression of respiratory centre.This depression is not prolonged and immediately mechanisms operate to decrease the pH and the changes occurring are:-

1.Active transport of H^+ into CSF causing a decrease in the pH and stimulates respiration.

2.Outward movement of HCO_3^- from CSF and brain tissue. This also decreases in the pH and stimulates respiration.

The decrease in PCO_2 also causes increase in pH of blood and this is brought to normal by increased excretion of HCO_3^- through the kidneys.

(ii) Increase in RBC count and hemoglobin concentration.

1. Hypoxia is a powerful stimulus for erythropoietin secretion. Erythropoietin activates erythropoiesis. This causes an increase in RBC count and there by an increase in hemoglobin concentration.
2. The oxygen carrying capacity of blood is increased.
3. Blood volume increased by 20-30%,PCV increases to 60% and Hb concentration is increased to 22gm %.
4. This increase in RBC production begins in 2-3 days of ascend and remains as long as the person is at high altitude.The subject will be polycythemic.

Increase in 2,3-BPG

The respiratory alkalosis initially shifts ODC to left but concomitant increase in 2, 3-DPG following hypoxia shifts the ODC to right. Net effect is a shift to the right and dissociation of oxygen occurs easily.

(iii) Changes in circulatory system.

1.Hypoxia increases tissue capillary density. Angiogenesis occur and more capillaries are opened.
2. Cardiac output is increased by 20-30%.
3. Redistribution of blood flow so that there is increased blood flow to the heart and brain and decreased in cutaneous and splanchnic circulation.

(iv) Increase in diffusing capacity for oxygen.

Oxygen diffusing capacity is increased at high altitudes and this causes greater transfer of oxygen from lungs to the tissues. This increase is due to

1.Increased pulmonary capillary blood flow volume which expands the capillaries and increases surface area through which oxygen can diffuse into the blood.
2.Increase in lung air volume (increase in surface area of alveoli)
3. Increase in pulmonary arterial pressure which forces blood into greater number of alveolar capillaries.

(v) Cellular acclimatization

Increased extraction of O_2 at tissue level due to,

1. Increase in number of mitochondria.
2. Increased cytochrome oxidase enzyme
3. Increase in myoglobin.

31. Caisson's disease / Dysbarism / Decompression sickness / Bends.

It is a condition which occurs when subjects exposed to an increased atmospheric pressure are suddenly brought to a decreased or lower atmospheric pressure.

It occurs in people working in caisson and deep sea divers.

• They are exposed to high atmospheric pressure which results in increased partial pressure of N_2 and elevated partial pressure forces gases into solutions in the body fluids and tissues. So, this makes the body fluids and tissues especially fatty tissue almost saturated with N_2 if the stay is prolonged at depth.

• At sea level only 1L of N_2 is dissolved in the entire body but at depth of 100m it increases about 10L.

• As long as the person remains in depth, N_2 remains in solution abd does not causes any problems.

• During ascend, the elevated partial pressure of N_2 falls which causes diffusion of N_2 from the tissues and body fluids into the lungs along the pressure gradient and thus removed by lungs.If the return to atmospheric pressure is gradual, no harmful effects occurs but if the ascend is rapid, N_2 escapes from solution rapidly and bubbles of nitrogen are formed in the tissues and blood produces symptoms of Decompression sickness and it causes damage to various tissues.Symptoms appear 10 to 30 minutes after the diver resurfaces and they progress.Symptoms are produced by bubbles blocking the blood vessels in different tissues resulting in tissue ischemia.

(a)85-90% cases present with pain in the joints (**bends**)due to bubbles in and around joints and pain in the muscles of legs and arms.

(b)5-10% cases present with nervous symptoms. This occurs due to obstruction of blood vessels supplying brain and spinal cord.

Symptoms include: - Dizziness, impaired vision, vestibular disturbances, parasthesia, motor weakness and finally paralysis.

(c)2% cases present with **chokes**.

Choke- a feeling of shortness of breath accompanied by coughing, this followed by pulmonary edema and death. Occurs due to obstruction of pulmoary capillaries.

(d)Bubbles in the coronary artery may cause myocardial damage and may cause myocardial infarction.

(e)Professional divers or caisson workers sometimes develop avascular necrosis of head of femur or other long bones in later life because necrosis of the bones occur due to intermittent obstruction of the vessels supplying, over many years.

Prevention: -

Can be prevented if the diver ascends slowly so that dissolved N_2 in the body can diffuse in to the blood without forming bubbles,and it diffuses in to lungs along the partial pressure gradien.In practice, divers stay paused for periods of time at different depths during the ascend. This is known as **Staging**.

Deep sea divers and underwater tunnel workers can use SCUBA(self contained underwater breathng apparatus).The disadvantage is that the person can remain in the depth only for a limited time.

Treatment: -

•It is by recompression in pressure chamber followed by slow decompression that is in the decompression chambers, the pressure is gradually lowered to normal atmospheric pressure.

•Risks of decompression sickness can be reduced if helium oxygen mixtures are breathed during the dive.

Hyperbaric oxygen therapy is also useful in treatment.

32. Periodic breathing (Cheyne stokes and Biots breathing)

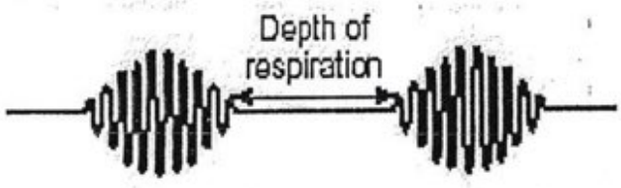
Periodic breathing is the abnormality of patient .It occur in various physiological and pathological conditions. Here a person breath deeply for a short interval and then breath slightly or not at all for an additional interval .The cycle repeats itself over and over again.

Two types of periodic breathing –

1 – Cheyne Stokes breathing

2 – Biots breathing

1 – Cheyne Stokes breathing – common type of periodic breathing. Here breathing is shallow to begin which increases gradually in amplitude to maximum and then diminishes gradually and then stops for a short time. This cycle is repeated and each cycle last for 40 – 60 seconds.



In this type of breathing regular alternating periods of hyperventilation and apnea are seen.

Cheyne stoke respiration occur physiologically

-in premature infants and newborn babies .
-during sleep in some normal individual
-in unacclimatized person at high altitude

Pathological cause –

-congestive cardiac failure
-renal failure and uremia
-patient with brain damage
-raised intracranial tension
-morphine poisoning

Basic mechanisms explaining Cheyne-stoke breathing

1.Some patients have increased sensitivity to CO_2 .It is due to the neural pathway,that normally inhibit the respiration may be disrupted .In these individual CO_2 causes relative hyperventilation. It lowers the pCO_2 resulting apnea. During apnea there is accumulation of

CO_2 and arterial pCO_2 rises again and stimulate the respiration centre producing hyperventilation.

CO_2 ⟶ Hyperventilation ⟶ decreased pCO_2 ⟶ apnea ⟶ increase pCO_2 ⟶ hyperventilation

2.In congestive cardiac failure there is another mechanism.Circulation is sluggish and prolongation of circulation time from lung to brain increases.Here it takes more time for changes in arterial gas tension to affect the respiratory centre.If this person hyperventilate there will be a decrease in pCO_2 and when this blood reaches the central chemoreceptor there will be marked reduction in pCO_2,and respiratory centre will be depressed leading to apnea.During apnea there is accumulation of CO_2 leading to increase in pCO_2 followed by increased ventilation.

2)**Biots breathing** – Here irregular periods of apnea alternate with hyperpnoea .The change from one to another is abrupt. The graded increase and decrease in amplitude is absent .Amplitude remains same and apneic interval differs .Biots breathing is seen in medullary lesions or injuries to brain and meningitis.

Physiological basis:

1.Lung alveoli are kept dry normally

Surfactant keeps the alveoli dry and thus help in the exchange of gases.Refer shortnote-5

2.Alveoli does not collapse in expiration

Refer shortnote-32 chapter CVS

According to Laplace's law,

$T=2S/r$

During expiration radius of alveoli decreases.In order to keep T constant S must also decrease.This is brought about by surface tension reducing substances present in lungs (surfactants).Tension is inversely proportional to surfactant/unit area.During expiration as the alveoli shrinks the surfactant/unit area increases,so tension decreases.This keeps the pressure constantly and alveali stable.

3.TB affect more at lung apex

Refer shortnote-17(High ventillation perfusion ratio)

4.Cyanosis is difficult to manifest in anemia

Refer shortnote-28

5.Peripheral chemorecptors are not stimulated in anemia or CO poisoning

Peripheral chemo receptors are not stimulated in anemia or CO poisoning.These receptors not stimulated because although the combined O_2 in the blood is markedly reduced the amount of dissolved O_2 reaching the chemoreceptor is normal and also in anemia there is increased blood flow.

6.IRDS more prone in childrenof Diabetic mother.

Due to hyper insulinemia surfactant synthesis isreduced Insulin decreases the surfactant synthesis.

Refer shortnote-6

Cardiovascular System

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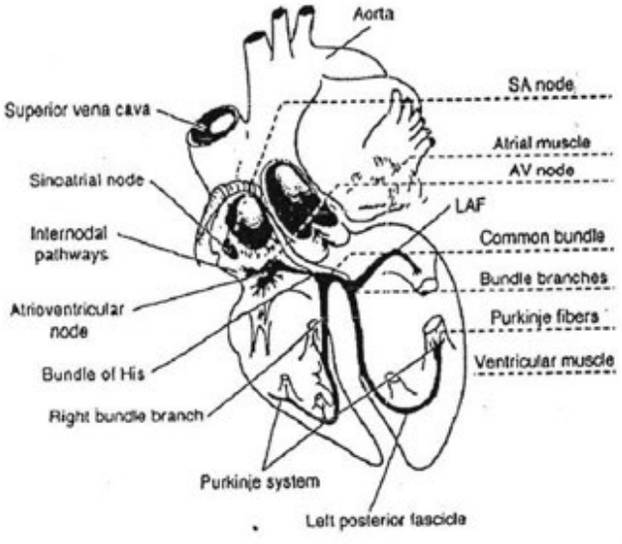
ESSAYS

1. Conducting system of heart:

Heart has a special conducting system which helps in the generation & transmission of impulses, which are responsible for contractility of heart. The generated impulse from SA node should reach all over the heart through conducting system.

Parts of the conducting system:

1)SA node
2)Inter nodal pathways
3)AV node
4)Bundle of His
5)Right and left bundle branches
6)Purkinje fibres



SA node:

Normal cardiac pacemaker located on the superolateral wall of right atrium, immediately below & slightly right to the opening of superior venacava.
It has 2 types of cells.

- P cells – the actual pacemaker cells. These are small round cells connected by gap junctions
- Transitional cells – lies in b/w P cells & myocardial cells

SA node fibers are continuous with the atrial fibers. It controls the heart rate. It's the portion of the conducting system where the impulse is generated. The cells of SA node shows a particular type of action potential called the "pre potential" or the "pacemaker potential". Rate of impulse production is 60-100/min or 70-80/min or an avrg of 72/min.

Even though SA node is the usual pacemaker, in cases of its failure, other parts of conducting system- mainly AV node- can take the function of pacemaker. But during such conditions, rate of impulse production is decreased. Conduction velocity of SA node is only about 0.05 m/s.

Inter nodal pathways:

There are 3 types of atrial fiber bundles that connect SA node & AV node. They have Purkinje type of cells with increased conduction velocity(1m/s). These include:

1)Anterior internodal pathway of Bachmann
2)Middle internodal pathway of Wenckeback
3)Posterior internodal pathway of Thorel

In addition to this, impulse directly reach to left atrium via inter atrial tract (from Anterior and posterior inter nodal tract) which helps in simultaneous depolarization of left atrium.

AV node:

Located on posterior septal wall of right atria behind the tricuspid valve.
It has 3 types of fibers. They are:

(a) Junctional fibers: - b/w atrial fibers & nodal fibers.
(b) Nodal fibers
(c) Transitional fibers: - continuous with the fibers of AV bundle.

AV node, like SA node shows low conductivity(.05m/s). This is because of the small Junctional fibers, less number of gap junctions & long refractive period of nodal fibers. Due to this there occurs a delay of 0.1 sec called AV nodal delay before the impulse is transmitted from atria to ventricles. This delay has got physiological significance. It ensures adequate ventricular filling before it contracts. The impulse production of AV node is 40-60/min.

Bundle of His , Right and Left bundle branches

It is the only conducting tissue b/w atrium and ventricle. AV node continues as the bundle of His which gives off a left bundle branch at the top of inter ventricular septum & continues as the right branch to supply the right ventricle. Left bundle branch divides into anterior & posterior fascicles which supply left ventricle & IV septum. Right branch & 2 fascicles of left branch run subendocardially on either side of the septum and divides in to smaller branches called Purkinje fibers. velocity of conduction through Bundle of His is 1m/s and the rate of impulse production is 30/min.

Purkinje fibres:

These are large fibers & have the largest conduction velocity(4m/s) among the parts of conducting system. This increased velocity is probably due to increased number of connections among the Purkinje fibre

cells. This allows immediate transmission of cardiac impulse throughout the entire ventricular system. Purkinje system is the continuation of the left & right bundle branches & spread from the apex of each ventricle, through the whole ventricle, & finally back to the base of the heart. Terminal Purkinje fibers end by penetrating 1/3rd of the muscle mass, beneath the endocardium.

2. Origin & spread of cardiac impulse:

Adult human heart contracts in an orderly manner,in a rhythemic rate of 72beats/min.This is the result of the property of self excitation & impulse conduction in specialized cardiac muscle fibers. The various parts of conducting system are:

- SA node
- Inter nodal pathways
- AV node
- Bundle of His and bundle branches
- Purkinje fibers

(Write something about the parts of conducting system)

Origin of cardiac impulse:

Normal site of impulse production is SA node. SA node has special cells called P cells / pacemaker cells. These cells have a fluctuating RMP of about -60 to -70 mV. This is because all Na^+ or Ca^{2+} channels are not fully closed even in resting state. Thus after each impulse, the membrane potential declines to firing level and triggers the next impulse. This is called pre potential or pacemaker potential. SA node produces impulses at a rate of about 72 times per min.Sometimes, SA node fails to function as the pacemaker. In such conditions other parts of conducting system take up that function. But the rate of impulse production will be less.

Part of conducting system	Impulse production Rate
SA node	72beats/min
AV node	50beats/min
Bundle of His	30beats/min
Atrial muscle	60beats/min
Ventricular muscle	30 beats/min

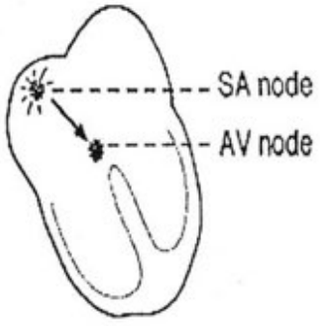
Spread of cardiac impulse:

In atrial musculature:

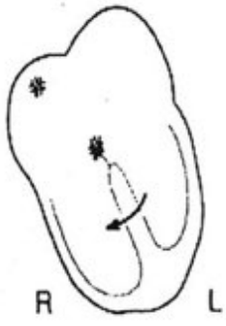
The impulse generated in SA node spreads radially through atria,inter nodal pathway and then converges on AV node. The ends of SA nodal fibers fuse with surrounding atrial muscle fibers, & action potentials originating in SA node spread into these fibers. In this way the impulse spreads through the entire atrial muscle mass. Conduction through these is slow, but there occurs more rapid conduction through the 3 inter nodal pathways, connecting SA node & AV node. These are specialized atrial muscle fibers. Atrial depolarization is completed in 0.1 sec.

In AV node:

As the conduction in AV node is slow, there is a delay of about 0.1 sec before the spreading into the ventricles. This is called AV nodal delay. Impulse from AV node spreads to bundle of His & its branches, & is relayed in ventricular myocardium by Purkinje fibers.



Atrial activation



Septal activation from left to right

Activation of anterosep region of the ventricula myocardium

Activation of major portion of ventricular myocardium from endocardial surfaces

Late activation of posterobasal portion of the left ventricle and the pulmonary conus

In Purkinje system:

Purkinje fibers have very large conduction velocity. This allows almost immediate transmission of cardiac impulse to ventricular system.

The rapid conduction in Purkinje fibers is due to:

(a)Large size of Purkinje fibers

(b)Increased No: of tight junctions b/w successive cardiac cells that make up Purkinje fibers. At these tight junctions, ions are transmitted easily from 1 cell to the next, thus enhancing the velocity of transmission.

(c)Purkinje fibers have only few myofibrils, i.e., they barely contract during impulse transmission.

From the time cardiac impulse 1st enters AV bundle until it reaches the terminations of Purkinje fibers, the total time lapse is only about 0.03 sec. So, once an impulse enters the Purkinje system, it spreads almost immediately to the endocardial surface of ventricular muscle.

In ventricular muscle:

Once the cardiac impulse has reached the ends of Purkinje fibers, it's then transmitted through ventricular muscle mass by the ventricular muscle fibers themselves. But velocity of transmission in these is only about 1m/s.

Thus, the total time for transmission of cardiac impulse from the origin of Purkinje system to the last of ventricular muscle fibers in normal heart is about 0.06 sec.

Depolarization of ventricular muscle starts in left side of interventricular septum and moves to right across the mid portion of the septum. Then it spread down to the apex of the heart. It return along the ventricular wall to the atrio ventricular groove. The last portion of the ventricle to be depolarize are the posterobasal portion of left ventricle, pulmonary conus & the uppermost portion of the interventricular septum.

Conduction speeds in cardiac tissue:

Tissue	Conduction rate(m/sec)
SA node	0.05
Atrial pathways	1
AV node	0.05
Bundle of His	1
Purkinje system	4
Ventricular muscle	1

3. Cardiac cycle & pressure volume changes:

The sequence of electrical and mechanical events taking place in heart from the beginning of 1 heart beat to the beginning of next beat is called cardiac cycle. When heart rate is 75 beats / min, the duration of 1 cardiac cycle is 0.8 sec.

Electrical events during cardiac cycle:

- Atrial depolarization
- Atrial repolarization
- Ventricular depolarization
- Ventricular repolarization

Mechanical events during cardiac cycle:

- Atrial systole – 0.1 sec
- Atrial diastole -0.7
- Ventricular systole – 0.3 sec
- Ventricular diastole – 0.5 sec

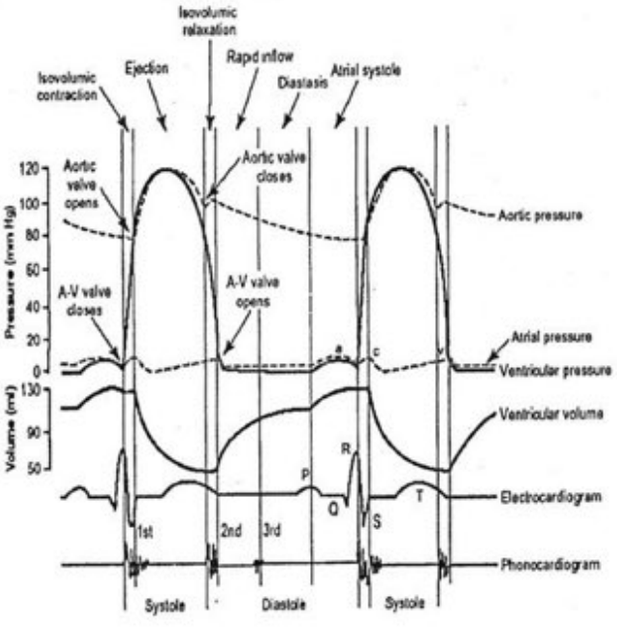
Cardiac cycle consists of a period of relaxation called diastole during which the heart is filled with blood, a period of contraction called systole. During systole, heart pumps blood into pulmonary artery & aorta. During atrial diastole, whole ventricular systole and ventricular diastole occur. Wrigglers on the basis of pressure volume changes, divided cardiac cycle in to 8 phases.

Phases of ventricular systole.

I. Isovolumetric ventricular contraction – 0.05 sec
II. Rapid ejection – 0.1 sec
III. Reduced ejection – 0.15 sec

Phases of ventricular diastole.

I. Protodiastole – 0.04 sec
II. Isovolumetric ventricular relaxation – 0.06 sec
III. First rapid filling phase – 0.1 sec
IV. Diastasis / Reduced filling phase – 0.2 sec
V. Last rapid filling phase/ Atrial systole – 0.1sec



Isovolumetric ventricular contraction

This is the 1st phase of ventricular systole. Both AV valves & semi lunar valves are closed and AV valves are in open state. Now, ventricular contraction occurs against a practically incompressible fluid. Pressure inside rises steeply.

PV changes:- In the beginning, semi lunar valves are closed but AV valves are not still completely closed. Intra ventricular pressure (IVP) is 0 mm/ Hg. As contraction starts, ventricular pressure rises, inorder to prevent back flow of blood AV valves closes firmly causing the 1st heart sound. Now each ventricle is a closed chamber. Compression of an incompressible fluid causes steep rise

in IVP. As IVP increases steeply, AV valves bulge into atria which produce 'c wave' in JVP. Here no ejection of blood in to aorta or pulmonary trunk but the pressure inside ventricle increases up to 80 mmHg in left ventricle(pressure of aorta is 80mm/Hg) and 10mmHg in right ventricle(P of pulmonary A is 10 mmHg). The volume of the ventricle (130ml) remains almost constant. Hence this phase is called Isovolumetric.

Rapid ejection:

As soon as the semi lunar valves open, blood from the ventricles flow rapidly into the corresponding arteries. Major part of ventricular ejection takes place during this phase. **PV changes**: As soon as IVP exceeds hydrostatic pressure of aorta(80mmHg) and pulmonary artery(10mmHg), ejection of blood begins in to aorta and pulmonary arteries.During rapid ejection phase 2/3rd of the stroke volume is ejected.Stroke volume is the volume of blood ejected by each ventricle per each beat.It is about 70-90ml(avrg 80ml).During this phase left ventricular volume increases maximum about 120mmHg and right ventricular P about 25mmHg .During this phase. Volume of ventricles undergoes rapid remarkable reduction during this phase.

Reduced ejection

As ejection of blood from ventricles continues its rate decreases and remaining 1/3rd of stroke volume is ejected.

PV changes: The rate of distribution of blood by aorta exceeds the rate of inflow into aorta, so that aortic blood pressure falls. Meanwhile, the ventricular pressure also falls & a time comes when ventricular pressure falls below aortic pressure. This marks the end of this phase. Atrial pressure rises to some extend because, it continues to receive blood from veins. Intra ventricular volume continues to decrease and at the end of this phase intra ventricular volume is about 50ml(130- 80).This volume is called end systolic volume.

Protodiastole

It's a short phase. Semilunar valves are not closed, but AV valves are. Relaxation of ventricles causes backflow of blood from aorta & pulmonary trunk into the ventricles. But this backflow is prevented by sharp closure of semilunar valves producing the 2nd heart sound. This phase of ventricular diastole up to closure of semi lunar valves is called Protodiastole.

PV changes: ventricles relax, ventricular pressure falls sharply below the aortic pressure. Since semilunar valves are still open, column of blood in aorta tends to flow back causing aortic valves to close. Because of sharp closure, blood column rebounds in aorta producing **incisura** in aortic pressure curve.

Isovolumetric ventricular relaxation

Both AV valves & semi lunar valves are closed. Ventricle is again a closed chamber. They relax isometrically until AV valves open which marks the end of this phase.

PV changes: Active relaxation of ventricles causes ventricular pressure to drop sharply. When it falls below atrial pressure, AV valves open. Ventricular pressure may fall almost to 0 mm/ Hg. Ventricular volume remains constant & hence this phase is called Isovolumetric ventricular relaxation.

First rapid filling phase:

Opening of AV valves results in rapid, passive flow of blood from atria to corresponding ventricles.

PV changes: As soon as the ventricular pressure falls below atrial pressure, AV valves open, blood rapidly enters the ventricles that produce vibration on ventricular valve causes 3rd heart sound. The volume of ventricles rises steeply. As blood flows from atrium to ventricle, atrial pressure falls slightly but still remains more than that of ventricles. Hence blood flow continues.

Diastasis / Reduced filling phase:

Initially ventricular filling is rapid,it is followed by slow filling Diastasis.Its duration strongly depends on heart rate.This first rapid and slow fillinng phases responsible for 70% ventricular filling.

PV changes: Ventricular volume continues to increase though very slowly. Here pressure slightly increase due to inflow of blood. When HR increases, duration of each cardiac cycle is cut short by reducing the diastasis phase. This phase contributes very little to ventricular filling. Hence, reducing this phase does not considerably affect the stroke volume.

Last rapid filling phase/ atrial systole:

Now, atrial contraction occurs resulting in active pumping of blood into ventricles. This accounts for about 30% of ventricular filling. With this 1 cardiac cycle ends & next 1 begins.

PV changes: ventricular volume rises & reaches end diastolic volume(130ml). Atrial systole causes slight rise rise (about 5 mm/ Hg) in atrial pressure curve. It corresponds to the feeble 4th heart sound.

4. Cardiac output & its regulation

It's the amount of blood ejected by each ventricle per minute.

Cardiac output = stroke volume x heart rate

Stroke volume is the amount of blood ejected by each ventricle per beat (about 80 ml/ beat).

Heart rate is the no: of heart beats per min (about 72 beats / min)

So,CO= 80 x 72 = 5.6 L/min

Cardiac index:It is the cardiac output expressed in relation to body surface area.normal value is 3.2L/min/m^2

Cardiac reserve:It refers the maximum increase in cardiac output above normal value.it is expressed in %.Healthy young adult cardiac reserve is 300-400%.

Regulation of CO:

CO = stroke volume x Heart rate

Regulation of cardiac output -by 2 mechanisms,

(a) Intrinsic regulation – by regulating SV.

Subdivide into:

- Homometric regulation – independent of muscle fiber length
- Heterometric regulation – depends on initial fiber length

(b) Extrinsic regulation-by regulating HR

Intrinsic regulation:

Stroke volume is controled by 2 mechanisms

(1)Homometric regulation:

Force of contraction does not depend on initial length of muscle fibre.Regulation is mainly by affecting myocardial contractility. Contractility can be regulated in following ways:

- Nervous factor- sympathetic stimulation increases contractility while parasympathetic stimulation decreases
- Chemical factors- contractility is increased by epinephrine, norepinephrine, caffeine, theophilline, glucagons,increased ECF Ca,thyroid hormones,digitalis and related drugs.
- Contractility is decreased by hypercapnoea, hypoxia,acidosis,drugs like guinidine,barbiturates and heart failure.

(2)Heterometric regulation:

Force of contraction depends on initial length of muscle fibre.This can be explained by Frank's Starling's law, which states that force of contraction is directly proportional to the initial length of muscle fiber within the physiological limits.in this mechanism preload is the main indicator.

Preload: It's the load acting before it starts contraction.It's the degree to which myocardium is stretched before it contracts. In case of ventricle, it's the amount of blood present in it before it starts contracting (end diastolic volume). When EDV is more, muscle fiber length Increases, Increasing the force of contraction.EDV depend on venous return.It's the volume of blood returned to the right atrium per min. Normally VR = CO due to closed system of circulation.

Factors Increasing venous return :

(a) Total blood volume:If blood volume is more venous return is more.

(b) Increased venous tone:Constriction of veins decreases the size of venous reservoir and decrease the venous pooling and increases venous return.

(c)Muscle pump: contracting skeletal muscle squeezes blood out of veins & increases VR.

(d)Thoracic pump:During inspiration intrathoracic pressure becomes –ve and there is increased venus return.At the same time, intra abdominal pressure rises due to descend of diaphragm. Because of Increased pressure gradient b/w intra abdominal part of IVC & right atrium, venous return increases.

(e)Body position: gravity causes pooling of blood in dependent parts of body. In standing posture, VR from head & neck is increased, while from lower extremities is decreased.

(f)Cardiac pump: 2 types – (1) Vis A Tergo – Here, VR is due to force acting from behind driving blood forwards. It's the propelling force imparted by contraction of ventricles along with elasticity of great vessels. (2) Vis A Fronte – force acting from front to attract blood in veins to heart. It has 2 components- ventricular systolic suction (Increase in pressure in atria & great vessels due to descend of AV junction during ventricular systole) & ventricular diastolic suction (ventricular diastole causes a sudden decrease in atrial pressure lower than that of great veins, thus increasing VR)

(g)Venomotor tone: smooth muscles in walls of veins are under sympathetic control. When these are stimulated, venoconstriction occurs increase VR

Factors decreasing venous return:

(a)standing posture

(b)Increased pericardial pressure

(c)Obstruction to large veins

After load: It's the load acting on the muscle after it starts contracting. In case of heart, it's the resistance against which blood is pumped from the ventricle, i.e., aortic impedance.When systolic pressure increases the after load is increased.There is a inverse relationship between afterload and stroke volume.

Extrinsic regulation:

Extrinsic regulation is by regulating heart rate.It can be neural or chemical.

Neural regulation:

Heart is innervated by both sympathetic & parasympathetic systems.

Sympathetic system (T1-T5) supplies SA node,AV node,atria and ventricles.It enhances heart rate & also inhibits vagal stimulation.Stimulation of sympathetic system causes +ve chronotropic,ionotropic,dromotropic and bathmotropic effect.Parasympathetic system via vagus supplies whole part of heart except ventricle. Stimulation of vagus produces -ve chronotropic,ionotropic,dromotropic and bathmotropic effect.When both influences are removed heart still continues to beat with a rate called 'intrinsic rate'.

At rest,there is a moderate amount of sympathetic disharge from neurons.At the same time there is a good deal of tonic vagal discharge (vagal tone). In human and other animals this vagal tone maintain heart rate between 70-80/min.That means parasympathetic effect predominates at rest.Cutting the vagus nerve or giving drugs like Atropin results increase in heart rate up to 160-180beats/min.During exercise, sympathetic effect is dominant.

Increase In HR within physiological limit (180 beats/min)increases CO. However, if HR increases beyond that CO falls. This is because HR affects cardiac cycle,

esp. diastasis. When HR is very high, time for ventricular filling is too short, thus CO decreases

Sympathetic & parasympathetic nerves are under control of:

- Several higher centers in CNS
- Various reflexes

Higher centers:

1)Medullary centers: Includes

- Sympathetic/ vasomotor center: RVLM (pressor area) &IVLM,CVLM(depressor area)
- Parasympathetic/ cardio inhibitory/ vagal center

2)Hypothalamic center: Hypothalamus is considered to be the highest center of ANS. Its stimulation activates ANS, esp. sympathetic system producing tachycardia.

3)Cerebral cortex:Frontal lobe stimulation Increases HR.

4)limbic system :Strong influence on heart rate and bp.Activation of limbic system in various emotions like anger, pain and sexual exitement – alter HR

Reflexes:

1)Reflexes from systemic arteries – Baroreceptor & chemoreceptor reflex

2)Reflexes arising directly from heart – atrial & ventricular receptors

3)Miscellaneous reflexes

Baroreceptor reflex:

BP causes Baroreceptors (carotid sinus & aortic arch) stimulated,impulses travel through buffer nerves, stimulates NTS, inhibits VMC & activates vagal center.BP & HR decreases.

Chemoreceptor Reflex:

Decrease of O_2, increase of CO_2 and H^+ causes chemo receptors (aortic & carotid bodies) stimulation: afferents via IX & X nerves, VMC stimulated,resulting in vasoconstriction, and increase in HR

Baroreceptor reflex from heart:

Increase venous return causes stimulation of B type atrial receptor. Increase in HR & reflex vasodilatation decreasing BP

Chemoreceptor Reflexes from heart:

Bezold Jarisch reflex: Injection of veratridin, capsaicin etc into coronary artery supplying left ventricle causing stimulation of C fibers resulting in apnoea followed by hyperpnoea,decrease HR and BP.

Miscellaneous reflexes:

J receptor reflex:J receptors of lung parenchyma when stimulated cause apnoea, hyperpnoea followed by increased HR. These receptors are also stimulated by injection of veratidin, capsaicin etc into pulmonary artery. This reflex is also called pulmonary chemo reflex.

Chemical control of HR:

- Adrenalin, thyroxin causes increase HR
- Digitalis decreases HR
- Increased temperature increases HR

5. BP & its regulation:

Blood pressure is the lateral pressure excerted by the column of blood on vessel wall.Maximum pressure during the systolic phase of cardiac cycle is called systolic pressure & mininmum BP recorded during diastole is called diastolic BP.

Normal values:

SBP = 100-140 mm/ Hg (avg: 120)
DBP = 60-90 mm/ Hg (avg: 80)
Systemic BP = 120/80 mm/ Hg

Pulse pressure:It is the difference between systolic and diastolic BP.

PP= SBP-DBP=40-50 mm/ Hg(avg: 40)

Mean arteraial pressure:It is the average pressure through out the cardiac cycle.It is not the arithemetic mean of systoic and diastolic BP because duration of systolic and diastolic is not same.

Mean arterial P= DBP + 1/3 Pulse pressure
= 93 mm/Hg

Variations of BP:

physiological variations:-

1) Age-As age advances both systolic and diastolic BP increases,but after 50-60 years diastolic BP begins to decrease due to increase stiffness of vessel.
2) Sex-low in females up to menopause.
3) Meal-slight increase after meal
4) Sleep-systolic BP decreases during sleep.In dreaming there is slight increase in systolic BP.
5) Emotion-Bp increases
6) Body weight-increases slightly in obeise individuals.
7) Gravity-Pressure in vessels above heart is less than that in below the heart.
8) Posture-in lying position SBP is more due to increased venous return.On standing position there is more DBP due to pooling of blood in to lowerlimbs,which causes stimulation of baroreceptors and increase DBP.
9) Exercise-In mild and moderate exercise there is increase in SBP no much change in DBP.IN severe exercise there is increase in SBP and decrease in DBP.

Determinants of BP:

Blood flow =pressure/resistance. so,
Blood pressure =blood flow x resistance ie.,
=cardiac output x peripheral resistance
SBP mainly depends on cardiac output and DBP depends on peripheral resistance.
Factors determining cardiac output(refer esssay 4)
Peripheral resistance is the resistance to the flow of blood.It depends on viscosity and diameter of the blood vessel.BP also depends on elasticity of blood vessel.

Regulation of BP: -

3 types,
1) Short term regulation
2) Intermediate regulating mechanism
3) Long term regulation

1) Short term regulation:occurs within seconds to minutes.

- Baroreceptor mechanism
- Chemoreceptor mechanism
- CNS ischemic response

Baroreceptor mechanism:

Baroreceptors are stretch receptors.They are stimulated while stretching the vessel wall.They are ssituated in the tunica adventitia.They are grouped in to,

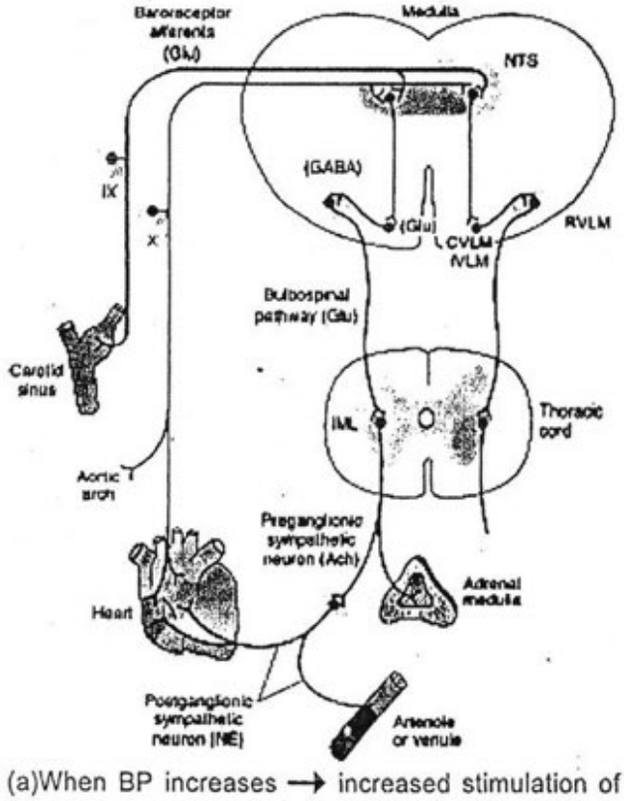
1) High pressure baroreceptor

eg.;-carotid sinus and aortic arch

2) Low pressure baroreceptors: they are collectevely called cardio pulmonary receptors,seen in atrial wall,entrance of superior venacava and inferior venacava,junction of pulmonary vein and left atrium.

Carotid sinus and Aortic arch are the main baroreceptors.Carotid sinus is a small dialatation of internal carotid artery just above the bifurcation of common carotid artery.Arch of aorta are situated in the wall of arch of aorta.

Carotid sinus baroreceptors are innervated by herrings nerve, a branch of glossopharyngeal nerve.All other baroreceptors are innervated by vagus nerve.These nerve are called buffer nerve.These nerve project in to NTS of medulla.



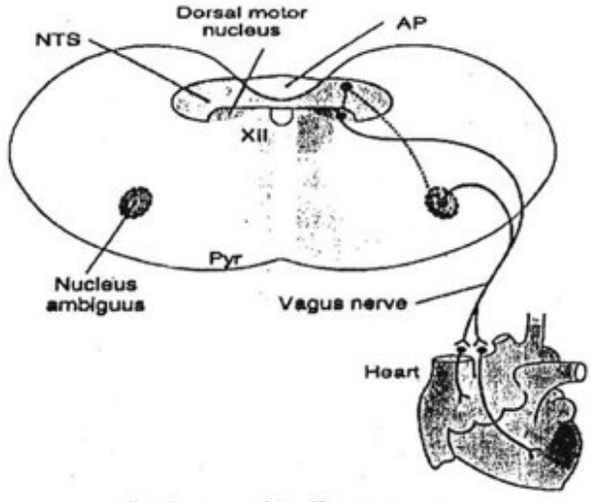
(a)When BP increases → increased stimulation of baroreceptors→ discharge of buffer nerves in to NTS→Increased secreation of glutamate from NTS in to CVLM & IVLM→Increased secreation of gaba in to RVLM→Decreased glutamate secreation from RVLM to IML results in inhibition of the sympathetic system.

Effects on heart;- Decreased stroke volume→decreased cardiac output→decreased BP

Effects on arteriole;-vasodialation→decreased peripheral resistance→decreased DBP.

Effects on veins;-venodialation→decreased venous return→decreased cardiac output→decreased SBP.

From NTS excitatory projection in to nucleus ambiguous and dorsal motor nucleus of vagus.As a result there is decreased heart rate and decreased myocardial contraction.



discharge of buffer nerves

Stimulation of CVLM & IVLM

Inhibition of RVLM

decrease impulses to IML cells

decrease sympathetic vasoconstrictor tone

decrease HR & peripheral resistance

BP decreases to normal

stimulates nucleus ambiguous & dorsal motor nucleus of vagus

increased vagal tone

decrease HR & force of contraction

BP decreases to normal

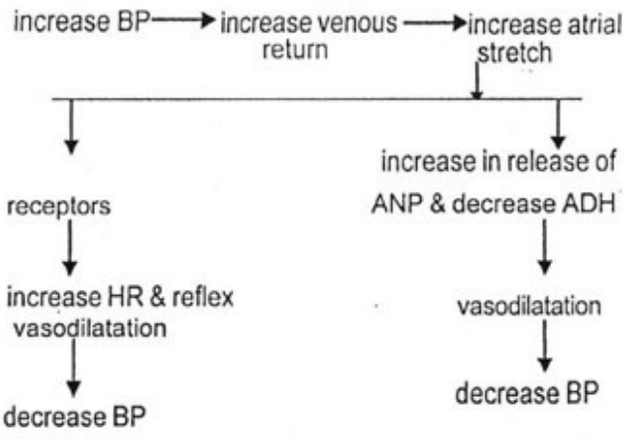
When BP decreases,baroreceptors are less stimulated and there is less secreation of gaba in to RVLM.So more sympathetic stimulation.

Baroreceptors respond better to rapid changes in BP.

Carotid sinus is sensitive to pressures b/w 50-180mm/Hg & aortic arch to levels 30mm/Hg or higher.

(b)Atrial receptors: These are low pressure receptors, i.e., detects BP changes in low pressure areas.

Bainbridge reflex-refer short note .



(c) Left Ventricular Receptors

increase BP causes increas distention of left ventricle which stimulates left ventricular receptors causing decreased HR & decreased BP

Chemoreceptor mechanism:

Chemo receptors are aortic & carotid bodies.they are not stretch receptors,they are chemosensitive cells which respond to hypoxia,hypercapnia and asidosis. Sensitive to pressure levels of 40- 80 mm/ Hg.Decreased BP causes decrease in O_2,increase in CO_2 & increase in H^+ causes chemo receptor stimulation which causes impulses to travel via buffer nerves.This stimulates vasomotor centre.There is increased vasoconstriction and increase in BP

CNS ischemic response:

Sensitive to BP below 50 mm/Hg.Decrease BP causes decreased cerebral blood flow leading to cerebral ischemia.This strongly stimulates Vasomotor Centre(VMC) and increases BP.This mechanism thus act as a last withstand to prevent the final demise of a person.

2) Intermediate term regulation: occurs within minutes to hours.

- Renin Angiotensin mechanism
- Stress relaxation and reverse stress relaxation
- Capillary fluid shift mechanism

Renin Angiotensin mechanism:

When there is decreased BP, Rennin secretion from JG cells increases which convert Angiotensinogen to Angiotensin I.Angiotensin I is converted to Angiotensin II by angiotensin converting enzyme(ACE).Angiotensin II is a powerfull vasoconstrictor.So there is increased arteriolar vasoconstriction and venoconstriction.This causes increase in BP.

Stress relaxation and reverse stress relaxation:

Hyper volemia causes continued stretching of blood vessels resulting in vasodilation and decrease BP.Opposite occurs in reverse stress relaxation in which there is constriction of blood vessels and increase in BP when there is hypovolemia.

Capillary fluid shift mechanism:

When BP increases→increase in hydrostatic pressure in capillary→More fluid comes out in to the interstitial space→Blood volume decreases and BP falls.

Decrease BP→decrease in capillary pressure→ fluid enters capillaries→Increased blood volume leading to Increased BP.

3) Long term regulation: Occurs within hours to days,weeks or month.Kidney play an important role in regulating blood volume.

- Renin Angiotensin aldosterone mechanism
- Pressure Diuresis & natriuresis
- ADH
- ANP

Renin angiotensin aldosterone mechanism:

Decrease BP causes increased renin secretion from JG cells,increase formation of Angiotensin II which has got following actions.

– Vasoconstriction of renal arterioles causes decrease in GFR & contraction of mesangial cells.

- Action on renal tubules causes increase in Na^+ and water reabsorption,increase in ECF volume and increase BP

– Vasoconstriction of arterioles causes increase in peripheral resistance(PR) and increase in BP

- Acts on zona glomerulosa and release of aldosterone.Increase aldosterone secretion causes increase Na^+ Reabsorption and increase BP

- Stimulate post ganglionic sympathetic neuron and release NE.Increase norepinephrine release causes increase vasoconstriction and increase in BP

Pressure Diuresis & natriuresis:

Increase blood volume & increase BP has direct effect on kidneys causes increase in GFR.This increases Na^+ & water excretion,decrease blood volume and BP.This is called pressure diuresis.When there is hypervolemia or increase in Na^+ concentration,atrial receptors are stimulated and release ANP.This ANP causes efferent arteriolar constriction,increase GFR and increase natriuresis.This is known as pressure natriuresis.

ANP:

Secreted in cases of increased BP. Actions include:

(a)vasodilatation of afferent arterioles & relaxation of mesangial cells increased Na^+ & water excretion: decreased BP

(b)Inhibits Na^+ Reabsorption:Increased Na^+ & water excretion:thus decreases BP

(c)Increased capillary permeability,cause vasodilatation, inhibit rennin secretion etc:

ADH:

Secreted from hypothalamus in case of hupovolemia (decrease BP). Actions include:

(a)Acts on V_2 receptors:Increase water reabsorption by increasing the permeability of collecting duct and distal convoluted tubule.Thus increases BP.

(b)Acts on V_1 receptors:Vasoconstriction of blood vessels(so ADH is also called vasopressin).Thus increases BP.

6. Shock & its types

It's a syndrome characterized by inadequate tissue perfusion with a relatively or absolutely inadequate cardiac output, thereby depriving the tissues of O_2 & nutrients.

Classification:

1) Hypovolumic shock
2) Distributive shock
3) Cardiogenic shock
4) Obstructive shock

Hypovolumic shock:

It's caused by inadequate amount of fluid in vascular system resulting in inadequate cardiac output. Subdivided into:

- Hemorrhagic shock
- Traumatic shock
- Surgical shock
- Burn shock
- Seen in fluid loss due to vomiting & diarrhoea

Hemorrhagic shock:

This is the most important cause for Hypovolumic shock.

Mechanism: decrease in blood volume→decrease in venous return→decrease in cardiac output→inadequate tissue perfusion →decrease BP

Characteristic features:

a) Cold, pale, clammy skin – due to decreased blood flow to skin & increased sweating as a result of sympathetic stimulation.
b) Cyanotic tinge of blood due to increased O_2 extraction from blood as a result of stasis in capillaries.
c) Tachycardia & decrease in pulse pressure – due to sympathetic stimulation (thin thready pulse)
d) increased rate & force of respiration – due to chemoreceptor activation
e) Oliguria – due to renal arteriolar constriction
f) Restlessness & apprehension – due to stimulation of reticular formation by catacholamines.
g) Intense thirst (only in conscious individuals)

Stages of hemorrhagic shock

a) Non progressive / compensatory stage
b) Progressive stage
c) Irreversible / refractory stage

Non progressive / compensatory stage

Here perfusion to vital organs is maintained. Normal compensatory mechanisms cause full recovery. Compensatory mechanism can be short, intermediate or long term mech.

Short term responses:

a)Baroreceptor reflex: Blood volume decreases→venous return decreases→decrease stretch of Baroreceptors→increase sympathetic stimulation→ arteriolar constriction→increase BP.

If mean BP is <60 mm/ Hg, no baroreceptor reflex

b)Chemoreceptor reflex: Loss of RBCs →decrease O_2 carrying capacity of blood →decreased flow in aortic & carotid bodies→anemia, stagnant hypoxia, acidosis→ chemoreceptor activation→respiratory stimulation & excitation of VMC →vasoconstriction→increase BP

It's activated when BP < 80 mm/ Hg

c)CNS ischemic response: Decrease BP→decrease cerebral blood flow→cerebral ischemia→strongly stimulates VMC→increase BP

Sensitive to BP below 50mm/Hg.

d)Increased levels of catecholamine:

hemorrhage stimulates adrenal medulla for their secretion. It causes relatively little vasoconstriction & reticular formation stimulation. It causes restlessness & apprehension→motor activity increases→muscular pumping of venous blood increase→venous return increases→CO increases→BP increases

Intermediate term responses:

a)Activation of rennin-Angiotensin mech:

Decrease BP→rennin secreation from JG cells→ increased formation of Angiotensin II → vasoconstriction → increase BP

b)Reverse stress relaxation:

Decrease BP →increase constriction of blood vessel → increase BP

c)capillary fluid shift mechanism:

hypovolemia→fluid absorbed in to circulation→ increase blood volume→ increase BP

Long term responses:

a)Restoration of plasma volume:
- Absorption of fluid from intestinal tract
- Absorption of fluid from interstitial spaces to capillaries
- Conservation of water & salt by kidneys
- Increase thirst causing increase ingestion of water & salts

b)Restoration of plasma proteins
- Rapid entry of preformed albumin
- Replacement of lost proteins by hepatic synthesis

c)Restoration of red cell mass: By 4 – 8 weeks
- Erythropoietin increase in circulation

•Reticulocyte count increased

Progressive stage

Structures of circulatory system begins to deteriorate & various +ve feed back mechanism develop. This leads to progressive shock. +ve feed back mech include:

- •Cardiac depression / cardiac failure
- •Vasomotor failure
- •Peripheral circulatory failure
- •Cardiac depression caused by endotoxin

Irreversible stage:

In this stage, the person dies even though vigorous treatment may still return CO to normal for short periods.

Traumatic shock:

It is due to trauma to tissues.

Causes:

•Hemorrhage directly leading to shock

•Extensive contusion → capillary damage → loss of plasma to tissue

•Traumatized tissues release toxic factors which leads to shock

This kind of shock is accompanied by damage to kidney & skeletal muscles.

Surgical shock

Causes:

•External hemorrhage

•Bleeding to tissues

•Dehydration

Burn shock

Causes:

•Exudation of plasma from burned surfaces increases hypovolemia

•Plasma loss → hemoconcentration → increase in PCV

Distributive shock / low resistance / vasogenic / warm shock:

Here blood volume is normal; but distribution to tissues is impaired due to vasodilatation in whole body.

Subdivided into:

- Neurogenic shock
- Anaphylactic shock
- Septic shock

Neurogenic shock

Fainting, vasovagal attacks occur. In this volume of vascular space is incresed, due to sudden burst of autonomic activity producing vasodilatation cooling of blood in extremities & fainting.

Causes:

1) Brain damage
2) Spinal anesthesia

Other forms are postural syncope, micturition syncope, carotid sinus syncope, deglutition syncope etc

Anaphylactic shock

It is a rapidly developing, severe allergic condition → decrease CO & BP. When an individual who's previously sensitized to an antigen is re-exposed to it, it causes antigen antibody reaction → histamine release → increase capillary permeability & arteriolar, capillary & venular dilatation → shock.

Septic shock

By Gram –ve bacteria infection. They release endotoxins which react with cell membran → releases inflammatory mediators → increase capillary permeability → vasodilatation → initiate cytokine & coagulant reaction → shock.

Cardiogenic shock

Circulatory shock syndrome characterized by inadequate pumping.

Causes:

1)Myocardial infarction.
2)Heart valve dysfunction
3)Arrhythmias
4)Congestive heart failure

Obstructive shock

It is due to obstruction of pulmonary blood flow (as in pulmonary embolism) or impairment of ventricular filling (as in tension pneumothorax, cardiac tamponade, cardiac tumors etc). Acute inflammation of blood in pericardial cavity due to any injury or trauma is called cardiac tamponade.

Treatment of shock:

Admit the patient in ICU. Treatment has 3 modalities.

(a)Replacement therapy
(b)Sympathomimetic drugs
(c)Other therapy

Replacement therapy

Whole blood is given. In burns, plasma or plasma substituents like dextrans are given. Balanced electrolyte solutions like ringer lactate can also be given.

This is not useful in Cardiogenic or obstructive shock.

Sympathomimetic drugs

Drug of choice is dopamine. Injection of adrenaline is life saving in anaphylactic shock.

This is useful mainly in distributive shock.

Other therapy

- •Head down position – to venous return
- •O_2 therapy
- •Glucocorticoids – in septic shock.
- •Antibiotics – in septic shock
- •Digitalis – in Cardiogenic shock
- •Treat the cause in obstructive shock

7. CVS changes in exercise:

Exercise is associated with extensive changes in circulatory & respiratory system. During exercise, active tissues require more O_2, & more CO_2 & heat need to be expelled. Exercise is of 2 types:

a) Mild to moderate exercise : All O_2 required is supplied during the exercise

b) Severe or strenuous exercise: muscles don't get all the O_2 required. So, O_2 debt is incurred.

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Circulatory changes in exercise:

Circulatory adjustments can be classified as

- Regional circulatory responses
- Systemic circulatory responses

Regional circulatory responses

Include changes in blood flow to muscles & other regions. These changes include

a)Increase Blood flow: -

When muscle contracts, blood vessels are compressed decreasing the blood flow. But blood flow is greatly increased in b/w the contractions, as high as 30 times the normal. Cause for this increase include

Neural mechanism:

- Stimulation of sympathetic vasodilator fibers → increase blood flow
- Decrease in tonic vasoconstrictor discharge
- Stimulation of adrenal medulla → release of epinephrine act on β receptors vasodilatation → increase blood flow

Local mechanism:

- Decrease in tissue pO_2
- Increase in tissue pCO_2
- Increase in temperature
- Accumulation of K^+ & other vasodilator metabolites
- Dilatation of arterioles & pre capillary sphincters causes 10 – 100 fold rise in number of open capillaries

b) Increase O_2 extraction by tissues: -

Dilatation of blood vessels decreases velocity of blood flow.

Increase in total muscle blood flow + decrese in blood velocity → rise in capillary pressure which exceeds oncotic pressure → increase transudation of fluid into interstitial spaces → increase lymph flow → ODC shifts to right → more O_2 is delivered → arterio-venous concentration difference increases.

c) Changes in blood flow to other regions

A) Skin: Skin blood flow is increased until 50 – 60 % of maximum work load is reached. This helps in body cooling. As exercise progresses, body fluid is lost through sweat & lungs, partial dehydration occurs increasing PCV. Further increase in work load decrease skin blood flow as cutaneous sympathetic vasoconstrictor tone continue to rise overcoming the thermoregulatory vasodilator response.

B) Brain: Cerebral blood flow almost remains constant.

C) Splanchnic blood flow decreases

D) Coronary blood flow increases

E) Renal blood flow decreases in short term exercise. In strenuous exercise, blood flow to kidney, GIT, liver etc maintained at adequate levels for continued functioning of these organs.

Systemic circulatory response

•In static/ isometric exercise, force is generated without muscle shortening, hence no external work performed.

•In dynamic/ isotonic exercise, muscle shortening occurs, external work performed

a)Changes in heart rate

Isometric exercise: HR increases

Isotonic exercise: HR increases, but increase is more abrupt

Cause for increased HR:

a) Psychic stimulation acting on medulla decreased vagal tone increase HR

b) Increased discharge of cardiac sympathetic nerves

c) Increased release of catecholamine from adrenal medulla

b)Changes in stroke volume:

Isometric exercise :Little change

Isotonic exercise :Marked increase in stroke volume due to increased myocardial contractility

Continued exercise :stroke volume decreases, due to high increase in HR & shortening of diastole.

Changes in peripheral resistance:

Isometric exercise → muscles tonically contracted → compression of blood vessels → increase PR

Isotonic exercise: vasodilatation of exercising muscle → decrease in PR

Changes in venous return:

Great increase in venous return due to:

- Increase activity of muscle & cardiac pumps
- Mobilization of blood from viscera
- Venoconstriction mediated by noradrenalin, no pooling of blood

Changes in cardiac output:

Isometric exercise: Little Increase

Isotonic exercise: Increase CO up to a maximum of 35 L due to:

- Increase sympathetic discharge, Increase HR
- Increase stroke volume, Increase venous return

Changes in blood pressure

Isometric exercise:

PR Increases → DBP increases

Moderate increase in HR & CO → SBP increases little

Isotonic exercise:

PR decreases → DBP decreases

Marked Increase in HR & CO → SBP increase with increase in pulse pressure

After exercise, for a small time, BP falls to subnormal values due to accumulation of vasodilator metabolites. After that BP returns to pre normal levels.

SHORTNOTES

1. Pacemaker potential:

Rhythmic type of action potential seen in rhythmically discharging cells like SA node, AV node, conducting system, some intestinal smooth muscles & some neurons in CNS controlling respiration.

In these cells there's unsteady RMP of about -60 to -70 mV. This is because all Na^+ or Ca^{2+} channels are not fully closed even in resting state. Thus after each impulse, the membrane potential declines to firing level and triggers the next impulse. This is called prepotential or pacemaker potential.

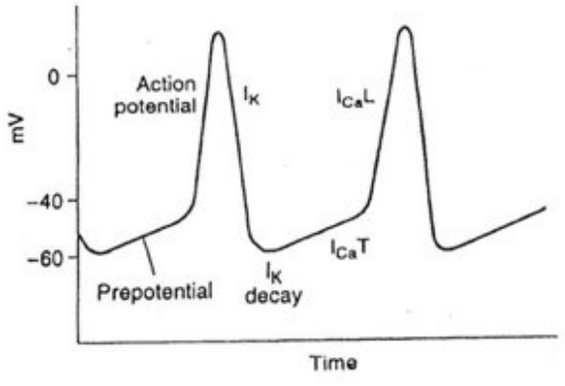
Ionic basis of action potential in pacemaker tissues:

(a)Repolarization: due to opening of voltage gated K^+ channels & K^+ efflux

(b)It reaches RMP

(c)Prepotential: earlier due to decrease in K^+ efflux & later due to Ca^{2+} influx (by opening of transient Ca^{2+} channels). Local Ca^{2+} release from sarcoplasmic reticulum (Ca^{2+} sparks) also contributes to prepotential.

(d) Depolarization: opening of long lasting Ca^{2+} channels leading to Ca^{2+} influx.

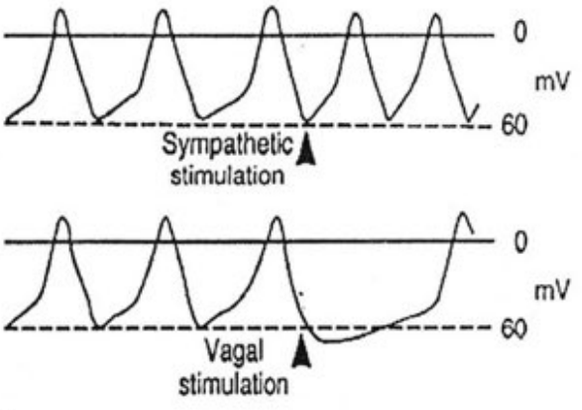


2.Autorhythmicity:

The property of spontaneous pre-potential followed by AP is called autorhythmicity.Because of this property heart can beat continously.This autorhythmicity is because of the presence of specialised tissue called pacemaker tissue that can produce AP.Action potential in pacemaker cells is called pacemaker potential.The impulse production is at a rate of 70-80/min or 72/min.Other parts of heart can also produce AP when SA node is diseased or blocked.The rate of production by SA node is more when compared to other parts,so SA node is called pacemaker.

Effect of vagal(cholinergic)stimulation:When cholinergic fibres to nodal tissue are stimulated heart rate decreases.Ach released at the nerve ending increases K^+ conductance at nodal tissue via m2 muscaranic receptors which via G-protein open a special set of K^+ channel.Here slope of pre-potential decreases.

Effect of sympathetic(noradrenergic) stimulation:When sympathetic cardiac nerves are stimulated heart rate increases.Noradrenaline from sympathetic nerve ending via β_1 receptor increases intracellular cAMP facilitate the opening of long lasting Ca^{2+} channels.Here slope of pre-potential increases.



3. AV nodal delay:

Our conductive system is well organized so that cardiac impulse from atria won't travel too rapidly to the ventricles. Always, there's a delay of 0.1 sec before the excitation of the ventricles. This is due to the low level conductivity of AV node. Velocity of impulse transmission in AV node is only about 0.05 m/ sec. About one half of this delay occurs in junctional fibers, which connect atrial fibers with the nodal fibers. Velocity in these fibers is about 0.01 m/sec which is only 1/15th of the normal conduction velocity. This delay is shortened by sympathetic stimulation while parasympathetic stimulation lengthens it.

Cause for AV nodal delay:

(a) Small size of Junctional fibers

(b) No: of tight junctions between cell membranes is greatly reduced b/w these cardiac muscle cells, thereby reducing the rapidity of ionic transport along the axis of the fiber.

(c) Long refractory period of AV nodal cells

(d) These fibers are made of a much more embryonic type of cells, with less differentiation

Physiological significance of AV nodal delay:

1) It ensures adequate ventricular filling before ventricular contraction begins

2) It allows atrial contraction to be completed before ventricular contraction

3) It acts as a filter which prevents too rapid entry of impulses from atria into ventricles (as in case of atrial fibrillation) & thus save ventricles from tachycardia.

4.Refractory period of cardiac muscle:

The period following AP during which cardiac muscle does not respond to any stimulus is called

refractory period.Cardiac muscle has a long RP ie.,250-300msec in ventricles and 150msec in atrium.In case of cardiac muscle whole systole and early part of diastole in absolute refractory period and rest is in relative refractory period.

Significance of long RP.

-It maintain the normal rhythm of heart.

-Summation and tetanus are not possible.Because summation and tetanus to be occur the second stimulus should fall during the contraction phase of previous one.In cardiac muscle whole systole is in ARP.Under normal condition it wont produce any exrasystole.If extrasystole occur compansatory pause help to establish the normal rhythm.

5.Staircase phenomenon:

Successive increase in force of contraction in first few contraction after the heart start beating is called staircase phenomenon or treppe.This is seen in after vagal stimulation,after stanneous ligature.When the heart stops, there occur increase in Na^+ and K^+ concentration inside the cell.This increases the Ca^{2+} influx.Thus there is progressive increase in Ca^{2+} concentration in sarcoplasm which cause this phenomenon.

6. ECG waves & intervals:

Body is a volume conductor because body fluids are good conductors of electricity.Therefore the elctrical activities are conducted all over the body and can be detected on body surface using suitable electrodes.This procedure is called Electrocardiography and the equipment is called electrocardiograph.The record of potential fluctuations during a cardiac cycle is called electrocardiogram.Electrical activity is the algebric sum of the action potential of cardiac fibres during each cardiac cycle.

A normal ECG has

- P wave
- QRS complex
- T wave
- Sometimes, U wave

P wave:

Usually it is a positive wave. It has a rounded summit. It's caused by atrial depolarization. The impulses reach AV node at the summit of P wave

QRS complex:

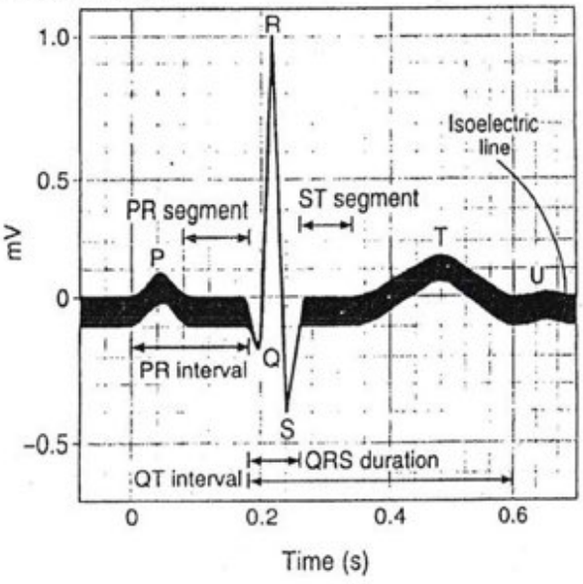
It has 3 waves- Q, R & S. It's produced due to ventricular depolarization before ventricular contraction. Q wave is a small –ve wave produced due to septal activation (left to right septal depolarization). It's most obvious in leads V_4, V_5, V_6 & is absent in leads V_1 & V_2. R wave is a +ve wave produced due to septal & left ventricular depolarization. It's prominent in leads L_1 & L_2, & in left sided chest leads V_3, V_4, V_5, V_6. S wave is a small –ve wave. It occurs due to late depolarization of ventricular wall, moving back towards AV groove.

T wave:

It's a broad based +ve wave with rounded peak. It's caused by ventricular repolarization. If ventricular repolarization has occurred in same direction as depolarization, a –ve T wave would have resulted. But, repolarization occurs in opposite direction (epicardium to endocardium). So a +ve T wave occurs.

U wave:

It's not always seen. It's a small +ve wave, produced by slow repolarization of papillary muscles. It's prominent in hypokalemia



WAVE	VOLTAGE	DURATION
P	0.1-0.3mV	0.08-0.12sec
QRS	1-1.5mV	0.04-0.1sec (avg:0.08sec)
T	0.2-0.3mV	0.27sec

Intervals:

•PQ/PR interval:

It is an interval from the beginning of P wave to beginning of QRS complex. Q wave is frequently absent in recording, hence called PR interval.

Duration : 0.12-0.2 sec

Events occurring : atrial depolarization & conduction through AV node & Bundle of His & its branches.

•QT interval:

From the beginning of Q wave to end of T wave

Duration : 0.26-0.45 sec

Events occurring : ventricular depolarization & ventricular Repolarization

• ST interval:

From end of S wave to end of T wave

Duration : 0.32 sec

Events occurring :ventricular repolarization

7.Leads in ECG:

A lead refers two electrodes and their wires.It is placed on the body surface and connected to ECG machine for measuring the potential difference between the two points.Usually there are 12 leads in ECG.Out of 12 leads ,6 leads are limb leads and 6 are chest leads.Limb leads are L I,L II,L III,aVR,aVL,aVF and chest leads are V1,V2,V3,V4,V5,V6.

These 12 leads are again devided in to unipolar and bipolar leads.The biplar leads are L I,L II,L III.They are calledbipolar limb leads or standard limb leads.

L I-Here we are measuring the potential difference between right arm and left arm

L II-measuring the potential difference between right arm and left foot.

L III-measuring the potential difference between letf arm and left foot.

In unipolar leads one electrode is active and other electrod is inactive or indifferent.Therefore the potential difference measured between them will be the potential of active one.There are 2 types of unipolar leads,unipolar limb leads and unipolar chest leads.aVR,aVL and aVF are the unipolar limb leads.Unipolar chest leads are V1 to V6 leads.

The indifferent electrode is kept at 0 potential by connecting the electrode from right arm,left arm and left leg to a central terminal through a 5000 ohm resistance.This is done automatically in ECG machine.In aVR active electrode is in right arm,in aVL active electrode is in left arm and in aVF active electrode is in left foot.We are not using unipolar limb leads aVR,aVL,aVF,instead we are using augmented unipolar limb leads.

8. PR interval and its significance-Wenkebach phenomenon

It's the interval from the beginning of P wave to the beginning of QRS complex.So this include P wave and QRS segment It corresponds to the interval b/w beginning of atrial contraction and the beginning of ventricular contraction.

Normal duration: 0.12 to 0.2 sec (avg: 0.18 sec)
It shortens as heart rate increases.

Events occurring:
(a)Atrial depolarization
(b)Conduction through AV node and AV nodal delay

Variations:
(a)Prolonged in:
- 1st degree heart block
- Wenkebach phenomenon
- Hypocalcaemia

(b)Shortened in:
- Wolff-Parkinson White syndrome
- Lown-Ganong-Levine syndrome

Wenkebach phenomenon

It occurs in a case of incomplete heart block. Here there are repeated sequences of beats in which PR interval lengthens progressively until a ventricular beat is dropped. PR interval of cardiac cycle that follows each dropped beat is usually normal or slightly prolonged.

9.Einthovans triangle:

In a volume conductor the sum of the potentials at the end points of a equilateral triangle with a current source at centre is zero.Einthovan selected 3 points in the body -(1)right shoulder ,(2)left shoulder,(3)left mid inguinal point.When the above points are joint together an equilateral triangle is obtained.Heart is assumed to be its centre and this triangle is called Einthovans triangle.For convienience electrodes are placed on both wrist and left foot.The effect is same because the potential are conducted to the limbs.

The 3 bipolar leads form a closed circuit.According to Kirchoff's law sum of the potential difference measured sequentially in any 3 bipolar leads completing a closed circuit would be zero ie.,I+II+III=0.Einthovan reverse the polarity of 2nd lead so according to Einthovans law Kirchoff's law becomes I+III=II.Einthovans law states that sum of the potentials of L I and L III is equal to potential in L II at any instant.

10. Stokes - Adams syndrome

In some patients with AV block, total block comes & goes. i.e., all impulses are conducted from atria to ventricles for a period of time, & then suddenly no impulses are transmitted. Immediately, after AV conduction is first blocked, ventricles stop contracting for about 5 to 10 sec. Then some part of Purkinje system, usually AV bundle itself starts discharging at a rate of 15-45 beats per min, & acts as pacemaker for ventricles. This is called ventricular escape. As brain can't remain active for more than 4-5 sec without blood supply, patients usually faint in b/w block of conduction & escape of ventricles, and then recover slowly because even the slowly beating ventricles usually pump enough blood to sustain the patient. These periodic fainting spells are called Stokes-Adams syndrome.

Treatment
(a) Implantation of electronic cardiac pacemaker with its tip on the right ventricle.
(b) Demand pacemakers
(c) Dual chamber pacemakers
(d) Drugs like digitalis-converts the syndrome into a total heart block as the former is more dangerous & can even lead to death.

11. WPW & LGL syndrome

WPW / Wolff Parkinson White syndrome:

It is a congenital anomaly where an accesso

muscular / nodal tissue connect right atria to ventricles called the bundle of Kent. This conduct impulses faster than the normal AV bundle resulting in the early excitation of one ventricle. Manifestation of its activation merges with a shortened PR interval & a prolonged QRS deflection slurred on upstroke. There's a normal interval b/w the start of P wave & the end of QRS complex (PJ interval). Paroxysmal atrial tachycardia seen in this syndrome often follows an atrial premature beat. This beat conducts normally down AV node, but spreads to the ventricular end of the aberrant bundle.

In some conditions, this syndrome is familial. There is mutation in gene coding for AMP activated protein kinase, which is involved in suppressing abnormal AV pathways during fetal development.

LGL / Lown – Ganong – Levine syndrome:

Attacks of paroxysmal supra ventricular tachycardia are seen in individuals with shortened PR intervals & normal QRS complexes. Here impulse is transmitted through an aberrant bundle which bye passes AV node & enters the conducting system distal to the node.

Normal sinus beat

Short PR interval; Wide, slurred, QRS Complex; Normal PJ Interval (W-P-W Syndrome)

Short PR Interval;Normal QRS Complex (L-G-L Syndrome)

12. Heart sounds

During each cardiac cycle 4 heart sounds are produced. This can be recorded phonographically & the recording is called phonogram. Only first 2 heart sounds are usually heard.

1st heart sound (S_1)

It's caused by vibrations set up by the sudden closure of mitral & tricuspid valves at the start of ventricular systole(isovolumetric contraction). It's also called M_1T_1.

Duration : 0.15 sec
Frequency : 25-45 Hz
Character : Relatively prolonged & low pitched. It resembles the syllable "lubb". It is heard best at mitral and tricuspid area. It coincides with the R wave of ECG. The intensity depends on the force of ventricular contraction.Loud S1 is heard in mitral stenosis.Muffled S1 is heard in mitral regurgitation and tricuspid regurgitation.

2nd heart sound (S_2)

It's caused by vibrations associated with the closure of aortic & pulmonary valves just after the end of ventricular systole(end of protodiastole). This sound is also called A_2P_2.

Duration : 0.12 sec
Frequency : 50 Hz
Character : Short, sharp, high pitched sound resembling the syllable "dub".It is best heard at aortic and pulmonary areas. During inspiration, S_2 becomes split normally. This is called physiological splitting of 2nd heart sound. Reason for this is that aortic valves close a little earlier than pulmonary valves due to low impedance in pulmonary vascular tree.Loud S2 is heard in systemic and pulmonary hypertension.

3rd heart sound

It is due to vibration produced by rush of blood from atria to ventricle during first rapid filling phase of ventricular diastole.It's soft, low pitched with duration of 0.1 sec.It may occur in healthy young adults and in pregnancy.Abnormal 3rd heart is heard in abnormal ventricular filling.eg.,mitral regurgitation,left ventricular failure.

4th heart sound

It is due to vibration produced by flow of blood from atria to ventricle during last rapid filling phase correspond to atrial systole.Heard just before 1st sound. This sound is not normal; occur only if there is high atrial pressure.

Added sounds

Heart murmurs:

Sound heard over heart other than heart sounds.

4 types:

1) Valvular – due to defect in valves.
2) Fistular – in ASD, VSD
3) Aneurismal – occurs in aorta
4) Hemic – occurs in anemia, decreased viscosity,decreased blood flow etc

Another type of classification:

- Systolic
- Diastolic
- Continuous

Murmurs due to abnormalities in aortic or tricuspid valves are heard during systole, while those due to insufficiency of mitral or pulmonary are heard during diastole.

Opening snap:

It is due to opening of mitral valve during ventricular systole.It is a sharp high pitched sound of 0.06-0.12 sec duration.It is seen in severe mitral stenosis

Ejection click:

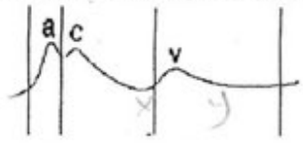
It is a sharp and high pitch clicking sound heard immediately after S1 due to sudden opening of aortic and pulmonary valve.Heard in stenosis of aortic and pulmonary valve.

Pericardial rub:

It is heard over the pericardium.Sound is superficial like noise of hair rubbing against the diaphram of the stethescope.Heard in pericarditis.

*13. Jugular venous pressure

Right atrium is in direct continuation with superior venacava & jugular veins. So, right atrial pressure is reflected into the pressure recorded in these veins.



Jugular venous pressure, showing a, c, and v waves

The recording of JVP reflects the phasic pressure changes in right atrium & consists of 3 +ve waves (a, c & v) & 2 –ve waves (x & y) waves.

- 'a' wave is produced due to venous distention caused by right atrial contraction. It is the dominant wave in JVP particularly during inspiration. A large 'a' wave is seen in tricuspid valve stenosis & pulmonary stenosis. It's absent in atrial fibrillation.
- 'c' wave is produced by bulging of tricuspid valve into right atrium during Isovolumetric right ventricular contraction. It's transmitted manifestation of rise in right atrial pressure.
- 'v' wave is produced by increase in right atrial pressure when the tricuspid valve is closed during which it gets distended with inflow of blood.Giant v wave is seen in tricuspid regurgitation
- 'x' descend is due to atrial relaxation & downward displacement of tricuspid valve during ventricular systole.
- 'y' descend is produced mainly by the opening of tricuspid valve & subsequent inflow of blood into right ventricle, i.e., atrial pressure decreases.

JVP is raised in congestive cardiac failure,pericarditis,tricuspid regurgitation,after massive fluid or blood transfusion.

Differences between venous and carotid pulsation:

Venous pulsation has definite upper leve,l but carotid has no definite upper level.

Venous pulsation falls during inspiration,but carotid does not change with inspiration.

Venous is more seen than felt,carotid is more felt.

Venous pulsation is more wavy and less sharp,carotid is jerky.

Venous pulsation is more prominant in lying position

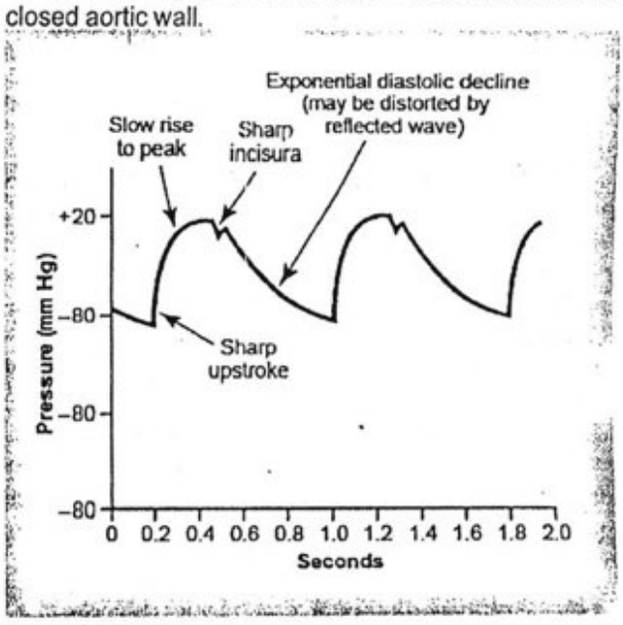
*14. Arterial pulse

Blood forced into aorta during systole not only moves the blood in the vessels forward, but also sets up a pressure wave that travels along the arteries. Pressure wave expands the arterial wall and the expansion is palpable as pulse. Usually the arterial pulse pressure is measured from radial artery while the volume and character of the pulse is often judged from carotid/brachial artery.

Pulse wave has a upstroke and a downstroke.

Different parts are,

- percussion wave(P):corresponds to rapid ejection phase of ventricular systole.
- Tidal wave(T):corresponds to falling of blood column during slow ejection phase
- Dicrotic notch(N):vibration due to the clossure of aortic wall at the end of protodiastole
- Dicrotic wave(D):due to rebound of blood column from closed aortic wall.



Rate of pulse:

Normal rate=60-100/min

below 60-bradycardia eg..hypothyroidism

above 100-tachycardia eg.,hyperthyroidism,fever

Rhythm of pulse:

Interval between two successive pulses(beats).If it is same,it is called regular rhythm.Irregularly irregular pulse is seen in atrial fibrilation and regularly irregular pulse is seen in extrasystole.

Volume of pulse:

High volume pulse is seen in fever,aortic regufgitation,mitral regurgitation,pregnancy.Low volume pulse is seen in aortic stenosis,pericardial effusion,cardiac failure.

Character of pulse:

Abnormal characters are,

Slow rising(anacrotic)-aortic stenosis

Collapsing(water hammer)-aortic regurgitation

Puses paradox-constrictive pericarditis

Pulses alternans-left ventricular failure

Bisferians pulse-combination of aortic stenosis and regurgitation

Pulses bigeminus-Digoxin toxicity

Velocity of the pulse:

Velocity of pulse wave is inversely proportional to the amount of elastic fibers in the arterial wall. Velocity is about 4m/s in aorta, 8m/s in large arteries & 16m/s in small arteries. Velocity of transmission of pressure pulse is much more than those of velocity of blood flow. Velocity increases with age due to a gradual decrease in elasticity of the arteries. This is as a result of increased pressure developed during systole due to loss of Wind-Kessel effect.

15. Coronary blood flow – features & graph

Myocardium of heart receives blood via 2 coronary arteries, right & left, arising from the root of aorta / sinuses of Valsalva. In humans, RCA is dominant in 50 % of people; LCA in 20% & 30% people have equal dominance to both. The dominant artery becomes larger & supplies a larger portion of heart than the other. For e.g.: In RCA dominance, RCA supplies right atrium, right ventricle & inferior surface of left ventricle, whereas it supplies only right atrium & ventricle in case of LCA dominance. Venous blood is chiefly drained by coronary sinus which in turn receives blood from great, middle & small cardiac veins. A small amount of blood is drained by anterior cardiac veins & thebasian veins.

Features:

1) Normal coronary blood flow is 250 ml/min.
2) O_2 consumption of myocardium is very high (19 ml/min).Capillary population in myocardium is very dense. Thus, distance b/w adjacent capillaries are very short. This ensures adequate O_2 supply to tissues.
3)Unlike other arteries, coronary arteries are filled during diastole.
4)Main coronary artery branch repeatedly on epicardial surface, finer branches emerge perpendicularly towards the sub endocardial region. Because of this arrangement, when ventricles contract, vessels get occluded. As left ventricle is thicker, occlusion is more there.
5)Coronary arteries are end arteries. But anastomoses are established in old age or in persons suffering from partial occlusion of coronary arteries for long.

Factors determining coronary blood flow:

I)Mechanical factors
II)Metabolic factors
III)Neural factors

Mechanical factors:

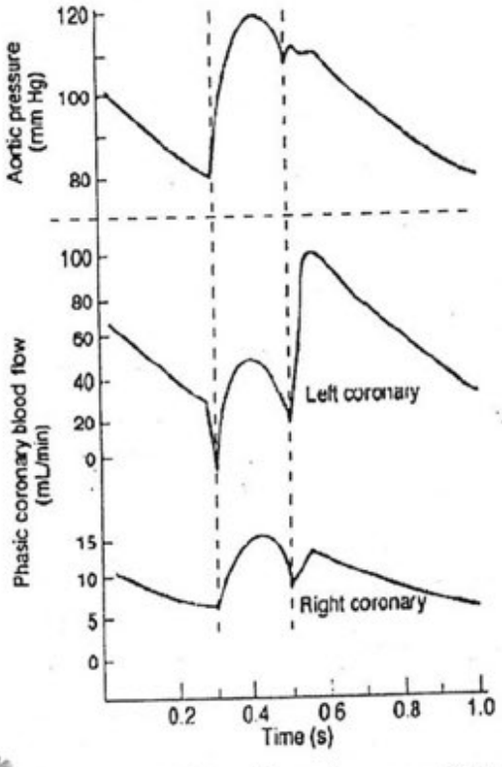
•Phasic blood flow: variations in coronary blood flow with phases of cardiac cycle

•Auto regulation: When mean BP in aorta is b/w 60 – 150mm/ Hg, coronary blood flow remains unchanged. It's due to the auto regulation, which operates even when the nerve supply is removed.

•Regional blood flow: Sub epicardial portion receives more blood than sub endocardial region.

Metabolic factors: Hypoxia causes formation of adenosine which enters extra cellular spaces & cause vasodilatation.

Neural factors: Parasympathetic effect is very less. Sympathetic supply on vascular smooth muscles is present.Alpha receptors produce vasoconstriction & β receptors mediate vasodilatation. At the same time sympathetic stimulation increased contractility & BP, thus increasing work load of heart.The resulting hypoxia in turn causes vasodilatation, so the net effect is vasodilatation.



16. Frank Starling law or Starling's law of heart

This law states that force of contraction is directly proportional to the initial length of the muscle fiber within the physiological limit. This law has an important role in the regulation of stroke volume, & hence cardiac output. When the initial length is more, force of ventricular contraction is more thus stroke volume is more. In case of intact heart, initial length is determined by end diastolic volume, i.e., amount of blood that remains in the ventricle at the end of diastole. EDV acts as the preload, while the aortic resistance acts as the afterload. Preload increases initial fiber length, while afterload decreases it.

Physiological significance of Frank Starling law

(a) This law explains why blood ejected by both ventricles is same. If right ventricular output is more than the left, blood accumulates in the left side leading to greater force of contraction of left ventricle, thus increasing the left ventricular output.
(b) It's the life saving mechanism in heart failure. In left ventricular failure, blood accumulates in left ventricle. Frank Starlings law starts to operate causing greater blood flow from left ventricle. If accumulation of blood exceeds the physiological limit, heart fails to operate leading to death.

17. Regulation of stroke volume: (refer essay 4)

18. Fick's principle- measurement of cardiac output

Fick's principle states that amount of a substance given up/ taken by an organ or whole body per unit time is equal to arterio-venous concentration difference times the blood flow through that organ. As per this principle, amount of substance 'x' taken up per unit time,

$Q_x = (A_x - V_x) \times$ Blood flow; or

Blood flow = $Q_x / (A_x - V_x)$ where,

A_x -arterial level of the substance X

V_x- venous level of the substance X

This principle is used the measurement of cardiac output.Left ventricular output is equal to right ventricular output.Right ventricular output is equal to the blood flow through the lungs in 1 minute.The substance measured here is O_2.

Cardiac output = O_2 consumption (in mL/min)/ arterio- venous O_2 concentration diff (in mL/L)

O_2 consumption by the body can be determined by measuring the O_2 concentration in inspired air and expired air.O_2 concentration in inspired air is same as that of atmospheric air. O_2 concentration in expired air is measured using a spirometer. The difference b/w the 2 gives the O_2 consumption per minute (avg: 250 mL/min) Arterial O_2 concentration is measured from any peripheral artery (avg: 190mL/L). Venous concentration is measured directly from right ventricle or from pulmonary artery by cardiac catheterization. (Avg: 140mL/L).

So A-V conc difference = $A_x - V_x$ = 190-140=50mL/L

As per Fick's principle,

Cardiac output = O_2 consumption/ AV O_2 conc.difference

=250mL/min/ 50mL/L

=5L/min

Cardiac catheterization can lead to hemorrhage, infarction etc. So, sometimes instead of making use of a substance added to blood by lungs, a substance removed by blood (CO_2) is used. Here,

CO = CO_2 expired in mL/min / veno-arterial concentration difference of CO_2

19.Regulation of heart rate:

(refer essay 4)

20. Why bradycardia is seen in increased intra cranial tension?

When intra cranial tension is increased, blood supply to brain decreases, causing local hypoxia & hypercapnoea. This in turn stimulates vasomotor centre which tend to restore normal blood supply to medulla by increasing BP.Increasing BP via baroreceptor stimulate the vagal outflow and decreases the heart rate.So increased intracranial tension is associated with increased systemic BP and Bredycardia.This is called cushing reflux.

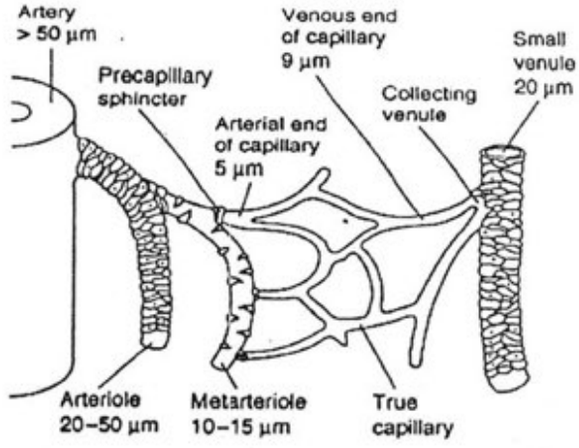
21. Types of blood vessels

Blood vessels act as means of transport of blood from heart to tissues and back to heart. Widely, they are classified into 3. They are

(a) Arteries & arterioles

(b) capillaries

(c) Veins & venules.



Arteries & arterioles

Arteries carry blood away from the heart. The walls of all arteries consist of 3 layers- outermost tunica adventitia, middle tunica media & an innermost tunica intima. The walls of aorta & other large arteries contain large amount of elastic tissue, which help them to stretch during systole & recoil during diastole. The walls of arterioles contain less elastic tissue, but more smooth muscles. Arterioles are considered as the "seat of peripheral resistance", since small changes in their caliber cause large changes in total peripheral resistance. So, they are called resistance vessels.

Capillaries

They are thin walled & formed of a single layer of endothelium on a continuous basal membrane with pericytes on the outer surface. Exchange of materials b/ w blood & tissues take place through capillaries (hence called exchange vessels). Capillary walls are porous due to the gap b/w the endothelial cells & also due to fenestrations. These pores as well as the large surface area of capillaries help in the exchange of substances across the capillaries.

Veins & venules

They carry blood towards the heart. They are thin walled & wider than arteries. They also have got 3 layers among which tunica adventitia is the thickest. They contain relatively little smooth muscles. The intima of the limb veins are folded at intervals to form venous valves that prevent backward flow of blood. No valves are present in very small veins, the great veins or the veins from brain & viscera. Veins act as important blood reservoirs. A large

amount of blood can be added to the normally collapsed veins, before there's much increase in venous pressure. Hence, they are referred to as capacitance vessels.

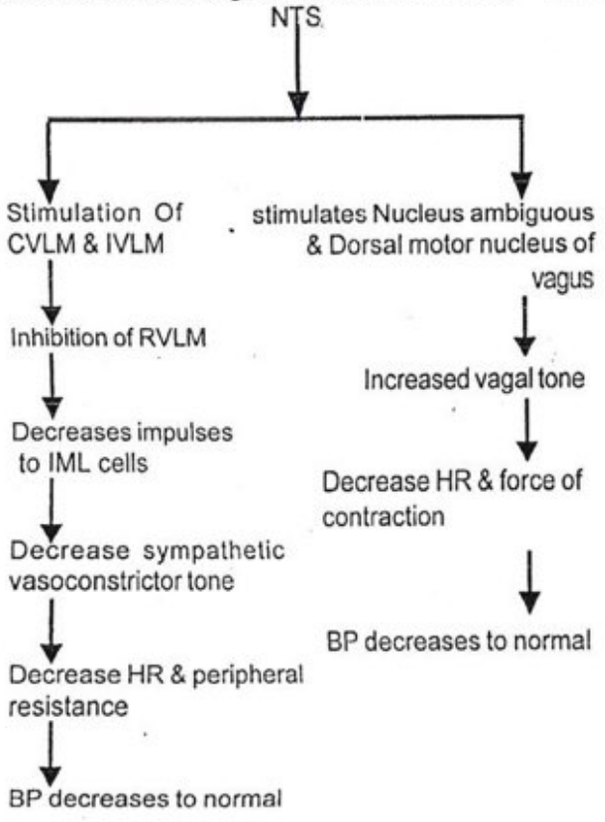
22. Windkessel effect

Although the mean velocity of blood in aorta is 40 cm/sec, flow is phasic. Velocity reaches about 120 cm/sec during systole, & falls back to a –ve value at the time of transient back flow before aortic valve closes in diastole. However, the vessel walls have plenty of collagen & elastic fibers. So they are compliant & are able to expand.

When blood is pumped into larger vessels like aorta, common carotid or subclavian during ventricular systole, these vessels will expand & accommodate some excess blood temporarily. During diastole, when heart is not pumping, their elastic wall recoils & blood is propelled forwards. This property of larger vessels is called Windkessel effect. These vessels are called Wind Kessel vessels.Windkessel is a German word meaning "elastic reservoir".

23. Baroreceptor reflex & Mary's law

Baroreceptors are receptors sensitive to changes in pressure.They are mainly located in carotid sinus & aortic arch.So baroreceptor reflex is also called Sino-aortic reflex.When there is Increase in BP → increased stimulation of these receptors → discharge of buffer nerves → (branch of glossopharyngeal in case of carotid sinus & branch of vagus in case of aortic arch) → NTS.



Carotid sinus is sensitive to pressures b/w 50-180mm/Hg & aortic arch to levels 30mm/Hg or higher.

Mary's law:

It states that is blood pressure inversely proportional to heart rate.This is mediated by baroreceptors,ie.rise in BP will stimulate cardiac inhibitory centre and heart rate will decrease.This law is obeyed by the body most of the times. But in case of exercise & some reflexes this law is not obeyed.

24. Bain Bridge reflex:

Rapid infusion of blood / saline in anaesthetized animal sometimes produces an increase in HR if the initial HR is low. This effect is called Bain Bridge reflex & was proposed by Bain Bridge. Normally, an increase in atrial pressure also causes an increase in HR even to about 100%. Part of this increase is caused by direct effect in increased atrial volume in stretching SA node (about 20-70%). Rest is done by Bain Bridge reflex.

The receptors are tachycardia producing atrial receptors.The reflux compete with the baroreceptor mediated decrease in HR produced by volume expansion.Afferent and efferent are through vagus and the centre is at medulla.It is diminished or absent when the initial HR is high.

This is a true reflex since it is abolished by bilateral vagotomy & infusion of fluids into animals with transplanted hearts increases the rate of recipient's atrial remnant but fails to affect the rate of transplanted heart.

25. Cushing's reflex & Bezold Jarisch reflex

Cushing's reflex

It's a special type of CNS ischemic response that results from increased intracranial tension (above 33 mm/Hg). When intra cranial pressure increases blood supply to vasomotor area is decreased.This creates a local hypoxia & hypercapnoea which stimulate VMC to rise arterial BP. When arterial pressure rises to a level above CSF pressure, blood flow to brain is restored thus relieving ischemia.When BP increases there is reflux reduction in heart rate.This is known as cushing's reflux.This is the only condition in the body where we have increased BP associated with decreased HR.

Bezold Jarisch reflex

When left ventricle is distended in experimental animals, there's a fall in systemic BP & HR. Injection of serotonin, veratridin, capsaicin etc into coronary artery supplying left ventricle → stimulation of C fibers → apnoea followed by hyperpnoea, decrease HR, decrease BP.This reflex is also called coronary chemo reflex. Receptors responsible are chemo receptors sensitive to certain alkaloids. Physiological role of this is unknown. But in patients with MI, substances released from infracted tissue may stimulate ventricular receptors & may lead to hypotension.

26. Triple response & axon reflex:

When the skin is stroked firmly with a pointed object, the 3 reactions which follow are called triple response. They include

(a)Red reaction: - Initial reddening at the site following the stroke. This appears in about 10 sec. This is due to capillary dilatation which occurs when capillaries are subjected to pressure.

(b)Wheal: - local swelling at the site which occurs in few minutes after red reaction. This local edema is caused by an increase in permeability of capillaries and post capillary venules with consequent oozing out of fluid.

(c)Flare: - diffuse, irregular red spots spreading out from injury. This is due to arteriolar dilatation. Flare is absent in totally anaesthetized or Denervated skin, but is present after a nerve block or section above the site of injury. This indicates that flare is due to axon reflex.

Axon reflex:

It's a response in which impulses initiated in sensory nerves by injury are relayed antidromically down other branches of the sensory nerve fiber. This is an example where a physiological effect can be brought about by antidromic conduction. It's one of the few reflexes in the body which doesn't involve CNS. The transmitter released at central termination of sensory C fiber neurons is substance P. It dilates arterioles & also causes extravasation of fluid.

27. Hyper tension:

It's the sustained elevation of systemic arterial BP >140/90 mm/Hg. In >90–95% cases, underlying cause can't be found. This is called Primary/essential hyper tension. In 5 % cases, this is due to specific disease or abnormality. It's called secondary hyper tension.

Causes of secondary hyper tension:

(a)Renal diseases – glomerulonephritis, renal artery stenosis, poly cystic kidney

(b)Endocrine diseases – Cushing's syndrome, Conn's syndrome, congenital adrenogenital syndrome, myxoedema, acromegaly, pheochromocytoma, hyper parathyroidism etc

(c)Drugs – oral contraceptives, anabolic steroids, corticosteroids

(d)Coarctation of aorta

(e)Toxemia of pregnancy

Experimental hyper tension:

- Interferes with renal blood flow (renal HTN)
- Interruption of afferent input from arterial Baroreceptors (Neurogenic HTN)
  - ❖Bilateral lesions of NTS
  - ❖Denervation of carotid sinus & aortic arch
- Treatment with corticosteroids
  - ❖Deoxycorticosterone & salt
  - ❖Other mineralocorticoids

Malignant HTN:

Sometimes in chronic HTN patients necrotic vascular lesions can occur with papilloedema, cerebral symptoms and renal failure. It's fatal if untreated. It can be reversed by proper antihypertensive therapy.

Complications of HTN:

a)Cardiac conditions: Left ventricular hypertrophy, cardiac failure, ischemia, myocardial infraction

b)CNS conditions: Cerebral hemorrhage, stroke

c)Retinal conditions: Hypertensive retinopathy papilloedema

d)Renal conditions: Renal failure

Treatment of HTN:

Primary HTN is treatable but not curable.

a)salt, calorie, cholesterol & saturated fat restricted diet

b)Avoid alcohol & smoking

c)Exercise

d)Drugs anti adrenergic drugs, ACE inhibitors, Ca^{2+} channel blocker, vasodilators, diuretics etc.

Secondary HTN is not only treatable but sometimes also curable.

28. Blood Brain Barrier:

The tight junctions between capillary endothelial cells in brain and between the epithelial cells in the choroid plexus forming a barrier which prevent the entry of certain substances is called blood brain barrier.

•Plasma proteins, lipid insoluble substances like proteins, polypeptides, protein bound hormones – impermeable

Functions of BBB:

•Maintains consistency of environment of neurons in CNS

•Acts as an additional defense which protects sensitive neurons from being subjected to ionic changes

•Protect brain from toxins

•Prevents escape of neurotransmitters into general circulation

Clinical application:

•Certain amines like dopamine, serotonin etc can't penetrate BBB, but their precursors like L-Dopa & 5-OH tryptophan can. So they are used for treatment.

•In cases of infections, injury, decreased BP etc it can break down

29.Circumventricular organs:

4 small areas in or near the brain stem, which stains like tissues outside brain, i.e., they are outside BBB. They have fenestrated capillaries & allow passage of substances. They are

(a)Posterior pituitary & adjacent ventral part of median eminence of hypothalamus

(b)Area postrema

(c) Organum vasculosum of lamina terminalis (OVLT)
(d) Subfornical organ

Functions of these organs:

•Post pituitary & median eminence: -

Function as neurohemal organs, i.e., areas in which polypeptides secreted by neurons enter circulation. ADH & oxytocin enter general circulation in post pituitary. Hypothalamic- hypophyseal tropic hormones enter hypophyseal portal circulation in the median eminence.

•Area postrema

It's a chemoreceptor trigger zone that initiates vomiting in response to chemical changes in plasma. It's also concerned with cardiovascular control. Angiotensin-II acts here to increase BP.

•OVLT

Angiotensin- II acts here to increase thirst. It's also the site of osmoreceptor, controlling ADH secretion. IL-II acts on OVLT to cause fever.

•Subfornical organ;

Site of action of Angiotensin-II, & thus help in increasing thirst.

30. CSF – formation & functions:

It's modified tissue fluid in CNS present in sub arachnoid spaces in brain & spinal cord, ventricles of brain & central canal of spinal cord.

Volume: 150 ml (15 % of brain volume)

Formation:

Site:

•Choroid plexus which extend into ventricles

•Blood vessels of meningeal & ependymal linings of CSF chambers

•A smaller portion by blood vessels of brain & spinal cord

Rate: 550 ml/ day. It turns over about 3.7 times a day.

Mechanism:

•Ultra filtration from plasma

•Facilitated diffusion

•Active secretion from choroid plexus – Presence of mitochondria, granules & vesicles in epithelial cells of choroids plexus indicate their capacity for active secretion. 1st, Na+ ions are actively secreted from plasma to CSF, followed by passive movt of Cl-, which together create an osmotic gradient that pulls water through the membrane to CSF.

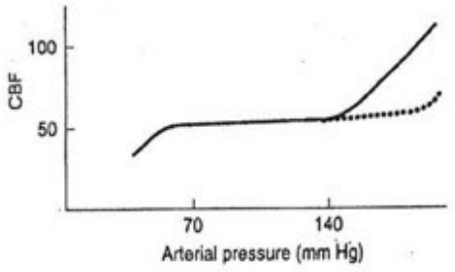
Functions:

- Protective function
  - Act as a cushion for brain within the vault of skull,thus decreasing effect of stress.
  - In water bath of CSF, net weight of brain is only 50 Gms, whereas its actual weight is about 1400 Gms.Brain float in CSF as both havethe same density. So CSF provides buoyancy to brain.
  - It decreases inertia of brain to gravity & acceleration
  - It prevents semisolid brain matter from coming in contact with cranial walls, thus preventing brain damage.
- It act as a reservoir & helps in regulating volume of cranial vaults
- Maintains proper ionic concentration for functioning of neurons in CNS
- Acts as the lymph system in CNS
- CO_2 alters pH of CSF & controls respiration by acting on medullary chemoreceptor.
- Acts as a medium for nutrient exchange
- Acts as a sensitive mirror which reflects diseases of CNS

31. Regulation of cerebral blood flow

CBF can be regulated in following ways

(a) Auto regulation: Blood flow to brain remains constant in spite of alterations in perfusion pressure. In brain, auto regulation maintains normal CBF at arterial pressures 65-140 mm Hg. 2 theories are proposed to explain this- myogenic & metabolic theories.



(b) Metabolic factors: Increased CO_2, Increased H^+ & decreased O_2 can cause an increase in CBF & vice versa. CO_2 combines with H_2O in body fluids to form carbonic acid which dissociates to provide H^+ ions. This H^+ can cause vasodilatation, increasing CBF. Similarly, substances like lactic acid, pyruvic acid etc which increase acidity also increase CBF.

Normally, O_2 utilization in brain remains within a narrow limit. In case of O_2 deficiency caused by decreased CBF, immediate vasodilatation can occur thus increasing CBF

(a Neural factors: With increased BP, there's increased discharge of sympathetic nerves & it decreases the increased blood flow. This prevents the high pressure from reaching smaller cerebral blood vessels & thus prevents vascular hemorrhages. Thus with sympathetic stimulation, constant blood flow/ plateau part of pressure curve is extended to right.

(b) Role of intra cranial tension: If it's > 33mm Hg→ decreased CBF→ ischemia→ stimulation of VMC→ increase systemic BP→ increase CBF→ ischemia relieved.This is called Cushing's reflex.

Protective mechanisms regulating CBF is proportional to increased intra cranial tension up to a point, but later cerebral circulation stops.

32. Laplace law- applications

It's an important physical principle which states that tension in the wall of a cylinder (T) is equal to he product of transmural pressure (P) and radius (r), divided by the wall thickness (w).

So, $T = Pr/w$

Transmural pressure is the difference in pressure outside & inside the cylinder. Since tissue pressure is low, it can generally be ignored & P = pressure inside the viscus. In a thin walled viscus, w is too small which can be ignored & P=T divided by the 2 principal radii of curvatures of the viscus.

$$P=T\ (1/r_1 + 1/r_2)$$

In a sphere, $r_1 = r_2$, so $P = 2T/r$. In a cylinder 1 radius is infinity, so $P=T/r$.

Applications:

(a)It explains the closure of vessels at an exact critical pressure level (pressure level at which the vessel can't be kept open). Force tending to stretch the muscles in vascular wall decreases when the distending blood pressure decreases (as they both are proportional to each other). At the same time, radius also decreases. As a result, the vessel wall is pulled inwards, making it to close.

(b)When the radius of heart chamber is increased, a greater tension must be developed in myocardium to produce any given pressure. Consequently a dilated heart must do more work than a non dilated heart.

(c)In lungs, radii of alveoli become smaller during expiration & if the transmural/ distending pressure are not kept constant the alveoli will collapse. As P = Tw/r, & r is decreased, in order to keep P constant T must also decrease.This is brought about by surface tension reducing substances present in lungs (surfactants)

(d)In case of urinary bladder, intra vesical pressure increases only very slowly, because as bladder is filled both tension & radius increases simultaneously causing only a slight increase in P.

33. Irreversible / refractory shock:

In some individuals, shock will progress to such a stage where transfusion or any kind of therapy becomes incapable of saving patient's life. This stage is called irreversible shock. Therapy can return arterial BP or even CO to normal, but circulatory system continues to deteriorate & death occurs in few min to hrs.

Cause for Irreversible shock:

- Depletion of high energy compounds like ATP, creatine phosphate etc. Adenosine formed by degradation of ATP, diffuses out of the tissues & gets converted into uric acid which can't diffuse back to tissues.
- In late stages of shock, heart fails to pump blood / fluid that we inject for the purpose of returning CO to normal.
- Severe deficiency of O_2 contributes to irreversibility of shock.

Various +ve feed back mechanisms contribute to this. They include:

- Severe cerebral ischemia leads eventually to depression of vasomotor & cardiac areas of brain, causing vasodilatation & decrease HR & decrease CO.
- In severe shock, coronary blood flow is decreased due to hypotension & tachycardia. The myocardial failure worsens the acidosis & shock.

physiological basis:

1.Subendocardial portion is more prone to ischemia

Pressure difference between aorta and left ventricle is negative during systole,so no blood flow occurs.The maximum decrease is seen in subendocardial portion.Blood flow occurs only during diastole.So this area is more prone to ischemia.

2.Rapid thready pulse seen in hypovolemic shock

Increased sympathetic stimulation via baroreceptor mechanism→increase HR(Rapid pulse).As there is decrease volume in shock pulse to be thready

3.Increased stroke volume during exercise

Refer essay 7(increase muscle pump→increase venous return→increase SV)

4.Palpatory method is done first before auscultatory method in measuring BP

Hint:Inorder to avoid auscultatory gap

5.In thyrotoxicosis systolic BP increases and diastolic BP decreases

Thyroid hormone increases HR & contractility→increases cadiac output→Increase systolic BP.

TH increases BMR→waste products increases→vasodialation→peripheral resistance decreases→decrease DBP

6.Bradycardia seen in increased intra cranial tension

Refer Short note-20

7.Splitting of heart sound more prominant during inspiration

Hint:During inspiration intra thoracic pressure decreases→time for right heart filling increases→systole lengthens, P2 slightly delayed..

Lt atrial & lt vendricular filling reduces→Le ft ventricular systole is shortened,→A2 occur earlier than P2

8.Heart rate increases during inspiration

During inspiration,stretch receptors in lung are stimulated and via vagus N the cardio inhibitory area is suppressed→increase in HR

Impulses are spread from medullary respiratory centre to vasomotor centre of medulla→increase sympathetic discharge→increase HR.

Gastrointestinal System

Prepared by
ADARSH I NATH
MUJEEB.TM

ESSAYS:

1.Phases and regulation of gastric secretion.

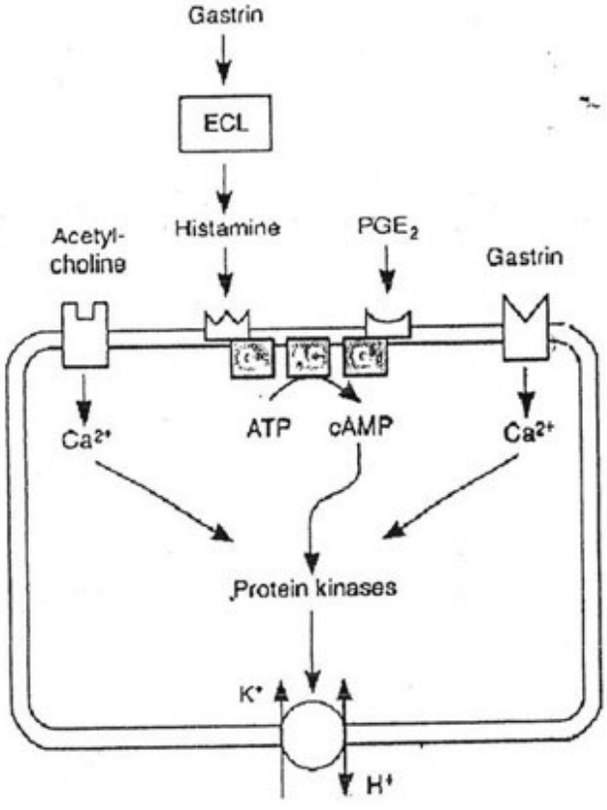
Gastric secretion is regulated mainly by:
- Neural mechanism
- Hormonal mechanism

NEURAL MECHANISM

i.Short cholinergic intragastric reflexes

ii.Impulses from CNS to the Vagus nerve increase the gastrin production by **G cells** (the neurotransmitter released is GRP [gastrin releasing peptide]).

Other vagal endings release Ach which directly acts on the fundus to increase HCl secretion. (Ach excites all types of cell viz peptic cells to produce pepsinogen, mucous cell to produce mucous



HORMONAL MECHANISM

Secretion of
- Histamine
- Gastrin

They act on parietal cells and cause increased production of HCl

Mechanism of Action:

Ach

- Released at parasympathetic nerve endings(vagal). The receptors for Ach are M_3 (muscharanic) on the cell membrane of parietal cells. Binding of Ach to these receptors increases the intracellular Ca^{2+} concentration by promoting release of Ca^{2+} from intracellular stores.
- Ca^{2+} acts via protein kinase to increase the H^+/K^+ ATPase and also more number of Cl^- channels to be inserted to the apical membrane and results in increased HCl production.
- In addition to the direct action Ach also stimulates ECL which produces histamine → acts in paracrine fashion → binds to H_2 receptor and increases the activity of G_s proteins and stimulates the adenylyl cyclase resulting in increased cAMP, increases the H^+ entry into lumen by H^+/K^+ ATPase and increases movement of chloride ions → increased HCl production. The rate of formation and secretion of HCl by parietal cells is directly proportional to the amount of **Histamine released by ECL**, which can be stimulated in several ways – potent of them being gastrin then Ach from vagal ending.

Gastrin has 2 modes of action
- Stimulates ECL
- Act on gastrin receptors → increase intracellular Ca^{2+} by mobilizing intracellular Ca^{2+} and influx of extracellular Ca^{2+} ions

For convenience, regulation of gastric secretion is discussed in terms of:
- Cephalic
- **Gastric**
- Intestinal
- Interdigestive phase (in between meals)

1.Cephalic Phase:

Occur before the foods enter the stomach.

This phase is initiated by sight, smell and taste of appetizing food. This is a conditioned reflex

- Mediated by branches of vagus nerve that synapse with neurons of ENS
- Neurogenic signals originating in cerebral cortex and appetizing centers of amygdala and hypothalamus → dorsal motor nucleus of vagus in medulla → stomach via vagus → stimulates parietal cells and indirectly stimulates G cells of pyloric area → increase gastric (acid) secretion.
- Afferent limb → taste impulses → via 7&9 nerve → nucleus tractus solitarius (medulla) → dorsal motor nucleus of vagus → efferent to stomach wall → stimulates parietal and G cells
- 20%of gastric secretion is produced during the cephalic phase

2.Gastric Phase:
- Increased secretion due to presence of food in stomach
- 70%secretion during this phase
- This phase mediated both neurally and hormonally

Neural Mechanism:
Distension of stomach by the bulk of food stimulate stretch receptors in stomach wall&increase gastric juice secretion by 2 reflexes;
*short intramural/local enteric reflex
*long vagovagal reflex

short reflex>
the reflex arc is suituated inside gastric wall.Fibres from the receptors reach **Meissner's/Aurebach's plexus** and synapse in the ganglion cells of stomach wall.The postganglionic fibres innervate the chief cells,mucous cells,parietal, cells etc..&increase their secretion.

long vagovagal reflex>
from the receptors,impulse pass through the vagus to the brainstem(DMN of vagus)&efferent fibres also pass through te Xth nerve to reach the ganglion cells of ENS.The postganglionic fibres innervate different cells of gastric glands to increase gsstric juice secretion.

Hormonal Mechanism:
•Mainly by the way of producing **gastrin**
The main stimulus is the presence of peptides and amino acids
•Inhibited by acidification of stomach below pH 2.5

3. Intestinal Phase:
Initially it is inhibiting.Presence of food in upper part of small intestine particularly in the duodenum causes the secretion of gastric juice in small amount initially and later on there is an inhibition of gastric acid secretion.
Several mechanism acts in intestinal phase 2 main mechanisms are
•**Enterogastric Reflex**:
Presence of food in small intestine initiates an enterogastric reflex.
Mediated by 3 pathways
1.Directly from duodenum to stomach thru the ENS in the gut wall
2.Extrinsic nerve prevertebral sympathetic ganglia → inhibitory sympathetic fibers to the stomach
3.vagus nerve → brain stem → inhibit normal excitatory signals transmitted to the stomach through the vagus nerve
•Hormonal Mechanism:
Presence of acid, fat and fat digestion products, products of protein digestion cause release of several intestinal hormones like Secretin, VIP, Somatostatin, peptide YY. All these hormones will inhibit gastrin secretion. These hormones are together called as enterogastrone

4. Interdigestive Phase:
•Small amount of secretion.
•In humans about 10%
•Lowest between 5-11am
•Highest 7pm-1am
•Secretion is usually non oxyntic,composed mainly of mucous and small amount of pepsin.
•Emotional stimuli increase the secretion, which has high amount of acid and pepsin.

2.Bile – Composition and regulation of secretion

Bile is formed continuously at the rate of about 30-65mL/hr or 500-1000mL/day.
Delivered via hepatic duct and released intermittently into the duodenum.
Bile is secreted in 2 stages by the liver
•Initial secretion is an active secretion by liver cells or hepatocytes and this secretion contains a large amount of bile acids and other organic constituents.
•During its course through the duct a second portion is added to the initial bile. It is a watery solution rich in HCO_3^- and Na^+.
Ductular secretion is initiated by secretin

COMPOSITION OF BILE
Bile is a yellow alkaline fluid, bitter to taste. The major organic constituents present in bile are:
- oBile pigments
- oBile salts
- oCholesterol

➢Yellow color of bile is due to the pigments bilirubin and biliverdin
➢Bile is stored in gall bladder. Here water is reabsorbed and bile becomes concentrated and color becomes darker. There is also reabsorption of HCO_3 so the pH decreases and bile becomes more acidic

❖Bile salts:
These are Na and K salts of bile acids. They are synthesized from cholesterol, supplied in diet or synthesized in liver. Cholesterol contains cyclopentano per hydro phenanthrene ring in nucleus.
The 2 primary bile acids are:
- •Cholic acid
- •Chenodeoxycholic acid

These are formed in liver from cholesterol and there are conjugated with glycine or taurine to form glyco and taurocholic acid
The Na^+ and K^+ salts of primary bile acids are secreted into bile within the large intestine the bacteria convert the primary bile acids to secondary bile acids.
❖BILE PIGMENTS
These are responsible for the golden yellow color of bile.They are the break down products of hemoglobin. Total plasma bilirubin includes free bilirubin and small amount of conjugated bilirubin. In liver they are converted to colorless urobilinogen, which is soluble. Some of urobilinogen is reabsorbed and re excreted by liver into bile.

•About 5% enters the general circulation and is excreted by the kidney thru urine
•Part of urobilinogen converted to stercobilinogen and excreted through faeces

Other substances excreted through bile:
oCholesterol 1-2g/day insoluble in water but the bile salts and lecithin keep them in solution
oSulphates or glucouronic conjugated of fat soluble vitamins A, D, adrenocorticoids and other steroid hormones are again reabsorbed and excreted thru bile (via enterohepatic circulation)
oSalts of heavy metals Cu, Zn and Hg
oSome drugs and toxins are also excreted thru bile

Regulation of secretion:

The liver cells continuously secrete bile. However certain factors influence them. The bile acid synthesis from cholesterol is under the negative feedback control
Major factors influencing synthesis of bile are
a)Bile acids and salts → choleretics

The amount of bile secretion by hepatocytes is highly dependent on bile salts reaching the cell by EHC some components of bile are reabsorbed in the intestine and are then excreted by the liver.

Several components undergo this circulation, most important being bile salts,

Secondly bile pigments, thirdly hormones adrenocorticoids and steroid hormones.About 90-95% of bile salts are reabsorbed from the small intestine mainly from the terminal ileum by an active transport mechanism – Na bile salt mechanism

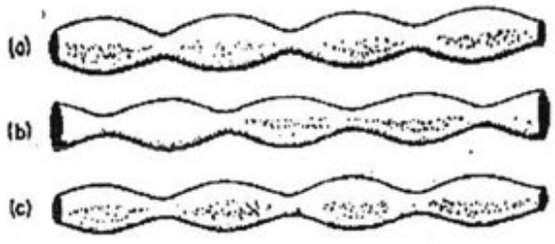
The energy needed for this is provided by Na^+ / K^+-ATPase at the basolateral membrane. The reabsorbed bile salts enter the liver by portal blood. They reach the sinusoids and are picked up by the hepatocytes.
•The small quantity of bile salts is excreted thru faeces and liver synthesizes that amount. The normal rate of bile acid synthesis is 0.2-0.4g/day and total bile salt pool is about 3.5g. This amount recycles repeatedly via the EHC. The amount of bile salts reaching the cells via EHC is more greater than the secretion of bile into biliary tree and reaches the intestine
•If more bile salts are lost to exterior, the liver increases synthesis of liver acids and bile salts and tries to bring the bile secretion to normal level.
•When concentration of bile acids in hepatocytes fail as in instances of bile acid malabsorption from intestine lead to increased bile acid synthesis.
b)Secretin
Causes increased secretion of bile. Actually only water and bicarbonate fractions of bile increase due to secretin.
c)Gastrin
Also increases the secretion of bile
d)Vagal stimulation also causes increased secretion of bile (mild choleretics)

3.Movements of small intestine:

Small intestine shows different types of movement.
They bring about:
•Mixing contents with the digestive secretions
•Brings it in contact with the absorptive surface of small intestinal mucosa
•Propels its contents slowly down the gut
•Propels unabsorbed residue into the colon
The different types of small intestinal movements are:

1.Segmentation contractions:

Ring like contractions appear at regular intervals and are replaced by another set of ring like contractions at the segments between previous contractions. This occurs when a portion of the small intestine is distended with chyme.
oInitiated by local increase in Ca, with waves of Ca spreading from each focus
oThe velocity is determined by the velocity of BER
oIt requires background excitation from the ENS
It causes
•Segmentation of intestine and chopping of chyme (2-3times /min) moves it to and fro
•Promotes mixing and increases exposure to the intestinal surface



Segmenting movement

2.Peristalsis:

Propel contents of small intestine to large intestine.Faster in proximal than in distal intestine.
Moves at 0.5-2cm/sec, but the net movement of chyme is slow (1cm/sec) Greatly increased after a meal
It is regulated by neural and hormonal mechanism
Neural Mechanism:

Stimulated by the entry of chyme into duodenum by GER (Gastroenteric reflex)→initiates signals thru myenteric plexus→ connected through walls of small intestine to increase the motility.
Hormonal Mechanism:
Gastrin, CCK, Insulin, Serotonin→ increases peristalsis
Secretin and glucagons decrease the peristalsis
It causes
•Propulsion of chyme
•Helps absorption by spreading out the chyme along intestinal mucosa

On reaching the illeocaecal valve, chyme is blocked for several hours until the person eats another meal.

3.Tonic contraction

Relatively prolonged contractions that isolate one segment of intestine from the other.

Segmentation and tonic contractions in effect prolong the transit of the chyme in the small intestine. So it allows longer contact of chyme with the enterocytes thus favoring absorption.

4.Pendular movements

Rhythmic to and fro movement similar to segmental contraction, but larger segments are formed and the portion of the intestine is first pulled in one direction and then in the opposite direction i.e. intestinal wall moves over its contents like a stocking drawn over the leg.

The exact function of this type of movement is not known, but probably it helps to expose a greater area of mucosa to chyme.

5.Movement produced by muscularis mucosa

Stimulus is contact with food or foreign body

- Contraction produces fold in intestinal mucosa→ increase surface area→ increases absorption
- In addition to this individual muscle fibers from the muscle extend into the intestinal villi and cause them to contract intermittently.
- The intestinal villi exhibit different types of movement. In fasting state, villi are inactive; they lie flat in the mucosal surface.

Mechanical or chemical stimulation by food result in to and fro movements and lashing movements.

- Shortening and elongation of the villi, which occurs alternatively

These movements milk the villi.The lymph from the antral lacteals moves into the lymphatics.It probably also increases the blood flow and causes stirring of the fluid bathing the surface of the villi favoring absorption.

Gastro intestinal hormones:

GI Hormones are chemicals produced by endocrinal cells present in betweem the epithelial cell lining the mucosa of GIT.

Almost all the GI Hormones synthesized are peptides.

The important GI Hormones are

i.Secretin
ii.CCK – Pancreozymin
iii.Gastrin
iv.GIP
v.Motilin

1)Secretin

- Polypeptide hormone synthesized by the S cells of mucosa of duodenum and jejenum
- The major stimulus for the secretion of secretin is acid in the duodenum
- If pH becomes less than 4.5 there is secretion of secretin
- Fatty acids also stimulate the secretion of secretin

Actions

The major effect of secretin is to produce secretion of pancreatic HCO_3, this neutralizes the acidity of the chyme released from the stomach. Pancreatic enzymes can work satisfactorily. No damage to duodenal and jejunal mucosa can occur

Mechanism of Action:

Cell membrane is the site of secretin receptor. It activates protein kinase A (via c AMP) and increases the intracellular c AMP levels

2)CCK – Pancreozymin

- Polypeptide hormone produced by I cells in the mucosa of duodenum and upper jejunum
- The main stimulus is the products of partial digestion of proteins and fats.

Actions:

Act on the acinar cells and cause release of zymogen granules producing increased pancreatic secretion rich in enzyme. Contraction of gall bladder (together with relaxation of sphincter of oddi)

Mechanism of Action:

The receptor for CCK is located in the cell membrane.

Receptor activates Phospholipase C → PIP2→IP3 + DAG

IP3 mobilization of intracellular stores of Ca ions like endoplasmic reticulum in cytoplasm

DAG acts thru activating Protein kinase C

3)Gastrin

From G cells of pyloric glands or antral glands in response to products of protein digestion and it reaches the parietal cells by means of endocrine mechanism

2 modes of action

- Stimulates ECL→increased production of histamine→Gs protein activity increases→increased c AMP → increased HCl production
- Act on gastrin receptors →increase intracellular Ca (mobilize intracellular Ca stores and extracellular influx)

4)GIP

These are secreted by the K^+ cells of the duodenal mucosa.

Major stimulus - fat in chyme

Actions:

- Increases insulin secretion
- Reduces HCl secretion
- Increases GI motility

4. Pancreatic juice and its regulation:

Pancreatic juice is the most powerful of all the digestive juices.

- Secreted around 1.5L/day
- 98.5% water
- 1.5% solid
- iso osmotic with plasma
- pH8
- colorless, opalescent, watery fluid

Solid component can be divided into organic and inorganic

Organic components:

i.Proteolytic

•Trypsin:

- ✓Most abundant and most important
- ✓Produced as trypsinogen and converted to active form by removing N terminal portion of the molecule and is activated by enterokinase when the pancreatic juice enters the duodenum
- ✓It's action is to convert Proteins to proteoses and peptones

•Endopeptidase

- ✓Attack peptide bonds in which –COOH groups are contributed by lysine and arginine
- ✓Ca^{2+} helps in activation of trypsinogen and also accelerates the action of Trypsin
- ✓Acts at an optimum pH of (7-8)

•Chymotrypsin:

- ✓Endopeptidase
- ✓Secreted as inactive chymotrypsinogen
- ✓Activated by Trypsin
- ✓Optimum pH 8

•Carboxypeptidase

- ✓Exopeptidase
- ✓Secretes as procarboxypeptidase
- ✓Activated by Trypsin
- ✓Hydrolyses the terminal peptide linkage and some amino acids are liberated

•Proelastase

- ✓Activated by Trypsin
- ✓Acts on elastin and cleaves bonds adjacent to aliphatic amino acids

ii.Amylolytic

•Pancreatic amylase:

- ✓Similar to salivary amylase and is secreted in active form by the pancreas
- ✓Acts on both cooked and uncooked starch.
- ✓It also acts on other related polysaccharides except cellulose.
- ✓Acts on α1,4 linkages
- ✓End products are oligosaccharides, disaccharides-maltose, trisaccharide, maltotriose

iii.Lipolytic:

•Pancreatic lipase

- ✓Hydrolyses neutral and long chain fats to monoglycerides, diglycerides, fatty acid and glycerol
- ✓Act in the presence of co lipase (released by pancreatic cells)
- ✓Cholesterol esterase
- ✓Cholesterol ester ==> cholesterol
- ✓Phospholipase A2
- ✓Act on phospholipids and converts them into lysophospholipids

iv.Nucleic acid splitting enzymes- Nucleases

Hydrolyses the internucleotide bond (endonucleotidase) and produce nucleotides

v.Other organic constituents

•Trypsin inhibitor

•Produced by acinar cells

•Inactivates the Trypsin activation and also the action of Trypsin by forming a stable complex with enzyme at its catalytic site(prevents disorders like pancreatitis

•Lysosomal enzymes

•Alkaline phosphatase

•Small amount of albumin

Regulation of Pancreatic secretion:

The pancreatic secretion is regulated both by hormonal and neural mechanism

❖The basic stimuli that increase the secretion are Secretin, CCK and Ach

- oSecretin
  - ▪Produced by S cells of mucosa of duodenum and jejunum
  - ▪Stimulus acid in stomach
  - ▪Acts on duct cells to increase HCO_3 secretion which is poor in enzymes (doesn't stimulate acinar cells)
- oCCK
  - ▪Produced by I cells of mucosa of duodenum and upper jejunum
  - ▪Act on acinar cells and cause release of zymogen granules, producing increased pancreatic secretion rich in enzymes
  - ▪Major stimulus products of partial digestion of proteins like proteoses and peptones
- oAch
  - ▪Vagal nerve endings and also from other cholinergic neurons in the ENS
  - ▪Acts mainly on acinar cells and produces secretion rich in enzyme

Pancreatic secretion is divided on the basis of ingestion of meal into:

➢Cephalic phase

Similar to gastric secretions, mediated neurally by vagus nerve (Ach is the neurotransmitter).Apart from Ach,VIP and GRP are also released. Ach acts on acinar cells,contribute to 20%of the pancreatic secretion.

➢Gastric phase

- oPresence of food in stomach, distension of stomach cause pancreatic secretion that is mediated neurally
  - ▪Vago vagal reflex
  - ▪Gastro pancreatic reflex
- oEnzyme rich secretion is produced
- oContribute 5-10%of pancreatic secretion
- oGastrin hormone does not mediate the pancreatic secretory response of pancreatic

stimulation. It is mainly mediated by neural mechanism.

➢ **Intestinal phase**

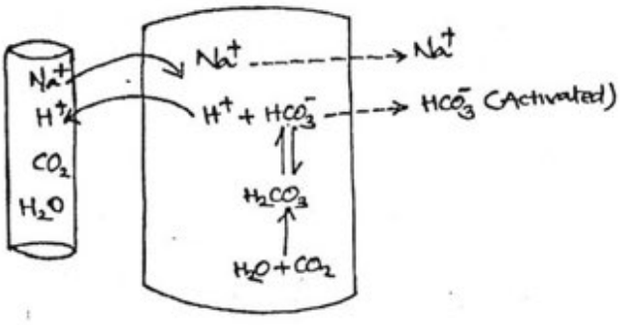
- After the entry of chyme into the small intestine pancreatic secretion increases mainly under the hormonal control(secretin and CCK)and also neurally mediated by the vagus(vago vagal reflex) and the enteropancreatic reflex
- It is the most important phase of pancreatic secretion and accounts for about 65-75% of the total secretion after the food intake

Increased volume and also osmolarity evoke the pancreatic secretion by stimulating the enteropancreatic reflex. Mainly acinar cells are stimulated along with the duct cells.

Inhibitors of Pancreatic Secretion:

- Inhibitory feedback exist between intraluminar pH and HCO_3 level
- Low pH==>increased secretion of secretin==> increased HCO_3 secretion
- Increased pH ==> decreases the HCO_3 release
- Sympathetic stimulation
- Pancreatic polypeptide, glucagons, somatostatin

Mechanism of HCO_3^-



- The epithelial cells lining the ducts and also the centeroacinar cell secrete HCO_3
- They contain a large amount of carbonic anhydrase and mitochondria
- CO_2 diffuses into cells from blood,combines with H_2O and forms H_2CO_3 under influence of carbonic anhydrase
- HCO_3 is actively secreted into lumen
- H^+ from cell is exchanged for Na^+ through the blood border of cell by $Na^+ - H^+$ antiport
- Na^+ ions are transported through the luminal border of the cell to the lumen to provide electrical neutrality
- The movement of $NaHCO_3$ into the lumen creates an osmotic gradient that causes movement of water into the pancreatic duct by the process of osmosis.

SHORT NOTES

1. Functions of saliva:

The major functions of saliva are

a)Digestive

Saliva contains 2 important enzymes that help in digestion

- Salivary α amylase/ptyalin acts on optimal pH of 6.7 and it acts specifically on the α1-4 linkages.
- Converts polysaccharide in the cooked starch to maltose, maltotriose, and α-limit dextrin.
- As the food remains in the mouth for a very short duration only 5% of the starch is digested in the mouth.
- Lingual lipase acts optimally in acidic pH.
- It is active even in the stomach.
- It acts on triglycerides hydrolyzing it.

b)Lubricative

Saliva moistens food and oral mucosa, softens foods and facilitates mastication and deglutition.

c)Facilitate speech

Keeps the mouth moist and aids the movement of lips and tongue

d)Cleansing action

Important in oral hygiene; washes away the bacteria and food particles

e)Antibacterial action

- Lysozyme attacks bacterial cell wall
- Lactoferrins is bacteriostatic and binds to Fe^{2+}
- Ig-A attacks viruses and bacteria
- Thiocyanate enters the bacteria and is bactericidal in nature

f)Acts as solvent

Saliva dissolves food particles and helps in appreciation of taste by stimulation of taste buds and helps in appreciation of taste.

g)Buffering action

HCO_3, PO_4^{3-}, and mucin present in saliva acts as buffer, this provides optimum pH for the action of ptyalin and is important for the prevention of dental caries and neutralize the regurgitated gastric acid

h)Excretory function

Many heavy metals like Pb,Hg,alkaloids like morphine,drugs like streptomycin,viruses of rabies,mumps,poliomyelitis etc..are excreted through saliva

i)Maintenance of water balance and thirst mechanism

Decreased body water can lead to dry mouth, which stimulates thirst resulting in water intake.

j)Middle ear pressure adjustment

k)Temperature regulation

l)Other compounds seen in saliva

- NGF (nerve growth factor) stimulates nerve growth
- EGF (epidermal growth factor)
- Kallikrein act as vasodilator

•Parotin hormone acting on mesenchymal tissue promoting growth and development.

2. Regulation of salivary secretion:

Most of the secretions in our body are controlled by both endocrinal and neuronal mechanism, but salivary secretion is different in the fact that its regulation is exclusively neural.

•Salivary glands have both sympathetic and parasympathetic innervations

•Parasympathetic fibres are called **secretomotor fibers** and they arise from salivary nucleus located between the pons and medulla

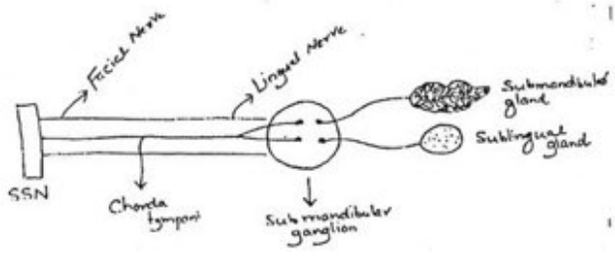
Parasympathetic stimulation

•The cranial part is known as **Superior Salivary nucleus**

•Caudal part is called Inferior Salivary nucleus

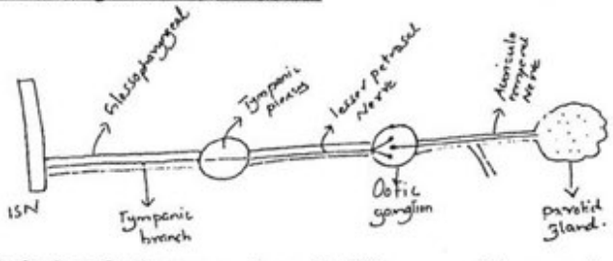
•Stimulation of parasympathetic fibres to the salivary glands causes **profuse**(abundant) secretion of **watery saliva** with a relatively low content of organic material.Along with Ach,a co-transmitter is aalso released at the postganglionic parasympathetic nerve endings,called **VIP**,along with **kallikrein** produces **vasodialation** in the gland.Kallikrein is produced from acinar cells.Atropin and other anticholinergic drugs reduces salivary secretion

Submandibular and subingual gland innervations



Preganglionic neurons are in Superiivary nucleus →facial nerve→ chorda tympani branch → lingual branch or trigeminal nerve→ Submandibular ganglion→ synapses→postganglionic secretomotor fibers innervates the glands

Parotid gland innervations



Inferior Salivary nucleus→ IX nerve → tympanic branch→tympanic plexus→lesser petrosal branch →the otic ganglion→synapses→postganglionic fibres→auriculotemporal branch of V nerve → gland

Sympathetic stimulation:

Sympathetic stimulation causes **vasoconstriction** and secretion of small amounts of saliva rich in **organic constituents**,especiallyy from the submandibular gland.A dry mouth is an important characteristic feature of sympathetic response to fear and stress.

>>Salivary secretion can be divided into:

•Spontaneous /basal/resting

•Stimulated /reflex

Salivary secretion as a result of reflex includes conditioned and unconditioned reflexes

Pathway:

Tactile or taste receptors in mouth, tongue and pharynx→chorda tympani, IX, X nerve→ nucleus tractus solitarius→ salivatory nucleus→ efferents VIII and IX nerve

3. Deglutition 2nd phase

In this phase the bolus pass through the pharynx and into the oesophagus.It is involuntary or reflex in nature, occurs in less than 2 seconds.The food that has reached the oesophagus from the oral cavity can pass into 4 possible routes.

1.Back to the mouth
2.Nasopharynx
3.Larynx and trachea
4.Down the esophagus

MECHANISM

➢Bolus of food in posterior mouth and pharynx →epithelial and mucous membrane receptors stimulated→ afferents via V, IX, X nerve→ reaches the nucleus tractus solitarius and nucleus ambigus → deglutition center (medulla and lower pons)→ efferents through V, IX and XII nerve→ to cause a series of automatic contractions

➢When food is in the oropharynx, esophagus should be open and other openings should be closed.

➢Movement of bolus back to the mouth is prevented by →approximation of posterior part of toungue against roof of mouth.

➢The entry of food into Nasopharynx is prevented by elevation of soft palate and closure of posterior nares

➢Entry into larynx and airway is prevented by:

- oApproximation of vocal cords
- oClosure of glottis
- oReflex inhibition of respiration – **deglutition apnea**
- oDeglutition inhibits the respiratory center of the medulla → respiration is temporarily inhibited during swallowing
- oMovements of larynx upwards and anteriorly by neck muscles
- oEpiglottis swings backwards over laryngeal opening.

➢Movement of food into the esophagus

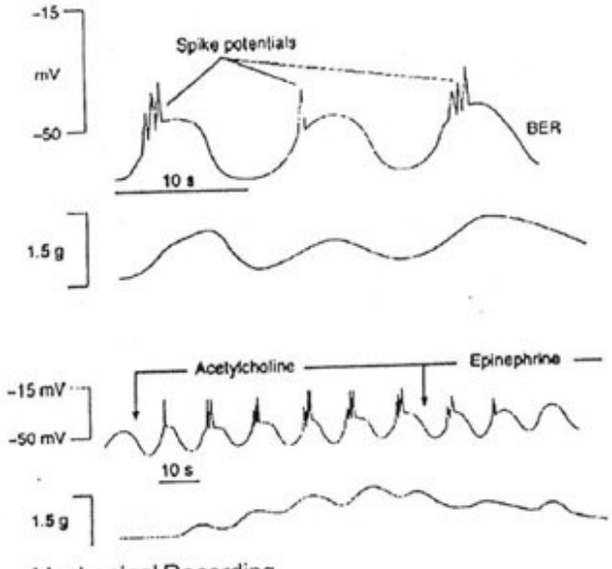
- oUpward movement of larynx pulls up and enlarges the opening of esophagus

- Esophageal inlet is aligned with the pharynx by strap muscles of the neck
- Contraction of **superior constrictor** muscle of pharynx in itiates **peristaltic wave** which moves the bolus through the pharynx in to the esophagus, by relaxing **upper esophageal sphincture**

4. BER and migrating motor complex:

Except in esophagus and proximal stomach the GI smooth muscles exhibit spontaneous fluctuations in RMP (-65--45mV) this regular rhythmic slow and periodic change in the RMP is called BER (basal electrical rhythm) Slow changes in the RMP are because of interaction between interstitial cells of Cajal and smooth muscles. Interstitial cells of Cajal are small stellate and mesenchymal cells wzith smooth muscle layer and send long multiple process into the smooth muscles with which they make synaptic connections.

They have unique ion channel, which generate slow wave like activity and they are located in the outer circular layer near the myenteric plexus in the stomach and small intestine and sub mucosal border in the circular muscle layer of colon.



Mechanical Recording

BER of GI smooth muscle:TOP:morphology & Relation of Muscle Contraction.BOTTOM:Stimulatory Effect of Ach& Inhibitory effect of epinephrine

Functions of BER"

- Excite the appropriate spike, which bring about muscular contraction
- Coordinates peristaltic and other motor activities

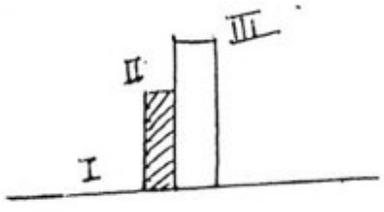
Migrating Motor Complex:

Occurs during fasting or Interdigestive periodical,i.e. 90-120 minutes after a meal

- The pattern of electrical and motor activity or in the GI smooth muscle becomes modified, so that cycles of electrical and motor activity migrate from the stomach to the distal ileum
- The MMC migrate aborally at 5cm/min, they occur at intervals of approximately 90 minutes
- It has 3 phases
  - Phase I quiescent phase/no spoke potential
  - Phase II irregular spike potentials
  - Phase III regular spike potentials
- MMC end with feeding when the peristaltic and other forms of basic electrical rhythm returns

FUNCTIONS

- Exact function is not clear but it is thought that it clears stomach and small intestine of luminal contents in preparation for the next meal. Bile flow and pancreatic secretion increase during MMC
- They are called Interdigestive house keeper



5.Cephalic phase of gastric secretion:

Phases of gastric secretion are;

1. basal secretion
2. **cephalic/psychic**
3. gastric
4. intestinal

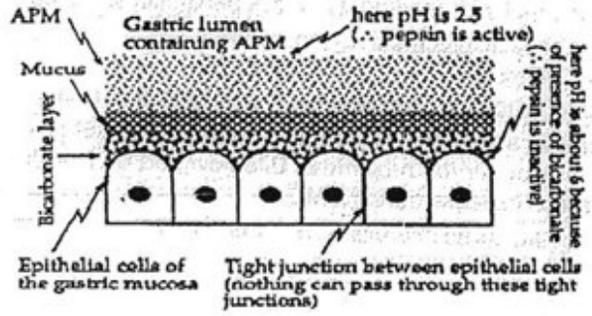
•Cephalic Phase:

Occur before the food enters the stomach,which accounts for about 20% of gastric secretion associated wih food intake

- This phase is initiated by sight, smell and taste of appetizing food.
- this is a **conditioned reflex**
- Mediated by branches of vagus nerve that synapse with neurons of ENSz
- Neurogenic signals that produce the cephalic phase arises from the centres of special senses in the **cortex** or in the appetite centres of **amygdala** or **hypothalamus** and reach DMN of vagus
- Efferent fibres come through vagus and this phase is basically under neural control.This phase is abolished by **vagotomy**/by parasympatholytic drugs like **atropine**
- the vagal efferents from the brainstem to stomach increase gastric acid&pepsinogen secretion by 2 mechanisms;
  1. Directly stimulating oxyntic glands
  2. Indirectly by increasing the release of gastrin from Gcells of pyloric glands

•This phase was experimentally demonstrated by pavlov using a technique called **sham feeding**(false feeding) ;resection of gastric antrum,whch is the major source of **gastrin**,reduces the acid secretion to sham feeding by50%.this proves that a portion of sham-induced acid response is mediated through gastrin.

6. Mucosal barrier



Gastric mucin is glycoprotein in nature.After release from mucous cell, they become filled with water, some lipids and proteins and finally a mucous gel is formed.
Namely the stomach releases 2 types of mucous and finally a mucous gel is formed.

➢**Visible mucous** is secreted by the surface mucous cells
Thick viscous, jelly like and forms the coating over the gastric mucosa.

➢**Soluble mucous** is produced from the neck mucous glands of gastric cells (mucous cells of cardiac and pyloric glands)

- •The surface mucous cells also secrete HCO_3^- → mucous is alkaline→stomach wall is not directly exposed to acid secretion
- •The protective mucous gel that forms on the luminal surface of the stomach and the alkaline secretion entrapped within it constitute the gastric mucosal barrier

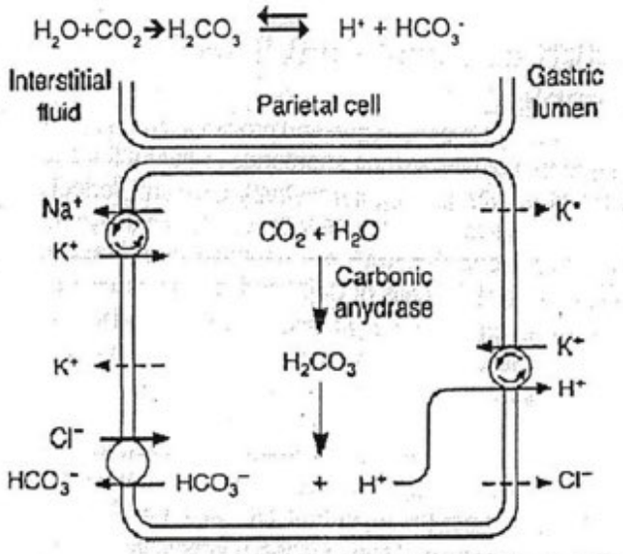
•The HCl secreted by the gastric glands crosses this barrier in finger like channels leaving the rest of the layers intact.

•The space between the gel and the surface epithelium contains HCO_3^- & thereforethe pH immediately adjucent to the surface epithelial cell is neutral,while pH within gastric lumen is 1-2.So,the pH of acid-pepsin mixture rises more&more as it comes nearer&nearer the epithelium.

•The gel thickeness is increased by **prostaglndin** E&decreased by Non-Steroidal AntiInflammatory Drugs(**NSAIDs**) like aspirin

7. HCl secretion

HCl is secreted from the parietal cells that are present in the gastric pit. When a parietal cell is stimulated, the **tubulovesicular structure** fuse with the **canalicular membrane**.More number of H^+- K^+ATPase molecule move to the **apical membrane** and H^+ ion is pumped out of the cell into the canalicular lumen in exchange for K^+, which is pumped into the cell from the canalicular lumen. The energy required is produced by the **hydrolysis of ATP.** This H^+ions come from H_2CO_3 which was in parietal cell as a result of combination of H_2O and CO_2



•The HCO_3^- ion that is produced within the cell is extruded across the basolateral membrane in exchange for Cl^- from the interstitial space by, **Cl^- /HCO_3^- exchanger.** The resulting increase in the chloride intracellular drives the Cl- through the conducting channel across the luminal surface of the cell.

Thus the HCl is formed inside the canaliculus, which is then secreted outwards through the open end of the canaliculus into the gastric lumen.

•After a heavy meal large amount of H^+ are formed and secreted into the canalicular lumen and large amount of HCO_3^- reaches the interstitium through the basolateral membrane. →pH increases and some amount of alkali is excreted in urine and urine becomes alkaline called as **post prandial alkaline tide.**

The increase in intracellular K+ and low Na+ is maintained by Na+/K+ pump at the basolateral pump. So the K+ ion moves from the cell through the conductive pathway into the lumen for providing K^+ ions for H^+/ K^+ATPase

Factors increasing HCl secretion

- •Histamine
- •Ach
- •Gastrin
- •Sight, smell, taste of food
- •Hypoglycemia
- •Small peptides and amino acids

Factors inhibiting HCl secretion

- •Prostaglandin E_2
- •Somatostatin

- Secretin
- GIP, Bombesin
- Ranitidine, Omeprazole and Atropine

8. Gastric emptying & factors affecting:

After a full fixed meal, the stomach is emptied after about 3 hours. This emptying is called gastric emptying. Gastric emptying is promoted by the intense peristaltic contraction in the gastric antrum and this is called **pyloric pump.**

Mechanism:

Most of the time the rhythmic gastric peristaltic contraction is weak and result in mixing. But 20% of the time when food is in the stomach the contraction becomes very intense,beginning in the mid stomach and spread towards the antrum as a strong peristaltic tight ring like contractions causing gastric emptying and these are 6 times more powerful than mixing contractions.The intensity of antrum peristalsis determines the rate of gastric emptying.

Factors affecting gastric emptying:

The rate of emptying is regulated by

- Signals from the stomach
  - ➢Volume of stomach – when increased promotes emptying.Because there is stretching of stomach wall which elicits local myenteric vagal reflex→ excites the pyloric pump and inhibits the pyloric pump
  - ➢Liquids empty faster than solids
  - ➢Chemical composition of food carbohydrates are emptied within a few hours, proteins more slowly and fats are emptied at the slowest rates. Some people drink milk, cream or even olive oil, before a cocktail party so alcohol is retained in the stomach as fat slows the emptying where the rate of absorption is slower than that in the small intestine
  - ➢Gastrin promotes emptying

    Hormone,gastrin which is produced in response to distension of the stomach and products of protein digestion
  - ➢ Emotional factors

    Excitement increases gastric emptying and fear slows gastric emptying

- Signals from the **duodenum** (which are more potent)

These mainly inhibit gastric emptying

➢Enterogastric nervous reflex

Food entering the duodenum elicits multiple nervous reflexes, which are initiated from the duodenal walls .It pass back to the stomach and slows or stops gastric emptying when the volume of chyme reaching the duodenum becomes too much

Factors eliciting this reflex

- Distension of the duodenum
- Irritation of duodenal mucosa
- Acidity of duodenal chyme
- Break down products of proteins and perhaps fa

These are mediated via

1. ENS from the duodenum to the stomach
2. Extrinsic nerves

The reflex has to inhibit gastric emptying, inhibit the pyloric pump activity and cause a slight to moderate increase in the tone of the pyloric sphincter.

➢Hormonal feedback from duodenum

- **CCK, secretin** and GIP
- Products of digestion → peptidases and amino acids as well as fats in the duodenum will cause release of CCK from the upper small intestine, resulting in decreased gastric motility
- Secretin and GIP also have similar effects on gastric motility

Gastric emptying occurs at a rate suitable for digestion and absorption

9. Hunger contractions:

Hunger contractions are the contractions of the empty stomach. When the stomach has been empty for several hours or in between meals, rhythmic peristaltic contractions occur in the body of the stomach and these are presumably associated with **MMCs**.

When successive contractions become extremely strong,they often fuse.This cause a continuous contraction that lasts for 2-3 minutes.During these contractions,the peron experiences pain called **hunger pangs.**It usually occurs after 12-24 hrs of starvation&maximum intensity is seen in 3-4days.

functions of hunger contractions ;

- clear stomach&small intestine in preparation for the next meal
- it also increase pancreatic,biliary&gastricsecretion

10.Regulation of pancreatic secretion:

Refer Essay 4

11.Enterohepatic circulation

Some components of bile are reabsorbed in the intestine and are then excreted by the liver. Several components undergo this circulation like:

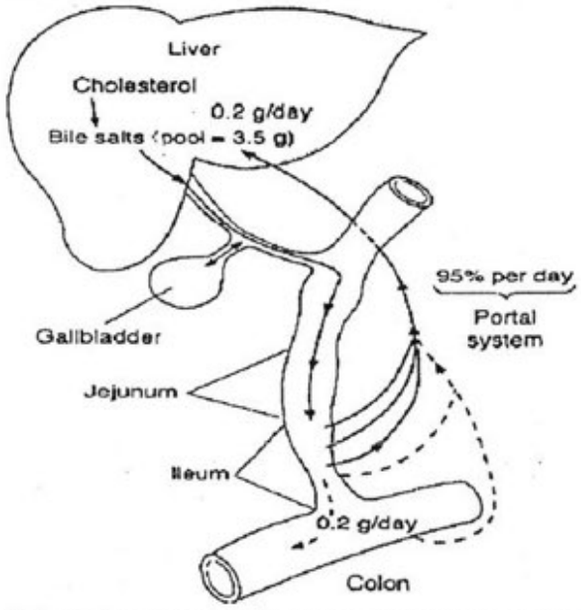
bile salts(most important),**bile pigments**, **hormones**(adrenocortical and steroid hormones) &some drugs.

➢About **90-95%** of bile salts are reabsorbed from the small intestine mainly from the terminal ileum by an active transport mechanism – Na -bile salt mechanism

The reabsorbed bile salts enter the liver by portal blood. They reach the sinusoids and are picked up by the hepatocytes and are again reexcreted through bile.This

circular route of bile salts, from intestine to the liver &then through bile back to intestine is called **enterohepatic circulation of bile salts**. Some amount is also reabsorbed by diffusion through mucosa in early part of the small intestine.

➢A small quantity of bile salts is excreted through faeces and liver synthesizes that amount. The normal rate of bile acid synthesis is **0.2-0.4g/day** and total bile salt pool is about **3.5g**. This amount recycles repeatedly via the EHC



➢The entire pool recycles **twice per meal** and 6-8 times / day on average and individual molecule makes entire circulation about 18 times before excreted in the faeces.

➢So it results in large mass of previously synthesized bile salts ,where they generate more bile flow and induce secretion of cholesterol and phospholipids.

➢When EHC is interrupted the liver cannot increase the rate of synthesis to a sufficient degree to compensate the loss and there will be increased amount of fat in the stool.(**steatorrhea**)

12. Functions of bile:

Bile salts are the most important constituents of bile. So most of functions of bile are due to the bile salts.

1. Bile salts are necessary **for digestion and absorption of fat**

oBile salts activate pancreatic lipase.

o**Emulsification and detergent action** of bile alts helps to reduce surface tension of fat particle and break them into smaller particles so that it can be acted upon by the pancreatic lipase.

oIt helps in transport and absorption of digested particle viz fatty acid, cholesterol and other lipids.

2. Bile salts are **amphipathic**,they have both hydrophilic and hydrophobic domains. The bile salts form minute complexes with lipids called **micelle**.

Above a critical concentration called critical micellar concentration (**CMC**) all the bile salts added to a solution form micelle.

The amphipathic glycerides and phospholipids line up with the head facing outside and hydrophobic tail in center. So micelle keep lipid in solution and transport them to brush bordered epithelium of epithelial cells and absorption.

3. **Excretory function**

Bile serves as a means of excretion of several products viz bilirubin, cholesterol, adrenocorticoid drugs, salts of heavy metals→ all thesebecause of their large size cannot be excreted through urine

4. Bile is usually alkaline in nature. It helps to **neutralize** the acid chyme entering the duodenum

5. Acts as **choleretic agents**,ie,ingestion of an excess of bile salt increases secretion of bile from liver.

6. Acts as **cholagogues**,indirectly by stimulating secretion of **CCK** which causes gall bladder contraction

7. Acts as mild **laxative agent** by stimulating peristalsis.Most of synthetic purgatives contain bile salt preparation

8. Increases the release of enterokinase from the duodenal mucosa

9. It has an **antiseptic action** and inhibits the growth of certain bacteria within the gut

13. Functions of gall bladder

1• One of the major functions for gall bladder is **storage of bile.**During fasting, rate of secretion of bile is slow and sphincter of oddi is in contracted state and bile is stored in the gall bladder.

2• **Concentration of bile**

H_2O and electrolytes viz Na^+, HCO_3 are reabsorbed. Na is actively reabsorbed or actively transported by gall bladder, Cl moves along with it and also HCO_3 is reabsorbed rapidly. H_2O absorption follows Na and Cl absorption

Thus concentration of solutes like bile salts, bile pigments etc increase by about 5-10 times. Although maximum volume of gall bladder is 50-60mL as much as 12 hours of bile can be stored due to its concentrating capacity.

3• **Acidification of bile** by reabsorption of HCO_3

4• Secretes mucous

5• **equalisation of pressure** in biliary system by absorption of water

6• **Evacuation of bile** into duodenum

The highest rate of discharge occurs during intestinal phase.Within 30 minutes of feeding, sphincter of oddi initiates and emptying occurs. Filling of gall bladder is continuous but emptying is intermittent.

Substances that cause contraction of gall bladder are called **cholagogue**. The most important is CCK. It

causes contraction of gall bladder and sphincter of oddi. The amino acid and presence of fat in duodenum induces production of CCK

Evacuation of gall bladder is also mediated necessarily by the vagal nerve stimulation.

14. Gastrin

Gastrin is a polypeptide hormone produced Gcells of pyloric gland.Gcell belong to the group of **APUD**(Amine Precursor Uptake&Decarboxylation)cells which are of **neural crest origin**.

A secondary type of gastrin producing cell,**TG cell** is present throughout the stomach&small intestine.It contains only **G34**&lacks G17.**G17** is the **principal form** of gastrin,with respect to gastric acid secretion.

chemistry of gastrin:gastrn is synthesised from **preprogastrin** which is processed in to fragments of various types;

- G34-big gastrin,present mainly in blood
- **G17**-little gastrin in tissues
- G14-minigastrin,in blood&tissues.

There is also a large form of gastrin,which contain more than 45 amino acid residues called **big big gastrin**.

Synthetic analogue of gastrin is **pentagastrin**

Actions of gastrin:

1.stimulate **parietal cells** to secrete acid&intrinsic factor of castle.

2.**trophic action**,ie stimulate growth of mucosa of stomach,small&lage intestine.

3.**increase tone** of stomach &upper small intestine&increase gastric motility

4.contraction of gastro-esophageal **sphincture**.

5.stimulate secretion of **histamine from ECL**.

6.increase secretion of Brunner's gland.

15. Succus entericus

The secretions of the small intestine are also known as succus entericus

➢The intestinal secretion are formed by the epithelial cells in the crypts of lieberkuhn

➢Isotonic and has a pH of 7.5-8

➢Watery, straw coloured fluid, cloudy in appearance due to mucous

➢Contains a large amount of cellular debris. These are made of numerous shed epithelial cells and enzyme activity is confined to the cellular debris.

➢98.5% water

➢1.5% solid

- Inorganic Na^+, K^+, Ca^{2+}, Cl^-, HCO^-_3
- Organic-chiefly proteins, mucous proteins, GI hormones, albumin, γ-globulin

➢Most of the intestinal enzymes are present within the cell and they appear in the secretion with in the lumen of the intestine as a result of desquamation of cells.

➢Enzymes are not secreted into the intestinal juice.These enzymes act on specific food substances while they are being absorbed

Succus Entericus contains

✓Enterokinase which converts trypsinogen to trypsin and activates it

✓Enteropeptidase proteolytic in nature

✓Amylolytic enzyme converts

- Maltase: maltose→ 2 glucose
- Sucrase: sucrose→ fructose + glucose
- Lactase: lactose→ galactose + glucose

✓Weak lipolytic enzyme is also present which splits neutral fat→ fatty acid + glycerol;

✓Nucleases are present for splitting nucleic acid

✓Other enzymes like

- Cholesterylesterase
- Phosphodiesterase
- Alkaline phosphatase

Mechanism of secretion of water:

Believed to involve atleast 2 active secretory processes

➢Active secretion of Cl ions into the intestinal lumen.The cell takes up chloride ions from blood stream across the basolateral membrane via Na^+-K^+-Cl^- co transport channel.Energy for this channel is by Na^+ / K^+ ATPase

Cl ions accumulate in the cell and then it passes into the lumen thru the chloride channels present in apical membrane. Then Na K ions follows passively according to the electrical gradient and water follows thru the tight junction between the enterocytes.

➢Active secretion of HCO_3^-

The upper part of the small intestine secrete more amount of HCO_3^- than the lower part via Cl^--HCO_3^- exchanger

Regulation of secretion:

- Nervous: parasympathetic increase secretion and sympathetic decrease secretion
- Locally mediated
- Vagally mediated
- Hormonal: Secretin, CCK, VIP increase secretion

16. Causes and mechanism of vomiting

Vomiting is a complex reflex act and it involves the forceful expulsion of contents from the **upper GIT** through the mouth.It has both somatic and visceral components.

Stimuli causing vomiting:

➢Excessive irritation, distension or excitation of upper GIT and duodenum produces the strongest response.

➢Stimulation of the chemoreceptor trigger zone which is a small area located bilaterally in the floor of the 4th ventricle near the area postrema outside the blood brain barrier.

CTZ is stimulated by

- Certain drugs – apomorphine, morphine and digitalis
- Motion sickness – the receptors of labrynth get activated → VIIIth nerve → cerebellum → CTZ
- Uremia

Head injury or increased intra cranial tension directly stimulates the vomiting center

- Diseases of liver, GB, genitourinary tract
- Psychic stimuli – unpleasant smell, sight etc
- Pregnancy – morning sickness

PATHWAY

- Afferents
  - From GIT – vagus, sympathetic
  - Labyrinth – VIII nerve
  - Afferents from CTZ,hypothalamus etc
- Vomiting center

Includes a group of neurons situated bilaterally in the medulla near the NTS at the level of dorsal motor nucleus of vagus

- Efferents

V, VII, IX, X, XII nerves to the upper GIT, spinal nerves to the diaphragm, abdominal muscles

Mechanism of Vomiting:

✓GI irritation or overdistension → antiperistalsis may be seen many minutes before vomiting as far down as ileum. The wave travels up at 2-3cm/sec

✓The intestinal contents are pushed back to the stomach at 3-5 cm/sec

✓Excessive salivation and nausea may precede vomiting

✓Salivation serves to dilute acid

✓At the onset of vomiting strong intrinsic contractions occur both in the duodenum and stomach along with the partial relaxation of LES. So the vomitus moves into the esophagus and from here specific vomiting act occurs.

Vomiting act

- A deep breath in mid inspiration
- Raising of hyoid and larynx to pull the UES open
- Closing of glottis
- Raising of soft palate to close posterior nares
- Strong downward contraction of diaphragm with simultaneous contraction of all abdominal muscles
- Stomach is squeezed between the diaphragm and abdominal wall resulting in increased intragastric pressure
- Complete relaxation of LES to expel the contents thru the mouth

Consequences of vomiting

a)Dehydration
b)Metabolic alkalosis
c)Hyperchloremia
d)Aspiration pneumonia

17. Defecation reflex

Most of the time the rectum is empty of faeces. Mass movements propel the faeces to the rectum initiating defecation reflex. It has two components;

Intrinsic reflex

When faeces enters the rectum distension of the rectum and stretching of the rectal wall occurs. It initiates afferent signals that spread through the **myenteric plexus** to initiate peristaltic wave in the descending colon, sigmoid and rectum forcing the faeces towards the anus. As the wave approaches the anus the **internal anal sphincter** is relaxed.

However this reflex is relatively **weak** and must be fortified by the parasympathetic defecation reflex.

Parasympathetic defecation reflex

It involves sacral segments of the spinal cord. Stimulation of nerve endings in the rectum send afferent impulses to the spinal cord and efferents are transmitted thru the **pelvic nerve** (parasympathetic) back to the descending colon, sigmoid, rectum and anus.Parasympathetic signal **intensify** peristaltic wave and relaxes the **internal anal sphincter.**

This converts the weak intrinsic defecation reflex to powerful process of defecation.This results in emptying large bowel from splenic flexure to the anus.If the conditions are **favorable** the **external anal sphincter** is relaxed and defecation occurs. If unfavorable it remains constricted.

18.Functions of colon

Absorptive

- The mucosa of colon has great absorptive capacity.
- Most of the absorption occur from the proximal half of the colon (absorbing colon)
- H_2O,Na and other minerals are absorbed from large intestine.
- About 1-2L of fluid reaches the colon from small intestine and of this only 200-250mL pass out through stool. The rest is absorbed.
- The Na is actively transported out of the colon into the cell water follows Na absorption

Secretive

- Colon secretes K, mucous and HCO_3 ions
- Colon has a bacterial flora. Colonic bacteria synthesis many vitamins. Of these, human body absorbs viz vitamin K and biotin.

19. CCK – PZ

Refer Essay 4

20. Sham feeding

This was an experiment conducted by **Ivan Pavlov** to show that the gastric juice secretion starts before the food reaches the stomach and the efferent limb of the reflex is vagus.

In this esophagus of a dog is divided transversely&both cut ends were brought out through an opening in the neck. so that when the dog eats something the food cannot reach the stomach but comes out thru

the esophageal wound. Side by side, another device is made so that the gastric juice of this animal can be collected.

Now allow the animal to take meal and note the stomach is secreting.

Vagotomy abolishes this response.

Mechanism: (refer **cephalic phase** of gastric secretion.)

21. Peristalsis:

It is a type of propulsive movement also known as **myenteric reflex**.

- Distension / stretching of GI wall by the food results in a circular contractile ring behind the stimulus and an area of relaxation ahead of the stimulus. This wave of contraction moves from an oral to caudal direction and propels contents.

Local stretch → serotonin secreted → activates sensory neurons → activation of myenteric plexus

From there

- Cholinergic neurons in a retrograde direction → activate neurons (Ach, substance P) → smooth muscle contractions
- Cholinergic neurons in an anterograde direction → activate neurons (NO, VIP, ATP) → smooth muscle relaxation

Features of peristalsis

- Peristalsis always occur in oral to caudal direction propel at the rate of 2-2.5cm/sec
- Intact myenteric plexus is essential for normal peristalsis.
- Increase or decrease by ANS but it doesn't depend on it.
- It is an excellent example for the integrated activity of ENS.

22. Peptic ulcer:

Gastric and duodenal ulcers are called peptic ulcers. They represent the excoriation of an area of the mucosa. The most **common sites;**

1. The first few cm of duodenum.
2. Along the lesser curvature of the stomach.

Cause :

There is an imbalance between the rate of secretion of gastric juice and the degree of protection afforded by gastro duodenal **mucosal barrier** and neutralization of acid by the alkalinity of the small intestinal secrtions.

The cause is thought to be multifactorial.

➢ Due to destruction of mucosal barrier

Causes for destruction of mucosal barrier

➢ infection by **Helicobacter pylori**

These bacteria colonize mucous layer of the stomach and it causes damage by secreting protein that stimulates cellular and immune mechanisms. There is release of digestive enzymes that destroy mucosal barrier.

➢ Certain groups of drugs Eg **aspirin** inhibit the production of prostaglandins and decrease the HCO_3 and mucous products

➢ Prolonged excessive secretion of acid (**Zollinger Ellison syndrome**)- gastrin secreting tumor and is commonly seen in pancreas and can also occur in duodenum and stomach.

➢ Alcohol & smoking causes damage to mucosa

➢ geneticpredisposition-**'o' group** individuals&nonsecretors are more prone to develop duodenal ulcer.

Clinical features:

❖ Abdominal pain - pain can occur in epigastrium

After food intake if discomfort is relieved,it's duodenal ulcer;else increase it's gastric ulcer

❖ heart burn.

Complications

- Hemorrhage
- Perforation
- Steatorrhea(hyperacidity leads to inactivation of pancreatic enzyme)

Treatment

i. Inhibiting acid production
ii. Enhancing mucosal resistance
iii. Medical management and rarely surgical management
iv. **Antacids** that neutralize acids
v. Ranitidine, Omeprazole, Atropine
vi. Gastrinoma surgical treatment
vii. Vagotomy

23. Functions of stomach:

1) Reservoir or storage function;

it act as a reservoir for the ingested food which is mixed with saliva. This is due to the receptive relaxation of stomach mtdiated by vagus. Max. capacity is **1.5L**

2) Mechanical function;

food is converted in to semi fluid mass, **chyme** by mechanical activity of gastric musculature&aided by digestive secretion of stomach. This results in breakdown of larger food particles in to smaller fragments.

3) stomach **regulates the passage of chyme** into small intestine. Food is released at a controlled, steady rate in to the duodenum to avoid the rapid delivery of highly acidic substance in to intestine.

4) Digestive function;

salivary digestion is completed in stomach. Enzymes of gastric juice also aids in digestion.

5) protective function;

HCL present in gastric juice destroy microorganisms in food.

6) hemopoetic function;

Intrinsic factor in gastric juice is necessary for absorption of **Vit.B12**, a maturation factor for RBC, whose deficiency leads to **pernicious anemia**. HCL is also needed for Fe absorption

24. Parasympathetic innervations of salivary gland: Refer short note 2

25. Mass peristalsis:

•It is a type of movement associated with **large intestine.**

•One or two mass peristalsis develop in a 24 hour period in a healthy, ring of constriction appears in the descending colon near the splenic flexure. This band of constrictions sweeps down the descending colon pelvic colon like a typical peristalsis and drives the content of the descending colon into the rectum.

•Normally rectum is empty. When something arrives in the rectum by mass peristalsis→ rectum becomes distended→urge to defecate develops→evacuations

•Mass peristalsis are facilitated by gastrocolic and duodenocolic reflex via ANS also irritation of the colon as in ulcerative colitis also increases the frequency of mass movements.

26. Difference between liver bile and gall bladder bile:

Composition of Bile

	Liver Bile	Gallbladder Bile
Water	97.5 g/dl	92 g/dl
Bile salts	1.1 g/dl	6 g/dl
Bilirubin	0.04 g/dl	0.3 g/dl
Cholesterol	0.1 g/dl	0.3 to 0.9 g/dl
Fatty acids	0.12 g/dl	0.3 to 1.2 g/dl
Lecithin	0.04 g/dl	0.3 g/dl
Na^+	145.04 mEq/L.	130 mEq/L.
K^+	5 mEq/L.	12 mEq/L.
Ca^{++}	5 mEq/L.	23 mEq/L.
Cl^-	100 mEq/L.	25 mEq/L.
HCO_3^-	28 mEq/L.	10 mEq/L.

the bile gets concentrated,when it is stored and also it becomes slightly acidic due to the absorption of HCO_3^-

27.Clay colored stools are seen in obstructive jaundice:

In obstructive jaundice the rate of bilirubin formation is normal. It passes back to blood.

Urinary urobilinogen is absent and stool is clay colored because of absence of stercobilin and other bile pigments in stool. Bile salt deficiency may lead to steatorrhoea.

28.Functions of liver

i.**Formation and secretion of bile**

ii.**Metabolism**

- •Carbohydrates gluconeogenesis, glycogen storage, glycogenolysis
- •Protein breakdown of protein and amino acid by deamination with formation of urea
- •Fat oxidation of fatty acids, synthesis of cholesterol, phospholipids and lipoproteins

iii.**Synthetic functions**

- •All plasma proteins except γ globulin
- •Proteins concerned with blood clotting like fibrinogen, prothrombin, factor VIII and IX
- •Synthesis of transport proteins mainly those transporting steroid hormones
- •Acute C reactive protein
- •Synthesis of urea and cholesterol

iv.**Storage functions**

- •Glycogen storage
- •Storage of fat soluble substances and vitamin B12
- •Excess of iron stored as ferritin

v.**Detoxification** & inactivation of various substances

- •Hormones – adrenocorticoid and gonadal hormones
- •Drugs like sulphonamides, penicillin, erythromycin

vi.Excretory function

- •Liver excretes cholesterol, bile pigments, alkaline phosphatase
- •Heavy metals like arsenic and bismuth

vii.Blood cleansing function by Kupffer cells

viii.Hemopoetic function

ix.Function as blood reservoir large volumes of blood can be stored and used at the time of emergency

29.Dumping Syndrome:

Dumping syndrome is a distressing syndrome that develop in patients that develop in pateints in whom portions of stomach have been removed or the jejenum has been anastomosed with the stomach.its of 2 stages:

a)Early:

Rapid entry of hypertonic meals to the intestine provokes movement of so much water into the gut which inturn leads to **hypovolemia.**

b)Late:

Two hours after meals,rapid absorption from intestine takes place that leads to increase in blood sugar level ⟶ increase in insulin level⟶ **reactive hypoglycemia** ⟶ dizziness and other symptoms of hypoglycemia.

RENAL PHYSIOLOGY

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ESSAYS

1.Renal blood flow-regulation & Special features:

Kidneys receive 23.3% of cardiac output ie,1.2-1.3L/ min ie, 2nd organ to recieve maximum blood supply(first is liver)

Circulation in Kidney:

Abdominal aorta-renal artery-segmental artery-inter lobular artery-arcuate artery-intra lobular artery-afferent arteriole-glomerular cappilary-efferent arteriole-vasa recta&peritubular cappilaries-peritubular vein-intra lobular vein-segmental vein-renal vein-inferior venacava

Special features:

- High blood flow(420ml/100gm/min)Renal arteries arise directly from aorta. The high pressure facilitates high blood flow.
- Differential flow to cortex & medulla.Filtration of large volumes of blood through the glomeruli make renalcortical blood flow relatively greater(about 90% 5ml/gm/min) Maintanance of osmotic gradient in medulla requires a relatively low blood flow ie,2.5ml/ gm/min in outer medulla&0.6ml/gm/min in inner medulla.
- Low oxygen extraction:Arterio-venous oxygen difference for whole kidney is only 14ml/L(since the main function is filtration)
- Oxygen consumption is 6ml/100g/min.it is high in medulla since80% of total energy is utilised for Na^+ reabsorption.
- Renal circulation has a double network of cappilaries
  - Glomerular capillaries-form a high pressure bed(~60mmHg).High pressure is maintained because the diameter of afferent arteriole is more than that of efferent arteriole. This high pressure favors filtration in glomerular capillaries
  - Peritubular capillaries:
- form the low pressure bed (13mmHg).It favours tubular reabsorption.
- Vasa recta -form the counter current exchanger to maintain hyper osmolarity of medullary interstitium

Regulation of renal blood flow:

Intrinsic regulation - Auto regulation
Extrinsic regulation- Neural regulation
Hormonal regulation
Autocoids

1. Auto regulation:

- It is the intrinsic ability of an organ to regulate its own blood flow inspite of variation in blood pressure.
- With in range of 90-180 mmHg arterial pressure, RBF & GFR changes very little (GFR is more efficiantly regulated)
- It is present even if kidney is denervated,or transplanted or **isolated and perfused** (so it is called **intrinsic regulation**)
- Main two mechanism of autoregulation are:
  - **Myogenic mechanism**:whenever BP increases - blood flow to kidney increases-strech affarent arteriole - opening of Ca^{2+} channel - Ca^{2+} influx-contraction of smooth muscle of afferent arteriole - vascular constriction-RBF decreases to normal.
  - **Tubuloglomerular feedback**:(in short note later)

2. Nervous regulation:

- Sympathetic vasoconstrictor tone(SVT) is minimum at rest
- Mild/moderate increase in SVT have little effect on RBF/GFR.
- Severe increase in SVT occurs in response to:
  - Baroreceptor mechanism
  - CNS stimuli like fright,pain,ischemia of brain etc.

3. Hormonal regulation & Autocoids:

Vasoconstriction(decrease RBF)
Epinephrine
Norepinephrine
Angiotensin II
Serotonine
Endothelin
ADH

Vasodialation(increase RBF)
Dopamine
Prostagladin
Acetylcholine
Bradikinin
ANP
NO
Also in pregnancy&high protien diet

Note:Include **PAH Clearance** also in the essay (to be dealt later)

2.GFR: measurement, values, factors ffecting:

- Total quantity of glomerular filtrate formed in all nephron of 1 kidney in one minute
- Normal value: 125ml/min(20% of renal plasma flow or 7.5L/hr or 180L/day)

Measurement of GFR :

By measuring excretion and plasma level of a substance that is freely filtered through glomeruli and

neither secreted nor reabsorbed by tubules.
i.e.,
excretion rate=filtration rate
concentration in urine X urine flow per minute
= arterial plasma level X glomerular filtration rate
GFR = Ux X V

Inulin is aplant polymer &GFR is measured by inulin clearance

Criteria for substance used:

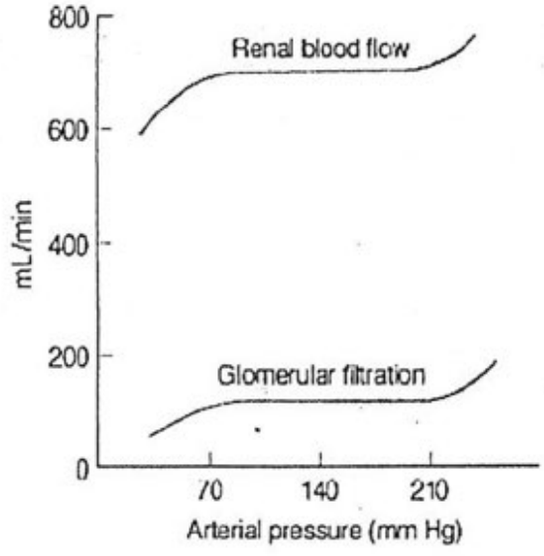
- Should be non toxic
- Shoud not be stored or metabolised in kidney
- Levels shoud be easy to measure in plasma &urine
- Shoud not alter GFR
- Shoud be freely filtered&shoud not be reabsorbed or secreted by tubules

Creatinine clearance is also used to measure GFR

Advantages of creatinine clearance:

- Substance is endogeneous&easy to measure.
- As production is continous,blood level will not fluctuate much
- Creatinine excretion is constant in a person

Factors Affecting GFR:



Autoregulation in the kidneys.

GFR = K_f X Net filtration pressure where,
Kf(ultra filtration coefficient)= glomerular capillary permeabilityXsurface area
Net filtration pressure= $(P_{gc}-P_t)-(Pi_{gc}-Pi_t)$ where,

P_{gc} = mean hydrostatic pressure in glomerular capillaries
P_t = mean hydrostatic pressure in tubules
Pi_{gc} = osmotic pressure in glomerular capillaries
Pi_t = osmotic pressure in tubules

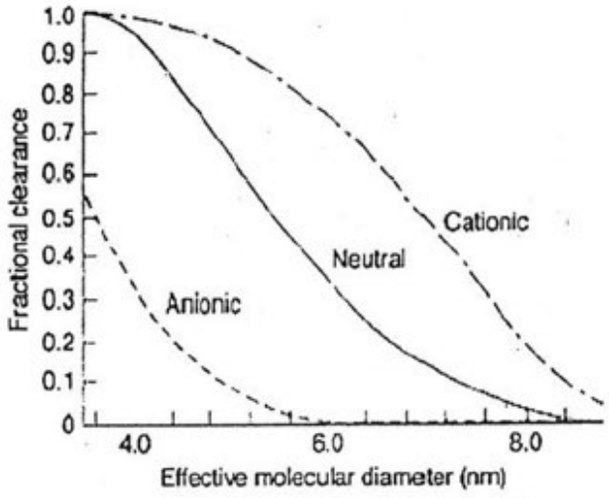
Value of net filtration is:

	Afferent	Efferent
Pgc	45	45
Pt	10	10
Pi gc	20	35
NFP	15	0

Permeability of capillary bed:

Permeability of capillaries is 50 times that of capillaries in skeletal muscle.**Sialo proteins** in glomerular capillary wall is **negatively** charged . Thus permeability varies for different charged components in blood.

- For neutral substances permeability depends on effective molecular diameter of the particle.
  - for substances with diameter < 4nm-freely filtered
  - if diameter is >8nm filtration approaches zero
  - if diameter is between4-8nm;filtration is inversely proportional to diameter



Effect of electrical charge on fractional clearance of dextran molecules of various sizes in rats.The negative charges in the glomerular membrane retard the passege of negatively charged molecules (anionic dextran) and facilitate the passage of positively charged molecules (cationic dextran)

- From the figure filtration of anionic substances with diameter ~4nm is less than half the permeability of neutral substances of same size.

Surface area of capillary bed

Normal surface area is about 0.8m X 0.8m.Contraction of mesangial cells decrease the surface area & hence decrease the GFR.Contraction of mesangial cells at the capillary bifurcation drive away the flow from some of the loops.

Agents that affect mesangeal cells are
Contraction
Relaxation

Agents causing contraction or relaxation of mesangial cells.

Contraction	Relaxation
Endothelins	
Angiotensin II	ANP
Vasopressin	Dopamine
Norepinephrine	PGE_2
Platelet-activating factor	cAMP
Platelet-derived growth factor	
Thromboxane A_2	
PGF_2	
Leukotrienes C_4 and D_4	
Histamine	

K_f value changes in chronic diseases like Diabetes Mellitus,Hypertension,Renal diseases like nephrotic syndrome, renal failure & after nephrectomy. An increase in K_f value is early manifested as proteinurea or albuminurea.

Regulation of GFR:

- Autoregulation
- Tubuloglomerular feedback
- Renin-Angiotensin mechanism:

When GFR increases -increased Na^+&Cl^- entry into macula densa-decreased renin secretion from the juxtraglomerular cells ⟶ decreased angiotensin II ⟶ vasodialation of efferent arteriole ⟶ Pgc decreased ⟶ GFR decreases to normal (Angiotensin vasoconstrict both afferent&efferent arteriole,but efferent is more sensitive)

- Sympathetic stimulation decreases GFR
- ADH,Endothelin,Serotonin,Adenosine decrease GFR
- Bradykinin, Prostagladin E2, Dopamine, ANP, Glucocorticoid, Pregnancy, high protein diet increase GFR.

3.Counter Current Mechanism:

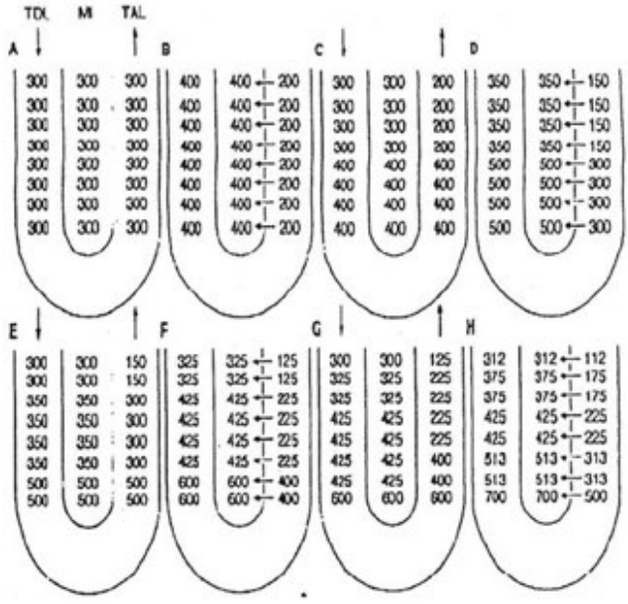
Concentration of urine depends on:

- Maintaining hyperosmolarity in medullary interstitium
- Adequate amount of circulating ADH.

The gradient of increasing osmolarity along renal medullary pyramids is produced by action of loop of Henle as conter current multipliers & is maintained by operation of the vasa recta as current exchangers.Counter current system is a system in which inflow runs parallel to,counter to & in close proximity to outflow for some distance.The system occurs both in loop of Henle &vasa recta.

Countercurrent Multipliers(in a cortical nephron)

Loop of Henle has a thick ascending limb with active trasport of Na^+&Cl^- into the interstitium & thin descending limb with high permeability to water.



The process of producing gradient of hyperosmolarity in medullary interstitium can be understood in few hypothetical steps(the course of these steps do not takeplace in vivo)

- Assume the continuous flow of isotonic fluid of osmolarity 300mosm/kg of H_2O through both the ascending and descending limbs.
- Thick ascending limb pumps 100 mosm/kg of Na^+ and Cl^- into the interstitium from the tublar fluid,increasing interstitial osmolarity into 400 mosn/kg of H2O.Water move out of thin descending limb loop of Henle and thus the contents equilibrate with the interstitium.
- Further flow occurs and fluid with osmolarity 300mosm/kg of H_2O flows into thin descending limb &hypotonic fluid from thick ascending limb flows to distal tubules.The hypertonic fluid lies in the bottam portion of both descending &ascending limbs.
- Step 2 repeats pumping of Na^+&Cl^- into interstitium produce an osmotic gradient of 200 mosm/kg H_2O horizontally and hypestonicity is produced to the apex of the loop(600 mosm/kg of H_2O at apex in cortical nephron).

In juxta medullary nephrons(1400mosm/kg of H_2Oat tfe apex)the loops are longer &it posses longer thin ascending limb.This thin ascending limbs are impermeable(relatively)to water&allow passive trasport of Na^+&Cl^- along the concentration gradient.So it acts in additional passive counter current multiplication.Thus the osmotic gradient is spread to a greater distance & the osmolarity at the apex of the loop is also greater. Thus counter current multiplication depends on:

a)Active transport of solutes mainly Na^+ & Cl^- out of thick ascending limb

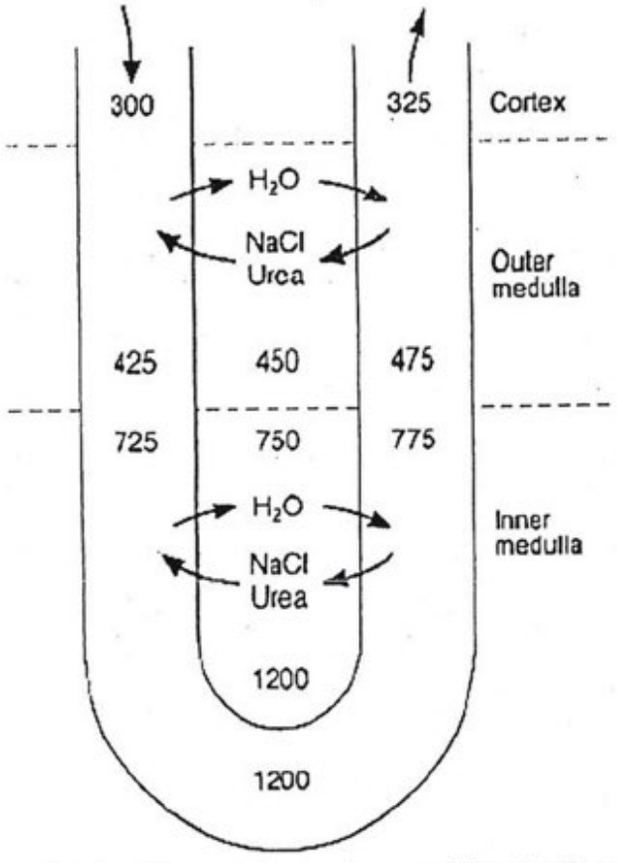
b)High permeability of thin descending limb to water.

c)Passive transport of solutes in thin ascending limb.

d)Inflow of isotonic fluid from PCT & outflow of more hypertonic fluid into distal tubules.

Countercurrent Exchanger

- Vasa recta operates as countercurrent exchangers.So solutes like Na^+,urea which produce hyper osmotic medullary interstitium is not washed away by circulation.



- Solutes diffuse out of ascending vessels(conduct blood towards cortex)&enter into descending vessels(blood into pyramids).On the other hand water diffuse from descending vessels&into ascending vessels.Thus water bypass medulla while solutes are restricted in medulla.
- Counter current exchange is a passive process & cannot maintain osmotic gradient if counter current multiplier is not working.
- Other examples of contercurrent exchanges in animals are, Heat exchange arteries&venaecomitants in limbs.It occurs to a minor degree in humans but plays a major role in conserving body heat in mammals living in cold water.

4.Tubular Reabsorption

a).Na Reabsorption:

Reabsorption of Na^+& Cl^- is important in body electrolyte &water metabolism.

About 99.4% of filtered sodium is reabsorbed.

Reabsorption occurs in,

PCT ⟶ 60-70%

Thick ascending limb of loop of Henle ⟶ 25-30%

DCT ⟶ 5-7%

Collecting duct ⟶ 3-4%

In tubular, cells reabsorptin occurs at two borders:

- At luminal border:By Na+ solute (glucose,amino acid, lactose)symport& Na^+-H^+ antiport
- At basolateral border: Active trasport by Na^+-K^+ ATPase.

Paracellularly Cl^- driven Na^+ transport also occurs.

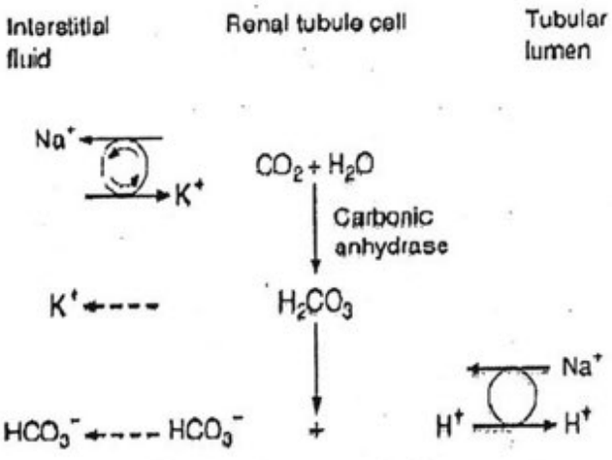
In PCT

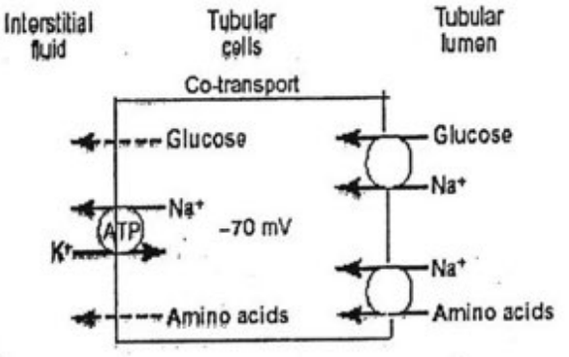
In first half:

- Na cotransported with glucose, amino acid , phosphate & lactose.
- Na conter transported with H^+ associated with HCO_3^- reabsorption.

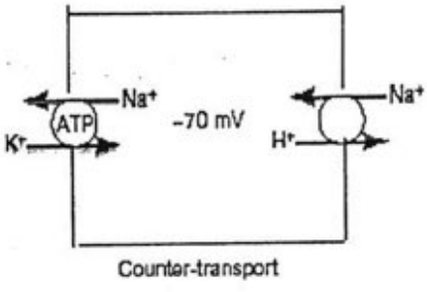
In 2nd half:

- Na countertrasported with H^+ associated with Cl^- reabsorption.
- Cl^- driven Na^+ transport -ie, paracellular





1st



Inside the Cell:

$H_2O+CO_2 \longrightarrow H_2CO_3 \longrightarrow H^+ + HCO_3^-$

This H^+ is conter trasported to lumen for Na^+ & HCO_3^- is reabsorbed into the ISF via carrier.

Within the lumen

$H^+ + HCO_3 \longrightarrow H_2CO_3 \xrightarrow{CA} H_2O+CO_2$(reabsorbed)

In 2nd half of PCT

1. Na^+-H^+ antiport with Cl^- reabsorption:

Na^+-H^+ antiport carry Na^+ to cell& H^+ to lumen.

In lumen:

H^+ + anion $\longrightarrow$ H^- $\longrightarrow$ enter cell by concentration gradient.

(anions are like OH^-, formate, oxallate, HCO_3^-, SO_4^{2-})

In the cell:

H anion $\longrightarrow$ H^+ + anion

H^+ enter lumen by Na^+-H^+ antiport .Anion enter lumen by Cl^- base exchanger.

Na^+ enter ISF by Na^+-K^+ ATP ase & Cl^- enter ISF by K^+ Cl^- symport.

2. Paracellular uptake of Na^+:

By continous secondary active sodium reabsorption,

- lumen become negative.Thus Cl^- moves into the cell passively along the concentration gradient.
- Osmosis of water from from the lumen. Thus concentration of Cl^- in the lumen increases& hence Cl^- moves passively into cell down the concentration gradient.

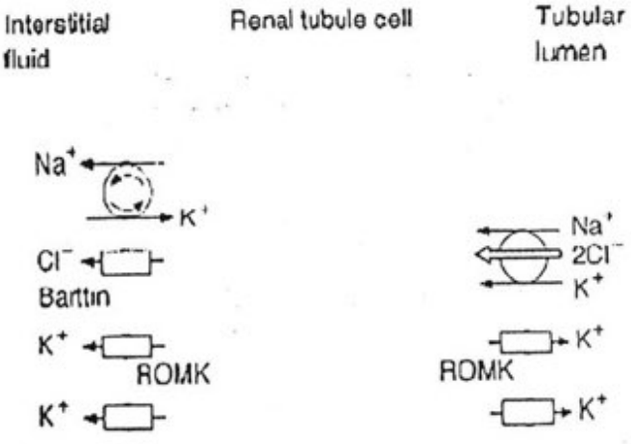
By these two reasons , lumen become more negative.Then Na+ move down the concentration gradient paracellularly.

Summarising Na^+ reabsorption in PCT;

Transcellular:	
Na^+ solute symport	10%
Na^+ H^+ antiport with HCO_3 reabsorption	20%
Na^+H^+ antiport with Cl^- reabsorption	50%
Paracellular:	
Cl^-driven Na^+ transport	30%

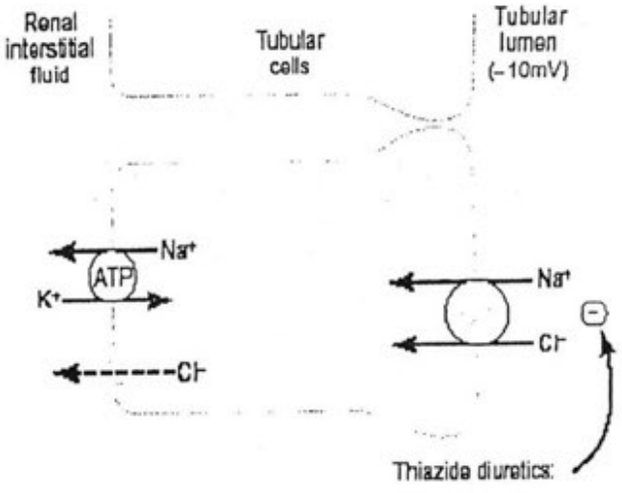
In loop of Henle:

- Thin descending limb is impermeable to Na^+
- Thin ascending limb is present only in juxtra medullary nephron.Here Na^+ is passively reabsorbed.
- Thick ascending limb of loop of Henle actively reabsorb Na+ with Na^+-K^+ ATP ase at basal border.In the luminal border 2 mechanisms operate:
  - Na^+- H^+ antiport.
  - Na^+- K^+ $2Cl^-$ symport.



- K^+ diffuse into ISF &lumen via ROMK , K^+ channels.

In DCT:



- Na^+-K^+ cotransported at luminal border.
- In basal border Na^+-K^+ pump operates.Na^+-K^+ pump extrude $3Na^+$ in exchange of $2K^+$ that are pumped into the cell .In later portion of DCT ,reabsorption is like in collecting duct .

In collecting duct

2 Types of cells are important (Strictly speaking applicable to cortical collecting duct):

- P cells-reabsorb Na^+ & water & secrete K^+. Aldosterone act on (stimulate) P cells & increase insertion of ENaC channel into luminal border & increase synthesis of EnaC
- I cells secrete H^+ &reabsorb HCO_3^-.

Regulation of Na+ Reabsorption

Na^+ is the most abundant cation in the ECF. ie, it constitute more than 90% of osmotically active solute . Na^+ is the prime determinant of ECF volume .Roughly , amount of Na^+ ingested.

Reabsorption of Na^+ is regulated by multiple regulatory mechanisms:

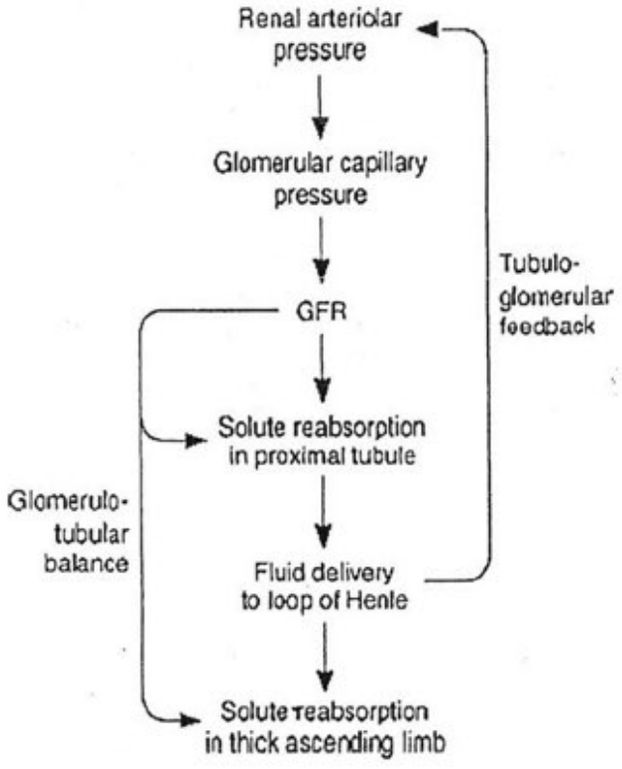
1.Glomerulotubular balance(refer short note)

Intrinsic ability of tubules to increase the reabsorption rate in response to increase in tubular load.Increased GFR ⟶ increased tubular load ⟶ increased reabsorption of NaCl & consequently water in PCT. Thus percentage of Na reabsorbed is kept constant. Na^+ & water balance of body is maintained.

Mechanism:

- GFR increases ⟶ increased osmotic pressure of efferent arteriole & peritubular capillary ⟶ increased H_2O & Na^+ reabsorption
- GFR increases ⟶ increased glucose & amino acid filtered ⟶ Na^+ reabsorption by symport

2.Tubuloglomerular feedback:



This mechanism minimises the changes in filtered load of Na i.e. maintain the costancy of load delivered to distal tubule.The sensor for this response is MACULA DENSA.

Mechanism:

When GFR increases ⟶ increased Na & Cl entry to DCT ⟶ increased Na^+ & Cl entry to macula densa via Na^+-K^+ $2Cl^-$ co transporter in the apical membrane ⟶ increased Na^+-K^+ ATP ase activity ⟶ increased ATP hydrolysis ⟶ increased adenosine ⟶ increased release of Ca^{2+} by the macula densa to vascular smooth muscle in the afferent arteriole ⟶ vasoconstriction of afferent arteriole & GFR decreases to normal

3. Starling forces across peritubular capillaries:

- Increased hydrostatic pressure of peritubular capillaries & increased osmotic pressure of interstitial fluid opposes reabsorption of Na+.
- Increased osmotic pressure of peritubular capillaries& increased hydrostatic pressure of interstitial fluid favours reabsorption of Na^+.
- When BP increases ,hydrostatic pressure increases
- When both afferent&efferent arteriole constrict hydrostatic pressure decreases.
- Osmotic pressure is directly proportional to filtration fraction.
- Increase in ultra filtration coefficient favours reabsorption.

4. Sympathetic stimulation increases Na^+ reabsorption.
5. Hormones:
   - ➢ Angiotensin II: Increase Na reabsorption in PCT
     Actions:Constrict efferent arteriole, there for,
     - Hydrostatic pressure of peritubular capillaries decrease
     - Increase filtration factor and thus osmotic pressure of peritubular capillaries increases
     - Directly act on PCT to increase activity of Na^+-K^+ ATPase and Na^+-H^+ antiport
   - ➢ Aldosterone
     - Stimulate P cells of collecting tubules to insert ENaC on luminal border. Also increase synthesis of EnaC
     - Causes K^+ Excretion
   - ➢ Glucocorticoid-increase Na reabsorption
   - ➢ ANP decrease NaCl & H_2O reabsorption in collecting duct
   - ➢ Dopamine decrease NaCl & H_2O reabsorption in PCT
   - ➢ PGE2 decreases Na reabsorption
   - ➢ Endothelin I&II decrease Na reabsorption.
   - ➢ Ouabain inhibit Na^+-K^+ ATPase .

Transport proteins involved in the movement of Na^+ and Cl^- across the apical membranes of renal tubular cells.[1]

Site	Apical Transporter	Function
Proximal tubule	Na^+/glucose CT	Na^+ uptake, glucose uptake
	Na^+/Pi CT	Na^+ uptake, Pi uptake
	Na^+ amino acid CT	Na^+ uptake, amino acid uptake
	Na^+/lactate CT	Na^+ uptake, lactate uptake
	Na^+/H^+ exchanger	Na^+ uptake, H extrusion
	Cl^-/base exchanger	Cl^- uptake
Thick ascending limb	Na^+, $2Cl^-$, K^+ CT	Na^+ uptake, Cl^- uptake, K^+ uptake
	Na^+/H^+ exchanger	Na^+ uptake, H^+ extrusion
	K^+ channels	K^+ extrusion (recycling)
Distal convoluted tubule	NaCl CT	Na^+ uptake, Cl^- uptake
Collecting duct	Na^+ channel (ENaC)	Na^+ uptake

[1] Uptake indicates movement from tubular lumen to cell interior, extrusion is movement from cell interior to tubular lumen. CT, cotransporter; Pi, inorganic phosphate.

Applied Physiology

- Addisons disease -decreased aldosterone causes hyponatraemia(low blood Na^+ level)resulting in hypovolemia,decreased blood pressure & hyperkalemia

(high blood K^+ level).

- Liddle's Syndrome-Mutation of ENaC gene making it constitutively active. Therefore increased Na reabsorption &hypertension results.
- Conn's syndrome -Increased aldosterone causes hypernatrimea resulting in hypertension &hypokalemia.
- Aldosterone escape-Inspite of increased aldosterone level,Na is excreted when plasma sodium is beyond a particular level.
- Angiotensin converting enzyme (ACE) inhibitors like captopril decrease Angiotensin II & directly BP & decrease BP by increased Na^+ excretion.

5.Water Reabsorption:

More than 99% of filtered water is reabsorbed since only 1-1.5L/day is the urine volume eventhough about 180L/day is filteredwater is reabsorbed by passive diffusion through aquaporins. Aquaporins are:

- Water channels ie, family of membrane channel proteins that serve as selective pores through which water crosses plasma membrane.
- 4 aquaporins found in humans-1,2,5&9.
- Most of them in the renal tubules especially aquaporin 2
- ADH increases water reabsorption in DCT & collecting duct by regulating aquaporins.
- Aquaporin 9 is found in- leucocytes, liver, lung & spleen.
- Aquaporin 5-in lacrimal gland
- Aquaporin 1 responsible for 80% of water reabsorption in PCT
- Nephrogenic diabetes insipidus is due to impaired function of these channels.

Water reabsorptioon takes place via:

1. PCT reabsorb 60-70% of total water absorbed.Water moves passively out of the tubule along a concentration gradient setup by active transport of solutes.This is called **obligatory reabsorption** of water.Thus isotonic fluid remains at the end of PCT. Aquaporin I is localised in PCT.

2. In the loop of Henle: Thin descending limb reabsorb 15% of the total while thick & thin ascending limbs are impermeable to water.Fluid in descending limb become hypertonic as water moves into hypertonic medullary interstitium.In ascending limb it becomes more dilute &when it enters DCT it is hypertonic to plasma due to movement of Na^+ & Cl^- out of tubular lumen.

3. In distal tubules its first part is relatively impermeable to water & continued.Removal of solutes in excess of solvent further dilutes tubular fluid.About 5% of filtered water is removed in this segment.In its distal part, permeability to water is controlled by ADH & is similiar to that of collecting duct. Hypotonic fluid enters collecting duct.

4. Collecting duct has two parts, a cortical part & medullary part.

With maximum ADH cortical part reabsorb 10% & medullary part reabsorb 4.7%. The key to action of ADH on collecting duct is Aquaporin-2.

Unlike other aquaporins this is stored in in vesicles in cytoplasm of principal cells. ADH causes rapid insertion of these vesicles into apical membrane of cells . These effect is mediated via vasopressin V2 receptor ⟶ cAMP ⟶ protein kinase A .

Thus hypotonic fluid entering cortical collecting duct become isotonic when it enters medullary collecting duct.In medullary collecting duct reabsorption of water into hypertonic medullary interstitium produces a concentrated urine.

When ADH is absent, collecting duct epithelium is relatively impermeable to water.Only about 2% of filtered water is reabsorbed.Thus the reabsorption of water under influence of ADH is called **facultative reabsorption.**

Concentration Of Urine:

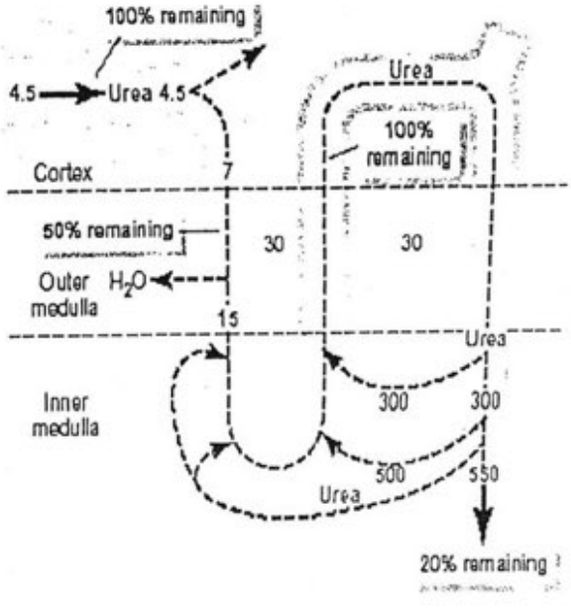
Process of concentration or dilution of urine rquire kidney to excrete water & solutes independently.ie, when water intake is increased ,water excreted in excess of solutes resulting in dilute of minimum osmolarity 30mosm/L.(urine flow may reach 15ml/min).

Or, when water intake is decreased, solutes are excreted in excess of water resulting in concentrated urine of maximum osmolarity of 1400mosm/kg of H_2O.

Basic requirement for concentration of urine are,

i)High osmolarity of renal medullary interstitium.

ii)Increased level of ADH.



Hyperosmotic medullary interstitium:
Increasing osmotic gradient that is present along medullary interstitium is produced by combined action of loop Henle & vasarecta as counter current multiplier & counter current exchanger respectively.

ADH stimulated water permeability allows water to be reabsorbed from collecting duct untill luminal fluid equilibrate with medullary interstitium.

Urea transport is mediated via urea transporters ie, by facilitated diffusion.There are atleast 4 isoforms of transport protein UT-A in kidney(UT-A1-UT-A4).ADH stimulates urea transporters& hence urea reabsorption.The amount of urea in medullary interstitium varies with amount of urea filtered &this in turn varies with dietary intake of protein.Thus a person withlow protein diet has a decreased ability to concentrate urine.

Thus factors affecting concentration/dilution of urine are:

- ADH
- Function of thick ascending limb of loop of Henle.
- Length of loop of Henle
- Urea
- Flow through loop of Henle.(high flow decreases concentrating ability)
- Flow through collecting duct.
- Flow through vasa recta (high flow decreases medullary gradient & hence decrease concentrating ability)
- Prostagladin (decrease concentrating ability of kidney)

Note:

- Cell shrinking in hyperosmolar interstitium is prevented by substances like sorbitol,inositol by cell.
- Concentrating or diluting ability of kidney can be assessed by clearance values like osmolar clearance,free water clearance etc.

6.Acidification Of Urine:

Acidification occurs by secretion of H^+ ions into the lumen by cells of PCT, DCT, collecting duct. pH of glomerular filtrate is 7.4.Changes are regulated by body buffers, respiratory system & kidney. Kidney excrete excess acid or base present in the body fluid.Urine is acidic in nature with a pH of 4.5-6.

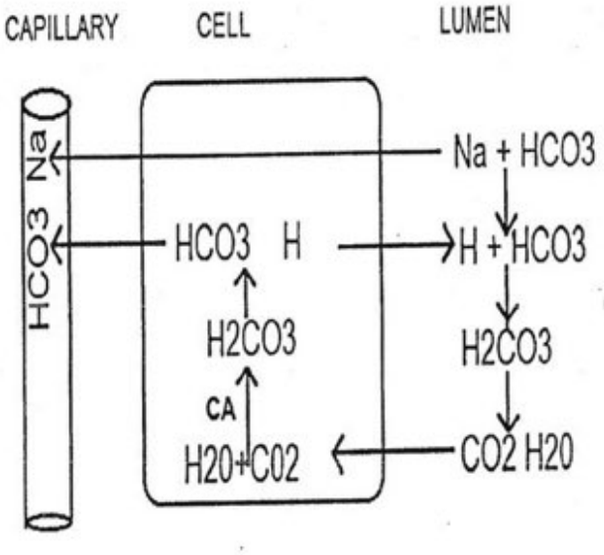
H^+ Excretion:
1)The cellsof PCT,thick segment of Loop of Henle(LH),DCT & CD secrete H^+.
In PCT,thick segment of LH,early DCT it occurs by Na^+-H^+ exchange.The H^+ comes from intercellular dissosciation of H_2CO_3 &HCO_3

2)In late distal & collecting tubules,H^+ is secreted by an ATP driven proton pump mechanism.secretion of H^+ occurs in a special type of cells called **I cells**.it occurs in luminal membrane where H^+ is transported directly by a specific protein,a hydrogen-transporting ATPase.The I cells contain an anion exchange protein called **Band3** which helps in exchange of HCO_3 &Cl.

Removal of H^+
If H^+ ion secreted into the lumen were not removed by time,acidity of urine increases rapidly & attains limiting pH which inhibits further secretion of H^+ by tubular cells.This is done in 3 mechanisms.

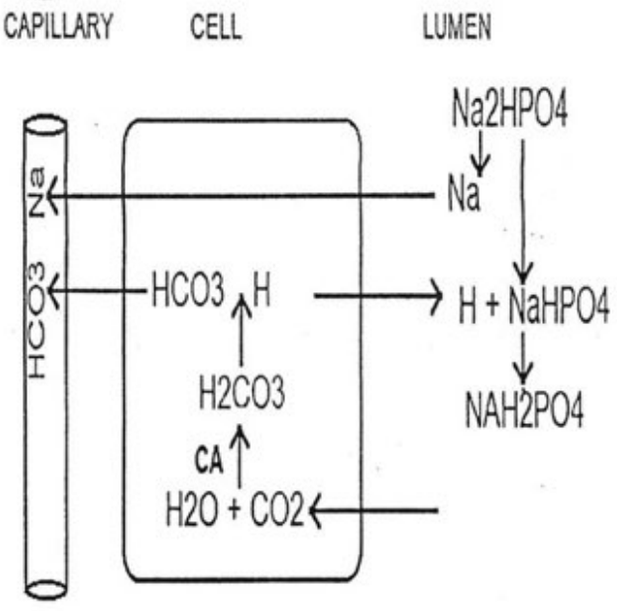
(**Limiting pH:** It is the maximal H^+ gradient against which transport meschanisms can actively secrete H^+. It corresponds to the lower limit of pH of urine ie,4.5(1000 times concentration of plasma).This is normally reached in collecting ducts.
If no buffers are present in urine to tie up free H^+ ion ,the limiting pH would be reached easily & H^+ secretion would stop.)

1)Bicarbonate mechanism:
The H^+ secreted into renal tubule combines with filtered HCO_3 forming H_2CO_3.H_2CO_3 dissoscites into CO_2 &H_2O.CO_2 diffuses into cell&it is used to form H_2CO_3.



Thus for each mole of HCO_3 removed from the tubular fluid 1 mole of HCO_3 diffuses into blood.This mechanism particularly takes place in PCT as carbonic anhydrase is present in brush border of cells.

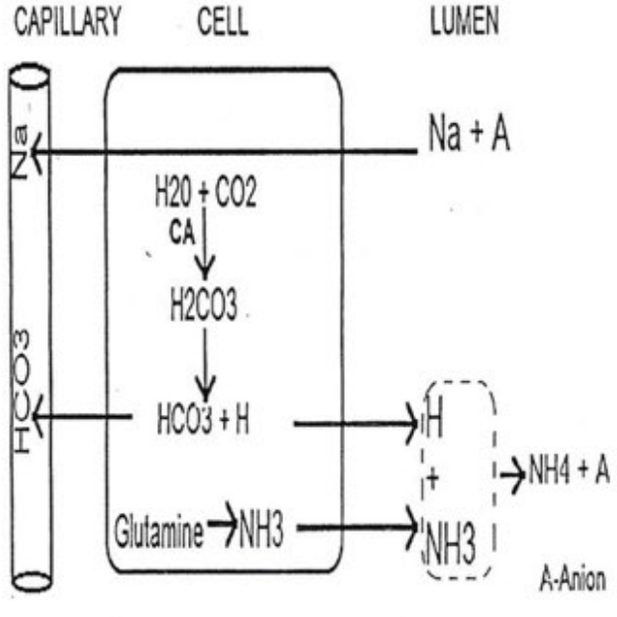
2)Phosphate mechanism:
In the tubular cell CO_2 combines with H_2O to form H_2CO_3. it immediately dissosciates to H^+ & HCO_3.HCO_3 from the tubular cells enters the interstitium,simultaneously Na^+ is reabsorbed.H^+ is secreted into the tubular lumen it reacts with sodium hydrogen phosphate($NaHPO_4$) to form sodium dihydrogen phosphate(NaH_2PO_4).NaH_2PO_4 is excreted in urine.This happens mainly in distal tubules & collecting duct.



3)Ammonia mechanism:

In the tubualr cells, NH_3 is formed from glutamine.Glutamine is first converted to glutamate by glutaminase.**Glutamic dehydrogenase** then catalyses conversion of **glutamate** to **α ketoglutarate**,with production of NH_3.

The NH_3 formed in the tubular cells is secreted to tubular lumen in exchange of Na ion.Here it combines with H^+ to form NH_4^+& is excreted



pH Changes in Tubular Fluid:

Fluid entering PCT has pH same as that of plasma (7.4).

Fluid leaving PCT has slightly less than or same as 7.

In DCT &collecting duct pH drop & approaches 6.

So normal urinary pH ranges between 5-7.Extreme ranges are between 4.5-8.

Factors that affect H^+ secretion along with HCO_3^- reabsorption:

Increase H^+ secretion & increase HCO_3^- reabsorption

- Increased pCO_2(in respiratory acidosis)
- Hypokalemia
- Increased aldosterone & adrenocortical steroids

Decrease H^+ secretion & decrease HCO_3^- reabsorption

- Decreased pCO_2
- Hyperkalemia
- Decreased aldosterone & adrenocortical steroids
- By carbonic anhydrase inhibitors.eg:acetazolamide

SHORT NOTES

1. Difference between cortical and juxtamedullary nephrons.

Based on situation of renal corpuscle there are 2 types of nephrons:

- Cortical nephrons
- Juxtamedullary nephrons

Cortical Nephron:

- Corpuscle is in the outer cortex of the near the kidney at the periphery.
- Loop of Henle is short.
- Hairpin bend penetrates outer zone of medulla.
- Blood supply via peritubular Capillaries.
- Function is formation of urine.
- Loop of Henle has thin descending and thick ascending limb.

Juxtamedullary Nephron:

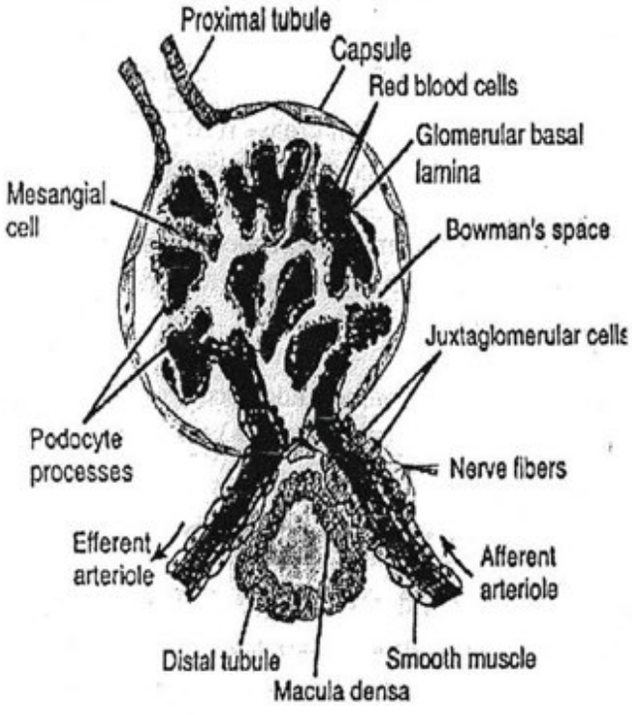
- Corpuscle is in the inner cortex near the medulla or at the corticomedullary junction.
- Loop of Henle is long.
- Hairpin bend penetrates up to tip of papilla.
- Blood Supply via vasa recta.
- Function is mainly urine concentration and formation
- Loop of Henle has thin descending and long ascending having both thin and thick segments.

2. Functions of Loop of Henle: *(refer essay 3)*

3. Autoregulation of renal blood flow:

(Refer essay 1)

4. Juxtamedullary Apparatus:



These are specialized cells at the junction of Loop of Henle & DCT. Formed by 3 types of cells:

- Macula Densa:

Specialized cells of the thick ascending limb that touch with arteriole (especially afferent) are called macula densa. These are tightly packed cuboidal cells. This sense the volume and composition of tubular fluid-mainly Na^+ & Cl^-.

- Juxtaglomerular cells:

The wall of afferent arteriole before entering Bowman's capsule is Thickened. It is formed by specialized type of smooth muscle cells called Juxtaglomerular cells. Main function is secretion of renin.

- Extraglomerular mesangial cells:

It is formed between efferent & afferent arteriole. It is called as **LACIS** cells. It also secretes renin. But function is unknown.

- Glomerular mesangial cells:

It is situated between Glomerular capillary loops. They are phagocytic.Secrete prostaglandins & cytokines. These cells are contractile also. Play an important role in Glomerular filtration

The apparatus play an important role in feedback mechanism called tubuloglomerular feedback-thus regulates blood flow & GFR.

5. Counter Current Exchanger: (Refer Essay 3)

6. Glucose Reabsorption:

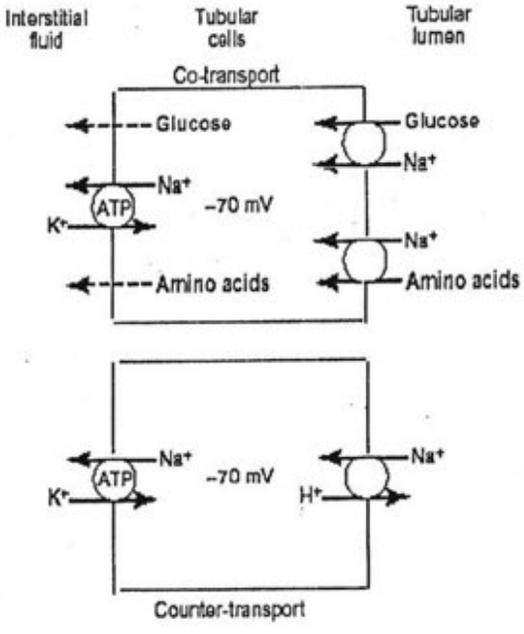
- Secondary active transport- mainly d-glucose is reabsorbed
- Occurs in early part of PCT and is symport along with Na^+ Reabsorption.

Glucose and Na+ bind to a common carrier **SGLT2** in luminal membrane.

Glucose is carried into the cell as Na move down its electrical and chemical gradient and is then pumped out of cell,Glucose combines with another carrier protein **GLUT2** on basal surface and moves into peritubular capillaraies by simple diffusion.

Characteristic of glucose transport

Rate of filtration of glucose at glomerulus
=Plasma glucose levelxGFR
=80mg%x125ml/min
=100mg/min



Transport maximum for glucose(Tm):

- Maximum rate at which renal active transport system can transport a particular solute in unit time.
- Amount of substance transported is directly proportional to the amount filtered up to Tm.
- Above Tm there is no further Reabsorption & excreted in urine.
- This excretion beyond Tm is due to saturation of carrier system.

Tm for glucose:

- Males - 375 mg/min
- Females - 300 mg/min

Renal threshold of glucose:

Plasma level at which glucose first appears in urine.

Predicted value = T mg/GFR

= 375 mg/min / 125 ml/min
= 300 mg/dl

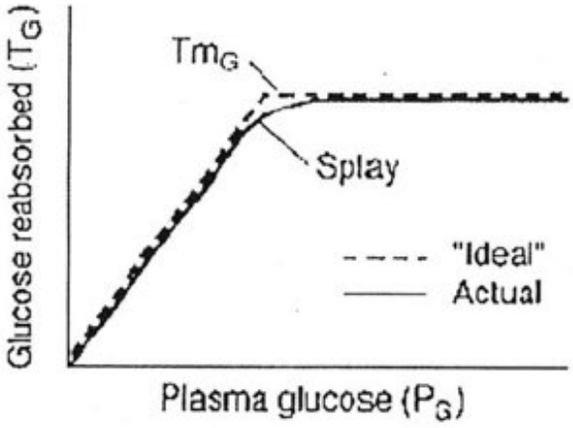
But actual value is:

- 200 mg /dl in arterial blood
- 180 mg/dl in venous blood

This variation from predicted value can be explained by **SPLAY**.

Splay:

Deviation from the ideal graph is called splay.



- In an ideal graph all the nephrons reach Tm at the same time ie all tubules function properly.
- Here T_m for all tubule will be identical & all the glucose will be removed from the tubule when the amount filtered was below the T_{mg}.

- Cause for the splay:
  1)At renal threshold glucose appear in urine before Tm is reached because all the Nephron does not have same Tm.
  2)Some Nephron excrete glucose in urine before the others reach the T mg-Heterogeneity of nephrons
- Magnitude of splay is inversely proportional to avidity with which transport protein binds to glucose.
- Normally plasma glucose never high enough to cause excretion.
- In Diabetes Mellitus, beyond renal threshold- Filtered load >Tmg

Glycosuria

- Renal glycosuria - Plasma glucose level normal but renal threshold is decreased due to disease i.e. in conditions like autosomal Recessive mutation of SGLT 2 gene
- Glucose transport in kidney is inhibited by phlorhizin which competes with d-glucose for binding to the carrier.

7.Tubuloglomerular feedback & Glomerulotubular balance. (Refer essay4)

8. Clearance value & their Uses:

Osmolar clearance:

Volume of plasma completely cleared off all osmotically Active solutes per unit time

$$C_{osm} = U_{osm} \times \frac{V}{P_{osm}}$$

C_{osm} ⟶ Osmolar clearance
U_{osm} ⟶ Urine osmolarity
P_{osm} ⟶ Plasma osmolarity
V ⟶ Urine volume

E.g.:- C_{osm} = 600 x 0.001/300
= 0.002L/min

i.e. 2 ml of plasma is cleared off solutes in each minute .

Free water clearance:

Volume of urine excreted per unit time in excess of that required to excrete the contained solutes i.e. difference between water excretion & urine flow rate.

C_{water} = V - Cosm

Negative free water clearance:

Water is conserved i.e. solute free water is absorbed i.e.

$C_{osm} > V$; C_{water} = -ve
$C_{osm} = V$ C_{water} = 0 ⟶ isotonic urine
$C_{osm} < V$ C_{water} = +ve ⟶ dilute urine

Clearance Tests:

1. Creatinine clearance test

Ideal substance for clearance tests since blood level won't fluctuate due to continuous production.

Values:
Males : 85-125 ml/min
Females : 80-115 ml/min

Use:

- Indicator of GFR
- Early detection of functional impairment of kidney
- Long term monitoring of patients with renal insufficiency

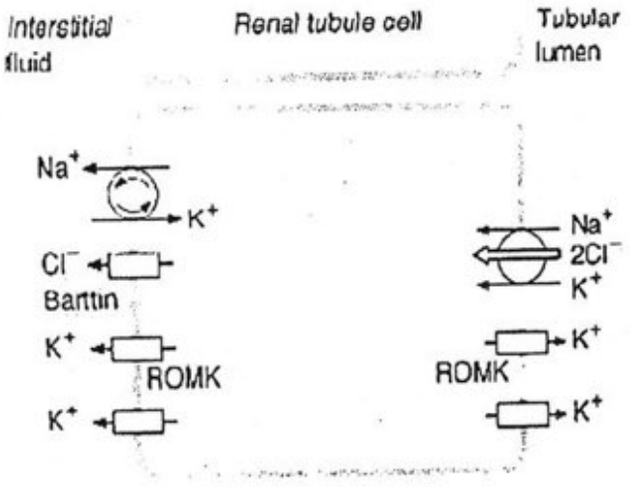
2. Urea clearance:

- Value less than GFR because partially reabsorbed
- Number of ml of blood which contains the urea excreted in a minute by the kidneys
- Normal values:
  - Maximum urea clearance - 75 ml/ min
  - Standard urea clearance - 54 ml/ min

Uses:
Value below 75% of the normal – abnormal kidney function

9. Aquaporins: (refer essay 5)

10. Bartter's Syndrome:



Condition caused due to defective transport in thick ascending limb.

Cause:

- Loss of function mutation in gene for any of the four
  - ➢ Na^+-K^+-$2Cl^-$ cotransporter
  - ➢ ROMK K^+ channel
  - ➢ ClC Kb Cl^- channel
  - ➢ Barttin: Integral membrane protein (necessary for normal functioning of Cl^--CKb-Cl^- channel)

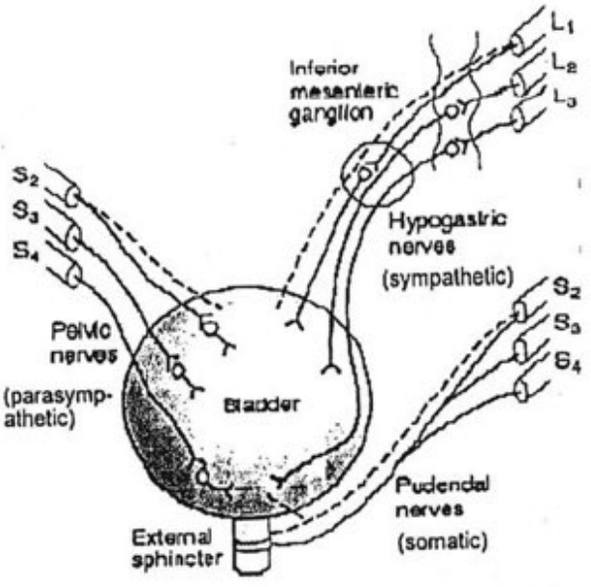
This syndrome is characterized by:

- Chronic Na^+ loss in urine
- Hypovolemia: Causes stimulation of renin & aldosterone secretion without hypertension.
- Hyperkalemia & alkalosis
- Patients with Barter's syndrome due to mutated **Barttin** are usually **deaf**.

11. Filtration Fraction:

- The fraction of the renal plasma which becomes the filtrate is called filtration fraction.
- The ratio between GFR & renal plasma flow
- Normal value - 0.16 - 0.20
- When there is fall in systemic BP in conditions like rapid compensatory phase of shock, both afferent & efferent vessels are constricted but efferent vessels are constricted to a greater degree
- Here GFR decreased, but renal plasma flow is decreased to a greater extent. So filtration fraction is increased
- Osmotic pressure of peritubular capillaries is directly proportional to filtration fraction.

12. Innervation of urinary bladder:



Parasympathetic Innervation:

- Root value - **S2, S3, and S4** -Pelvic nerve ⟶ ganglion cells are close to the bladder wall ⟶ Short post ganglionic fibers
- Effect - Contraction of bladder, relaxation of trigone & internal urethral sphincter
- **Pelvic** nerves- Nervi Ergintes or Nerve of **emptying**

Sympathetic Innervation:

- Root value - **L1 & L2** - hypogastric nerves ⟶ sympathetic chain ⟶ Inferior mesenteric ganglion post ganglionic fibers to bladder
- Effect - Relaxation of bladder & contraction of internal sphincter
- **Hypogastric** nerve - Nerve of **Filling**

Somatic nerves:

- Root value-**S2, S3, and S4** -Pudental nerve ⟶ external urethral sphincter
- Effect -Contraction of external urethral sphincter. During micturition external urethral sphincter is relaxed

Sensory Innervation:

- Sensitive to pain & touch
- Afferent sensory fibers ⟶ through pelvic & sympathetic nerves. Afferent fibers of micturition reflex are carried in pelvic nerves

Abnormalities of micturition:

Bladder dysfunction due to neural lesions:

1. Effect of Deafferentiation: (Atonic, tabetic, Bladder)
   Damage to dorsal afferent nerve root

Causes:

- Due to syphilis causing constrictive fibrosis around nerve root- **Tabes Dorsalis**
- Due to crush injury to sacral region of spinal cord.

Effect:

- Prevents transmission of afferent stretch impulses from bladder.
- Reflex contraction of bladder is abolished bladder become distended- Hypotonic, Flaccid, Atonic Bladder.
- Bladder fills to capacity & overflows i.e. a few drops at a time- **Overflow Incontinence**
- Some contraction occurs due to intrinsic response of smooth muscle to stretch.

2. Effect of Denervation: (Autonomous Denervated Bladder)

- Due to tumor of cauda equina.
- Afferent & efferent nerves are destroyed.
- Initially bladder is over distended & flaccid (Atonic)
- Gradually muscles of Denervated bladder become active.
- Frequent waves of contraction.
- Hyper active state can be due to Denervation Hypersensitivity
- Urinary bladder become shrunken & hypertrophied

3. Effect of Spinal cord Transection:

- Transection of spinal cord above sacral region-
  - Micturition reflex occurs but there is no control from higher centers.
  - In Stage 1 or Stage of Spinal Shock- bladder is unresponsive & flaccid (over flow incontinence).
  - In Stage 2 or Stage of reflex Activity- When reflex activity returns, micturition reflex without any voluntary control (Automatic bladder).
  - Sometimes micturition reflex ⟶ hyperactive shrunken & hypertrophied bladder ⟶ Spastic Neurogenic Bladder.
  - Stage 3 of Stage of Failure of Reflex Activity- urinary retention & overflow incontinence occurs.

13. Cystometrogram:

- Graph showing relationship between intravesical pres sure & intravesical Volume

Procedure:

Catheterize bladder & empty it. Introduce 50 ml increments of water & air each hour & measure the intravesical pressure. The graph has 3 stages:

- Ia : 5-10 cm H_2O pressure for 50 ml.
- Ib : Only slight increase in pressure for volume 50-400ml.
- II : When volume increases >400,pressure increases steeply.

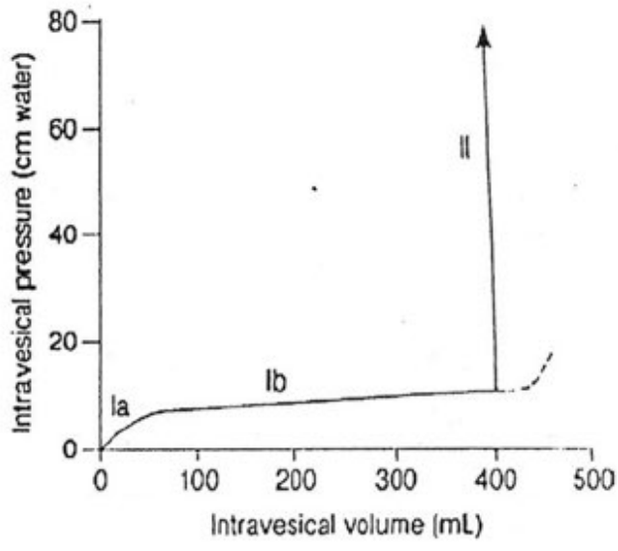
Causes for each stage:

- Ia - Initial increase in pressure when volume increases.
- Ib - flat segment- manifestation of **Law of Laplace:** States that pressure in a spherical viscous is equal to twice the wall tension divided by radius.

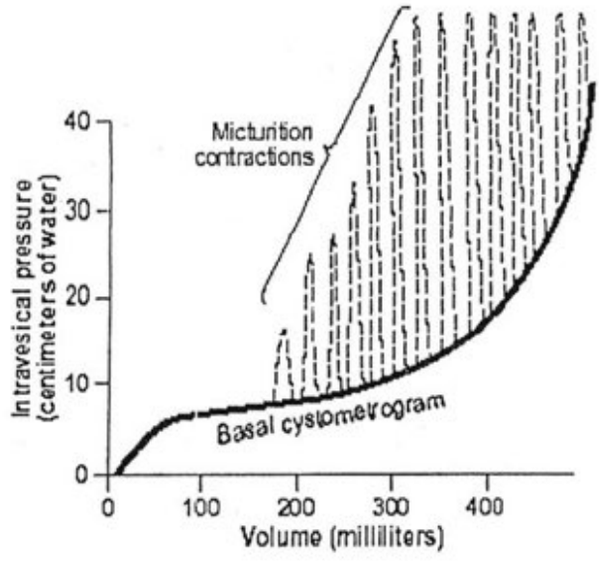
$$P = \frac{2T}{r}$$

Tension increases as bladder fills but so does the radius.So theres a slight increase in pres sure

- II - Steep increase in pressure as micturition reflex occurs



Micturition waves:



It is a periodic acute rise in pressure lasting from few seconds to more than a minute which is superimposed on tonic pressure change.

Note: The 1st urge to void is felt at 150 ml & a marked

sense of fullness is felt at 400ml.When it is increased beyond 450ml,pain & discomfort occurs.

14. Micturition reflex:

Micturition: Process of excretion of urine

As bladder fills micturition contraction appears & spontaneously relaxes after a few seconds.

As bladder continues to fill micturition contractions become more frequent & strong. Desire to void can be controlled /inhibited by higher centers

Micturition reflex:

Receptor ⟶ Sensory stretch receptors in urinary bladder wall

Afferent ⟶ Pelvic nerve

Centre ⟶ S2, S3, S4

Efferent ⟶ Pelvic nerves (parasympathetic fibers)

Effector organ & Effect ⟶ Contraction of detrussor muscle, relaxation of internal sphincter

Once this reflex become powerful it causes another reflex; i.e. inhibition of Pudental nerve -inhibition of external urethral sphincter ⟶ voiding of urine occurs.

Regulation from Higher centers:

Inhibitory	Facilitatory
Cortical centers	Pons (Barrington's centre)
Midbrain	Posterior hypothalamus

- Higher centers keep micturition reflex partially inhibited except when desired.
- Prevent micturition even if micturition reflex occurs by tonic contraction of external sphincter.
- Initiates voluntary urination ⟶ voluntary facilitation of micturition reflex possible even if bladder contain few ml of urine.

Mechanism of Voluntary Urination:

Voluntary relaxation of pelvic floor muscles ⟶ downward tug of Detrussor muscle ⟶ Bladder contraction. Voluntary contraction of abdominal muscle ⟶ increase in pressure in bladder ⟶ stimulation to micturition reflex. Voluntary inhibition of the reflex by contraction of external sphincter & perineal muscles.

- Female urethra- emptied after urination by gravity
- Male urethra - by contraction of bulbocavernosus muscle

Micturition Reflex in Infants:

It starts in intrauterine life. Remains involuntary (automatic bladder) until 2½ years i.e. control from higher centers not well established. Complete control established about 4½ years.

15. Obligatory Urine Volume:

It is the minimum amount of urine volume necessary to get rid body off solutes to be excreted.

E.g.:- Solutes to be excreted per day - 600mosm /day
Maximum concentrating ability - 1200mosm/L
Obligatory urine volume = 600/1200 = 0.5 L/day

16. Diabetes Insipidus:

Refer endocrinology

17. Endocrine functions of Kidney:

Kidney produces 3 hormones:

1. Renin
2. Erythropoietin
3. 1, 25 Di Hydroxy CholeCalciferol (1, 25 DHCC)

1.Renin Angiotensin System:

Renin is a glycoprotein secreted by Juxtaglomerular cells located in tunica media of afferent arteriole as they enter the glomeruli.

Renin is synthesized as large Preprorenin.

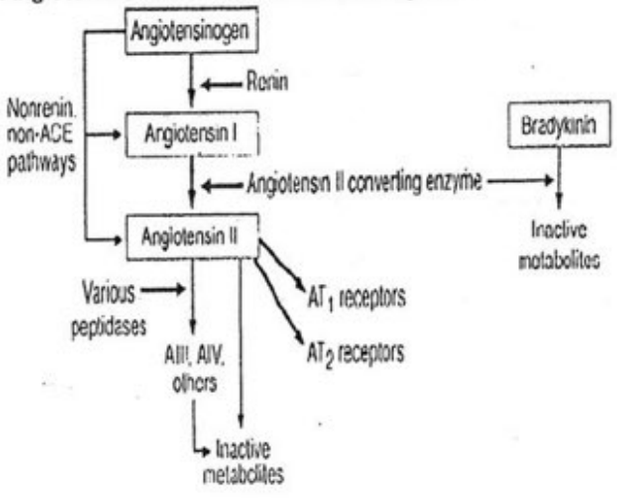
Preprorenin ⟶ Prorenin ⟶ Renin (biologically active)

Function of renin:

- Angiotensinogen ⟶ Angiotensin 1

Angiotensinogen is seen in α2 globulin fraction of plasma. It is synthesized in liver and the circulating level is increased by glucocorticoids, thyroid hormones, estrogen, several cytokines & Angiotensin II.

Angiotensin I is physiologically inactive. Angiotensin Converting Enzyme (ACE) which is present in endothelial cells of blood vessels in lungs converts Angiotensin I to Angiotensin II.ACE also acts on Bradykinin:



Receptors: There are 2 major types of Angiotensin II receptors AT_1 & AT_2

AT_1 : Serpentine receptors - coupled by G protein to phospholipase C - increases free Ca2+. 2 subtypes of AT1 receptors:
- AT_1A - in blood vessel wall & in brain
- AT_1B - in anterior pituitary & adrenal cortex

AT_2 : G protein - activate various phosphatases. Plentiful in fetal & neonatal life & persist in brain in adults.

Actions of Angiotensin II:
- Also known as hypertensin / angiotonin. Causes vasoconstriction and can increase systolic & diastolic BP (one of the most potent vasoconstrictor).
- Renin Angiotensin system is the major regulator of aldosterone secretion from adrenal cortex.
- Facilitates release of nor epinephrine by direct activation on post ganglionic neurons.
- Contract mesangial cells and thus decrease GFR
- Direct action on brain to decrease sensitivity to baroreflex and thus potentiate its pressor effect. The action is on **area postrema** (a circumventricular organ).
- Acts on another circumventricular organ i.e. subfornical organ and OVLT to increase water intake (Dipsogenic effect)
- Increase secretion of vasopressin and ACTH from pituitary gland

Angiotensin III has about 40% pressor activity and 100% aldosterone stimulating activity.

Conditions that increase renin secretion:

Sodium depletion
Diuretics
Hypotension
Haemorrhage
Upright posture
Dehydration
Cardiac failure
Cirrhosis
Constriction of renal artery or aorta

All these decrease central venous pressure causing increased sympathetic activity by baroreceptor mechanism. This cause constriction of renal artery or aorta and thus renal arteriolar pressure is decreased.

Factors that affect renin secretion:

Stimulatory
Increased sympathetic activity via renal nerves
Increased circulating catecholamines
Prostaglandins

Inhibitory
Increased Na^+ & Cl^- reabsorption across macula densa
Increased afferent arteriolar pressure
Angiotensin II
Vasopressin

2.Erythropoietin:

Site of production in adults:
- 85% from kidney
- 15% from liver

In kidneys it is produced by interstitial cells in peritubular capillary bed.

Action:
- The level of erythropoietin is increased in anemia. It increases the number of erythropoietin committed stem cells in bone marrow, that are converted to RBC precursors and mature RBCs.
- In brain it exerts protective effect against excitotoxic damage triggered by hypoxia.
- In uterus & oviduct, where it is induced by estrogen & appears to mediate estrogen induced angiogenesis.
- Recombinant erythropoietin (Epoietin α) is used in clinical practice against anemia due to renal failure .
- Receptors has **tyrosine kinase** activity.

Metabolism:

Principle site of inactivation is liver. Half life of hormone is 5 hours. However increase in circulating RBC takes 2-3 days to appear since RBC maturation is relatively slow process.

Regulation:

Hypoxia, Androgen, Cobalt salts. Alkalosis that develops at high altitudes etc. facilitates secretion of erythropoietin.

More details refer BLOOD

3.1, 25 DHCC:

Refer Calcium & Phosphorus metabolism:

18. Henderson –Hesselbachs Equation:

The relationship between pH, pKa, Concentration of acid and conjugate base (or salt) is expressed by Henderson –Hesselbachs Equation.

$$\text{i.e.} \quad pH = pKa + \log \frac{[\text{base}]}{[\text{Acid}]}$$

$$\text{or} \quad pH = pKa + \log \frac{[\text{salt}]}{[\text{Acid}]}$$

pKa:
- The pH at which the acid is half ionized is called pKa of an acid.
- It is constant at a particular temperature & pressure.
- Strong acids will have low pKa & weak acids have higher pKa.

- When [base] is equal to [acid]; pH=pKa
- When acid is half ionized pH & pKa have the same value.
- Buffer capacity is determined by absolute concentration of salt & acid.
- pH of buffer is dependant on the relative proportion of salt & acid.

This equation has great practical application in:

- Assessing the acid -base status.
- Predicting the limit of concentration of body buffers.

19. Difference between Water & Osmotic Diuresis:

Diuresis -The condition where urine output is increased

Water Diuresis:

- Increased water intake ⟶ decreased plasma osmolarity ⟶ decreased ADH ⟶ decreased water Reabsorption in collecting duct ⟶ dilute urine.
- At the moment of drinking water, ADH is secreted.
- Effect of secretion of dilute urine starts 15 minutes after the ingestion of the water load and reaches a maximum at 40 minutes.
- Thus a maximum urine flow of 16 ml/ min is produced.

Water Intoxication:

- If water is ingested at higher rate ⟶ hypotonic ECF ⟶ cells will swell.
- In case of edema of brain ⟶ convulsion, coma & death.
- If exogenous ADH administration and water intake is not decreased ⟶ water intoxication.

Osmotic Diuresis:

- Presence of large quantities of unreabsorbed solutes in tubules can cause increased urine volume called osmotic Diuresis.
- Medullary hyper tonicity is decreased when ascending LH cannot reabsorb Na maximally. It causes decreased water Reabsorption from descending loop of Henle ⟶ more fluid enter collecting duct.
- Thus marked increase in urine volume and increased Na and solute excretion.
- Osmotic Diuresis can be induced by:
  - Administration of mannitol to patients of cerebral edema.
  - Infusion of large amount of NaCl & urea.
- In diabetic patients infusion of large amount of glucose cause polyurea.

20. Diuretics:

Substances that cause increased Na and water excretion in urine

In PCT:

Carbonic anhydrase inhibiter is a diuretic - Acetazolamide in the inhibitor

- With inhibitor ⟶ decreased hydration of CO_2 in the cell ⟶ decreased H^+ availability Na^+/H^+ antiport ⟶ decreased Na Reabsorption
- Also decreased dehydration of H_2CO_3 in lumen ⟶ less CO_2 diffuses into the cell ⟶ decreased Na^+ & HCO_3^- Reabsorption.
- But this is a weak diuretic because Na Reabsorption is balanced at distal portion of tubules.

In Loop of Henle:

Inhibitors of Na^+-K^+-$2Cl^-$ cotransporter i.e. Furosemide- Powerful diuretic (loop diuretic). Thus it increases Na^+, K^+, H_2O excretion. Abolishes hyperosmolar medullary interstitium.

In DCT:

Inhibitor of Na^+-Cl^- cotransporter- thiazide-increase Na^+ & H_2O excretion- medium efficiency

In Collecting Duct:

K Sparing diuretics- weak diuretic

- Aldosterone antagonist - Spironolactone- competitive inhibitor of intracellular aldosterone receptor.
- Epithelium Na+ channel inhibitor- Amiloride- Increases both Na^+ & H_2O excretion & cause K^+ conservation.

Mechanism of action of various diuretics.

Agent	Mechanism of Action
Water	Inhibits vasopressin secretion.
Ethanol	Inhibits vasopressin secretion.
Antagonists of V_2 vasopressin receptors	Inhibit action of vasopressin on collecting duct.
Large quantities of osmotically active substances such as mannitol and glucose	Produce osmotic diuresis.
Xanthines such as caffeine and theophylline	Decrease tubular reabsorption of Na^+ and increase GFR.
Acidifying salts such as $CaCl_2$ and NH_4Cl	Supply acid load; H^+ is buffered, but an anion is excreted with Na^+ when the ability of the kidneys to replace Na^+ with H^+ is exceeded.
Carbonic anhydrase inhibitors such as acetazolamide (Diamox)	Decrease H^+ secretion, with resultant increase in Na^+ and K^+ excretion.
Metolazone (Zaroxolyn), thiazides such as chlorothiazide (Diuril)	Inhibit the Na^+-Cl^- cotransporter in the early portion of the distal tubule.
Loop diuretics such as furosemide (Lasix), ethacrynic acid (Edecrin), and bumetanide	Inhibit the Na^+-K^+-$2Cl^-$ cotransporter in the medullary thick ascending limb of the loop of Henle.
K^+-retaining natriuretics such as spironolactone (Aldactone), triamterene (Dyrenium), and amiloride (Colectril)	Inhibit Na^+-K^+ "exchange" in the collecting ducts by inhibiting the action of aldosterone (spironolactone) or by inhibiting the ENaC (amiloride).

21. PAH Clearance:

- To measure renal plasma flow a substance which is filtered and secreted but not reabsorbed is used E.g. Para Amino Hippuric Acid(PAH)
- Secretion of PAH into renal tubules increases when plasma PAH level rises until a maximal rate of secretion is attained.(Tubular maximum for PAH)
- PAH Clearance is high when plasma PAH level low.

But as plasma pH rises above Tm PAH, PAH clearance falls progressively & it approaches clearance of inulin. This can be explained as amount of PAH secreted becomes smaller & smaller fraction of total amount excreted as plasma level of PAH increases.

- Use of PAH clearance to measure effective renal plasma flow is described be
- EPRF is used instead of renal plasma flow to indicate that level in renal venous plasma is not measured.

$$EPRF = \frac{U_{PAH} \times V}{P_{PAH}} = C_{PAH}$$

U_{PAH} - Urinary PAH concentration
P_{PAH} - plasma PAH concentration
V - Urine volume

$$\text{Actual RPF} = \frac{\text{EPRF}}{\text{Extraction Ratio}}$$

- Since 90% of filtered PAH is excreted, extraction ratio = 0.9

- Extraction ratio=
  $\frac{\text{Arterial concentration - Renal venous concentration}}{\text{Arterial concentration}}$

$$RBF = \frac{RPF}{1 - \text{Hematocrit}}$$

22. How renal medullary interstitium kept hypertonic: (refer essay 5)

23. Role of Urea in concentrating urine: (refer essay 5)

24. Dialysis:

End stage of renal diseases requires heamodialysis. Toxic substances causing uremia symptoms can be removed by dialyzing blood of the patient against a suitable composition in an artificial kidney.

Indication:

- Chronic renal failure
- Some cases of acute renal failure(to over come the critical period)
- Permanent renal failure
- Removal of kidney

Principle:

Heamodialysis is the process of diffusion across a semi permeable membrane (E.g.:- cellophane) to remove unwanted substances from blood & to add desirable substances to blood.

Physiological basis:

1.Renal medullary interstitium is kept hypertonic
Refer essay 5.hyper osmotic medullary interstitium;page no 82

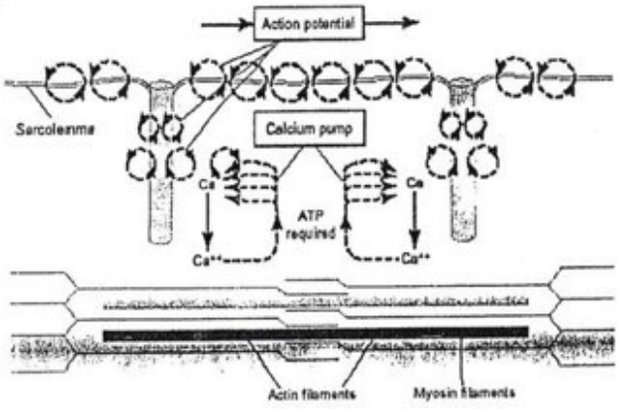
2.Filling and emtying of urinary bladder
Refer shortnote -14

Nerve and Muscle Physiology

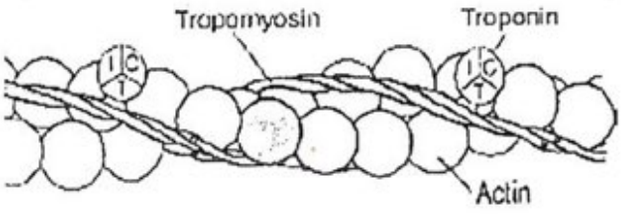
Prepared by
SREELAKSHMI.P
AMEER.VM

Essays

1.Excitation Contraction Coupling:



During resting stage, troponin I is tightly bound to actin and tropomyosin covers the active site of actin. This troponin-tropomyosin complex prevents the interaction between myosin head & actin. Therefore troponin & tropomyosin are together called relaxing proteins

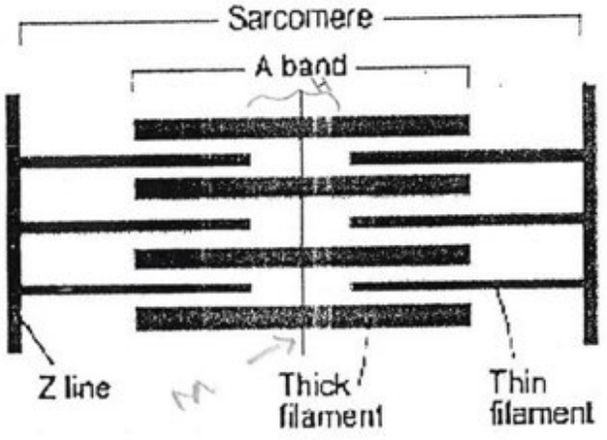


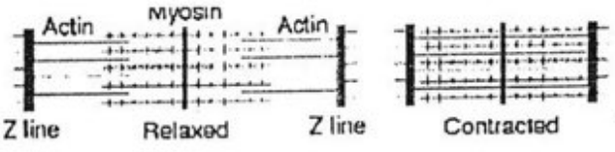
Events leading to contraction & relaxation of Skeletal Muscle:

1. Discharge of motor nerve: Action potential reaches the end field nicotinic Ach receptors in the motor end plate.
2. Generation of end plate potential & AP: AP travels through the T-tubule to the interior of the muscle fiber.

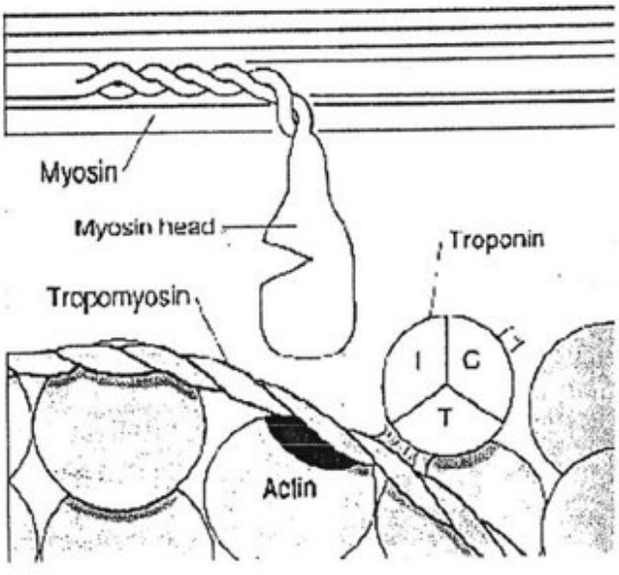
Depolarization of T-tubule activates the SR via dihydropyridine receptor. They are voltage gated channel and they serve as voltage sensor &cause release of ca from SR. The receptors in the SR is called ryanodin receptors which are not voltage gated. AP causes release of Ca^{2+} from SR to sarcoplasm. It is called Ca^{2+} pulse. Normally the concentration of Ca in sarcoplasm is less than 10^{-7} molar. Release of Ca from SR raises the Ca level to $2x10^{-4}$M.

Before contraction begins, the head of the cross bridge binds with ATPase activity of myosin head cleaves the ATP to ADP &P_i. In this state, conformational change in the head is such that it extends perpendicularly towards the actin filament but not attached to it.





The Ca^{2+} in the sarcoplasm binds to troponin C. This leads to the weakening of the linkage between troponin I & actin. Tropomyosin moves laterally exposing the site of actin.7 active sites are exposed or uncovered for each molecule of troponin binds to Ca^{2+} cross-linkages are formed between actin and myosin leading to contraction. The process by which depolarization of muscle fiber initiate contraction is called excitation-contraction coupling & the linkage between these excitation & contraction is calcium.



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- Use of PAH clearance to measure effective renal plasma flow is described be
- EPRF is used instead of renal plasma flow to indicate that level in renal venous plasma is not measured.

$$EPRF = \frac{U_{PAH} \times V}{P_{PAH}} = C_{PAH}$$

U_{PAH} - Urinary PAH concentration
P_{PAH} - plasma PAH concentration
V - Urine volume

$$\text{Actual RPF} = \frac{EPRF}{\text{Extraction Ratio}}$$

- Since 90% of filtered PAH is excreted, extraction ratio = 0.9

- Extraction ratio=

$$\frac{\text{Arterial concentration - Renal venous concentration}}{\text{Arterial concentration}}$$

$$RBF = \frac{RPF}{1 - \text{Hematocrit}}$$

22. How renal medullary interstitium kept hypertonic: (refer essay 5)

23. Role of Urea in concentrating urine: (refer essay 5)

24. Dialysis:

End stage of renal diseases requires heamodialysis. Toxic substances causing uremia symptoms can be removed by dialyzing blood of the patient against a suitable composition in an artificial kidney.

Indication:

- Chronic renal failure
- Some cases of acute renal failure(to over come the critical period)
- Permanent renal failure
- Removal of kidney

Principle:

Heamodialysis is the process of diffusion across a semi permeable membrane (E.g.:- cellophane) to remove unwanted substances from blood & to add desirable substances to blood.

Physiological basis:

1.Renal medullary interstitium is kept hypertonic

Refer essay 5.hyper osmotic medullary interstitium;page no 82

2.Filling and emtying of urinary bladder

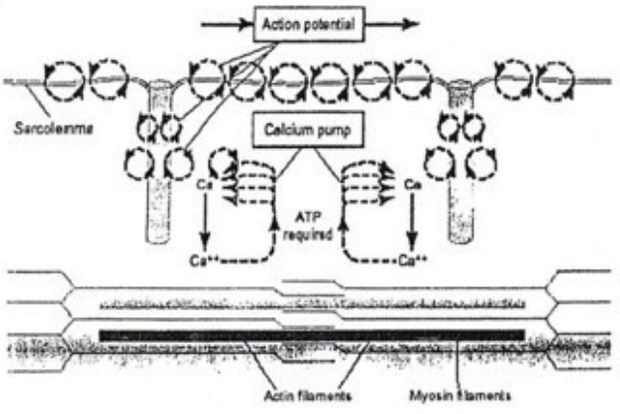
Refer shortnote -14

Nerve and Muscle Physiology

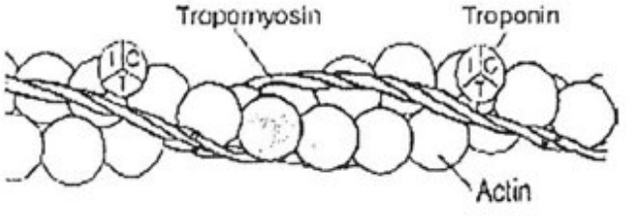
Prepared by
SREELAKSHMI.P
AMEER.VM

Essays

1.Excitation Contraction Coupling:



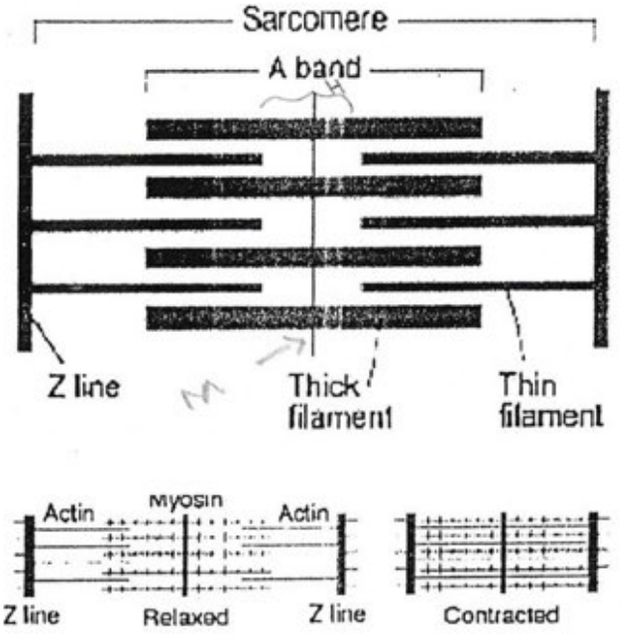
During resting stage, troponin I is tightly bound to actin and tropomyosin covers the active site of actin. This troponin-tropomyosin complex prevents the interaction between myosin head & actin. Therefore troponin & tropomyosin are together called relaxing proteins



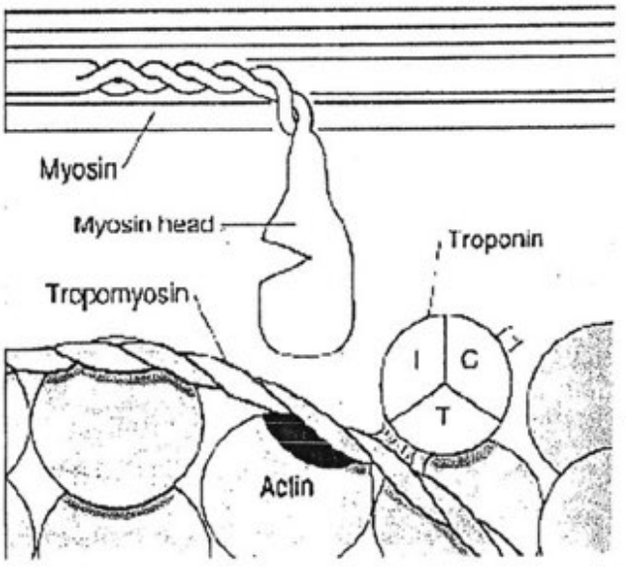
Events leading to contraction & relaxation of Skeletal Muscle:

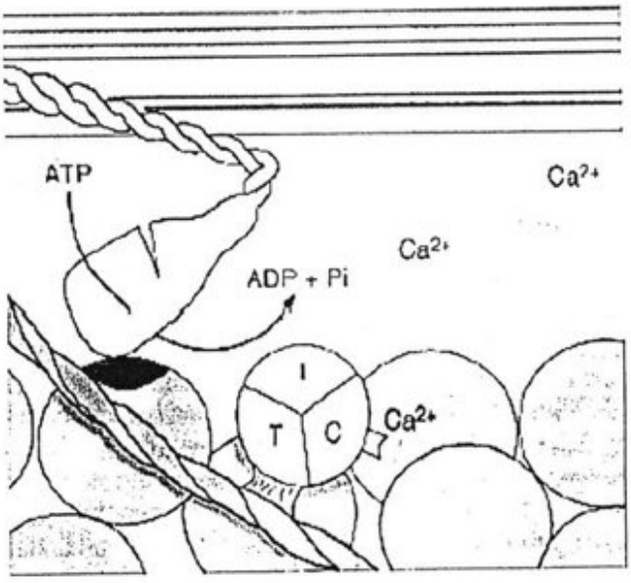
1. Discharge of motor nerve: Action potential reaches the end field nicotinic Ach receptors in the motor end plate.
2. Generation of end plate potential & AP: AP travels through the T-tubule to the interior of the muscle fiber. Depolarization of T-tubule activates the SR via dihydropyridine receptor. They are voltage gated channel and they serve as voltage sensor &cause release of ca from SR. The receptors in the SR is called ryanodin receptors which are not voltage gated. AP causes release of Ca^{2+} from SR to sarcoplasm. It is called Ca^{2+} pulse. Normally the concentration of Ca in sarcoplasm is less than 10^{-7} molar. Release of Ca from SR raises the Ca level to $2x10^{-4}$M.

Before contraction begins, the head of the cross bridge binds with ATPase activity of myosin head cleaves the ATP to ADP &P_i. In this state, conformational change in the head is such that it extends perpendicularly towards the actin filament but not attached to it.

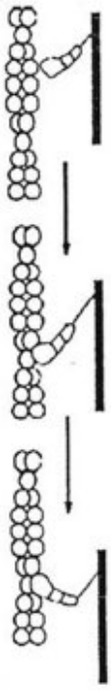


The Ca^{2+} in the sarcoplasm binds to troponin C. This leads to the weakening of the linkage between troponin I & actin. Tropomyosin moves laterally exposing the site of actin.7 active sites are exposed or uncovered for each molecule of troponin binds to Ca^{2+} cross-linkages are formed between actin and myosin leading to contraction. The process by which depolarization of muscle fiber initiate contraction is called excitation-contraction coupling & the linkage between these excitation & contraction is calcium.





When myosin head binds to the active site, the head tilts & forms power stroke for pulling the actin filament. It requires energy. Energy is already stored before contraction by cleaving ATP.



Once head of cross bridge tilts, this causes release of ADP &PI that were previously attached to the head & at the site of release of ADP, a new molecule of ATP binds. This binding causes detachment of myosin head from actin. ATP cleaved again to ADP &Pi and next cycle leading to new power stroke. The molecular basis of this contraction is called **Cross bridge Theory** or **Rachet Theory** or **Walk along theory.**

Relaxation: Shortly after releasing Ca^{2+}, the SR begins to reaccumulate it by ATP –mediated active transport of it into the longitudinal portions of the reticulum. The Ca^{2+} then diffuses to the terminal systems , where it is stored until released by the next AP. Once the Ca^{2+} concentration outside the reticulum had been lowered sufficiently, chemical interaction between myosin and action stops, and the muscle relaxes. Note that ATP provides the energy for both contraction and relaxation. If transport of Ca^{2+} to SR is inhibited relaxation does not occur even though there is no more AP.

Short Notes

1. Resting Membrane Potential-Ionic Basis:

During resting stage there is a steady or constant potential difference across the cell membrane. This steady potential is called RMP or Transmembrane potential. It is negative because the inside of the membrane is negative with reference to outside.RMP arises due to concentration gradient of ions across the cell membrane. RMP of a neuron is -70 mV

Ionic Basis:

RMP is devoloped by Diffusion potential and Activity of Na^+ - K^+ pump.

Diffusion

A large conc.gradient exist for ions across the resting cell membrane.Ratio of conc. of K^+ inside to outside is 140:4.So K^+ moves passively out of the cell through K^+ selective leak channels.More over the negative anion do not diffuse along with K^+.More over the negative anion do not diffuse along with K^+.Concentration of Na^+ outside is high when compared to inside(142:10).This result in passive movement of Na^+ in to the cell.Membrane permeabilty of K^+ is about 100 times greater than Na^+ and there more open K^+ channels than Na^+ channels at resting state.So there is slight excess of cations on the outside than anions inside.The diffusion potential that develop depend on

1) polarity of electrical changes of each ion
2) Permeability of membrane to each ion (P)
3) Concentration of respective ion inside (i) and outside (o).

According to Goldman Hodgkin–Katz equation, the membrane potential inside the membrane when two univalent positive ions Na and K and univalent negative ion Cl are involved is:

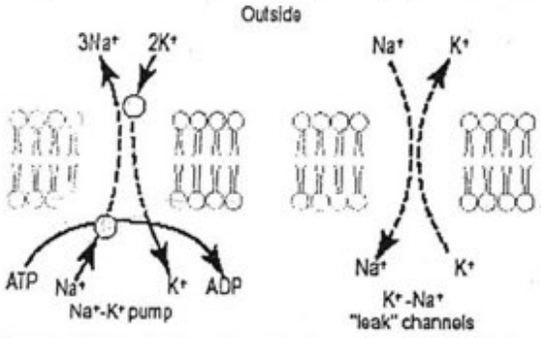
$-61\log(C\,Na_i\,P\,Na + C\,K_i\,P\,K + C\,Cl_o\,P\,Cl / C\,Na_o\,P\,Na + C\,K_o\,P\,K + C\,Cl_i\,P\,Cl)$.

According to this Equation the internal membrane potential is -86 mV which is nearer to the K potential. Permeability of Na and K channels undergoes rapid changes during transmission of nerve impulse where as that of chloride channels do not change greatly. Hence

the changes in K and Na permeability are primarily responsible for signal transmission in the nerve.

Contribution of Na^+ K^+ pump.

Na^+ - K^+ pump pumps $3Na^+$ to outside for each $2K^+$ pumped to inside. This create a -ve potential inside. Passive ion leaks are occuring for both Na^+ and K^+ along their conc.gradient. Na^+ - K^+ pump is an electronic pump which actively moves Na^+ and K^+ against their conc.gradient creating additional degree of negativity (-4 mV) inside.



Functional characteristics of the Na^+-K^+ pump and of the K^+-Na^+ "leak" channels. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

In short,

1) Na+ K+ leaky channels : -86 mV.
2) Na-K pump : -4 mV

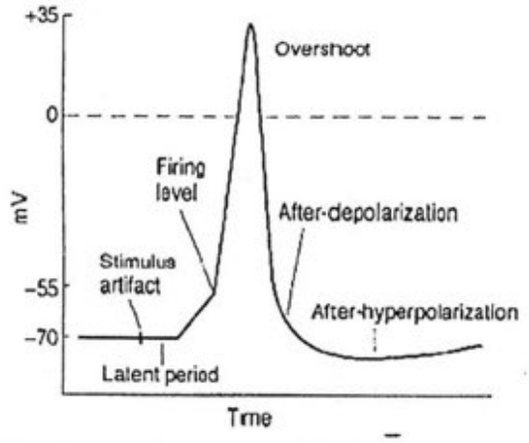
RMP= -86+-4 = -90mV(skeletal muscle fibre)

2.Action Potential and its Ionic Basis:

The brief sequence of changes occurring in the RMP of an excitable tissue following excitation is called action potential. Each action potential begins with a sudden explosive change from the normal resting membrane potential to a positive potential and then ends with an almost equal rapid change back to the negative potential

Action potential can be divided into 3 stages:-

1. Resting stage
2. Depolorization
3. Repolarization



Resting membrane potential of a neuron is -70mv. when a stimulus is applied ,there is a brief deflection of the base line. It is called Stimulus artifact. This is due to current leakage from the stimulating electrode to the recording electrode .It marks the point of stimulus.Stimulus artifact is followed by an isoelectric potential interval or latent period .It corresponds to the time taken by the impulse to travel along the axon from the site of stimulation to the recording electrode.Duration is propotional to the distance between he electrodes and inversely proportional to the velocity of conduction.Latent period end with the start of AP.

Depolarization or Reverse Polarization:

Reduction of the membrane potential from negative value towards zero & positive value.From 7-15mV there is non propagated potential changes occurs. After an initial 15mV depolarization ie, when the MP reaches -55mV the rate of depolarization increases suddenly. The point at which the change in rate occur is called firing level or threshold level. There after the tracing rises rapidly, then overshoot the zero potential line to approximately +35mV.This is depolarization.

Repolarization:

After reaching +35mV the MP falls rapidly towards the resting level.When the repolarization is about 70% completed, the rate of repolarization decreases and the tracing approaches the resting level more slowly. The sharp rise and fall are the spike potential. The slower fall at the end of spike potential is called after depolarization.Duration of after depolarization is 4ms.

After reaching the previous resting level, the tracing over shoots in the hyperpolarizing direction to form small but prolonged after hyper polarization. It is 1 to 2 mv & lasts about 40ms.if the nerve has repetitively conducting for a long time, the after hyperpolarization is usually quite large without charge in the rest of the action potential. The duration of AP in a mammalian neuron is not more than a few second. But in cardiac muscle fiber the duration is 200 -300msec.

Ionic basis:-

RMP: Is -70mV factors responsible for this are:
1.Na^+-K^+ leaky channels 2.Na^+-K^+ pump.(refer SN 1)

Depolarization: When we give threshold stimulus, there is initial 7 to 15 mv slow depolarization. This is due to the opening of some of the voltage-gated sodium channels. When it reaches -55mV (firing level).most of the voltage gated sodium channels open & there is rush of sodium ions into the cell through them.

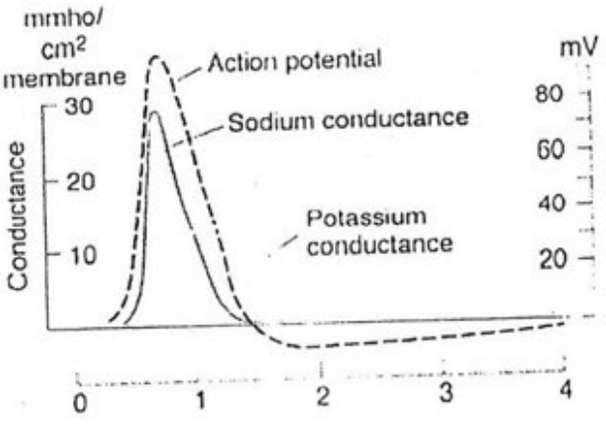
Sodium Channels-There are two gates-outer activation and inner inactivation gates. During resting condition activation gate is closed preventing the entry of Na+ in to the cell. When the membrane potential falls from -70 to-55 mV, conformational changes occur in the activation gate and it is fully opened this is called activated state. During this state there is an increased movement of Na into the cell through this channel and an increase in the Na permeability by 500-5000 folds.The same increase in voltage that opens the activation gate, closes the in activation gate.This occurs few 10000 of a second after the activation gate is opened. This closing of inactivation

gate is a slower process than the opening of the activation gate. As a result Na no longer can be poured into the cell. This causes repolarization and the membrane potential begins to recover back towards the RMP. Till reaching or nearly reaching the original RMP, inactivation gate will not open. Only after reaching the original resting level outer activation gate closes and inner inactivation gate opens.

Repolarization: It is due to decrease in Na^+ influx due to closure of Na+ channels and opening of voltage gated K^+ channels and K^+ efflux.

1. When firing level is reached, rush of Na^+ along the concentration and electrical gradient in to the cell occurs. The equilibrium potential for Na^+ by NERNST Equation is +61mV. But the membrane potential does not reach this value because increased Na^+ conductance is short lived and Na+ channel rapidly enter a closed state called the inactivated state and remain so for a few milliseconds before returning to the resting state.
2. The direction of electrical gradient of Na^+ is reversed during the overshoot and the membrane potential is reversed and this limits the Na^+ influx.
3. Opening of voltage gated K^+ channels – It has only one gate present inside the membrane. During resting condition it is in a closed state. When the membrane potential rises from -70 to 0mV, there is slow conformational change occurring in the K^+ gate. However because of the slowness of the opening of the K^+ gate, they open just at the same time the Na^+ channels are beginning to close (due to inactivation) .Repolarization is due to K^+ efflux. During after depolarization the K^+ efflux is slowed down. The cause of hyper polarization is that the K^+ channel takes time to close (slow return of K^+ channels to the closed state)

Changes in Na^+ and K^+ conductance during AP



Contribution of Na^+-K^+ Pump:

Even after restoration of RMP at the end of repolarization there may be slight concentration difference of K^+ and Na^+ inside and outside. There may be a slight excess of Na^+ inside and K^+ outside. So Na-K pump pumps three Na^+ ions out and two K^+ ions in reestablishing the RMP.

Role of Calcium in Na^+ Channel:

Calcium binds to the external surfaces of Na^+ channel. The positive charge of calcium alters the electrical state of the sodium channel altering the voltage level required to open the gate. A decrease in extra cellular calcium concentration increases the excitability of the nerve and muscle cells by decreasing the amount of depolarization. There fore hypocalcaemia causes spasm of muscles (tetany). Increase in extra cellular calcium stabilizes the membrane by decreasing the excitability.

3. Difference Between Action & Graded Potential:

Action Potential: It spreads over the membrane covering relatively much larger area and is propagating in nature i.e. it travels for considerable distance over the membrane without decrement. It is always a depolarizing potential. Summation of AP is never possible be cause it exhibits refractory period, so it obeys "All - or - None" Law. It is always a depolarization with an overshoot. It has a threshold that is usually 10-15mV depolarized relative to the resting potential. AP has a constant amplitude for a given cell.

Graded Potential: A change in the membrane potential confined to a relatively small region of the membrane and is non propagating in nature. It can be either depolarizing or hyperpolarizing potential. It shows graded response i.e. summation is possible. So its magnitude is proportional to the strength of stimulus i.e. it does not obey "All-or-None" Law. It has no threshold. It has variable amplitude, the size of the potential decreases with distance.

4. Refractory Period:

A new action potential cannot occur in an excitable tissue as long as the membrane is depolarized from preceding AP. It is called refractory period. During rising and falling faces of action potential, neuron is refractory to second stimulus. Two types of refractory period are there

1) Absolute refractory period (ARP)

It is the period during which no stimulus however strong it is , can produce an action potential. In the case of nerve, it begins from firing level up to one third of repolarization. In a large myelinated fibre it is about 0.4-1msec.

Causes of ARP:- Shortly after the initiation of action potential, sodium or calcium channels or both are inactivated. Inactivaton gates are closed.

No amount of excitatory signal applied to these channels at this point open the inactivation gates until MP reaches almost to the original RMP.

2) Relative refractory period: (RRP)

Stimulus stronger than normal can cause excitation. It starts from end of ARP to the star t of after depolarization. It is about ¼ to ½ of ARP.

Causes of RRP- some of the Na channels have not been reversed from their inactivated state. K channels are open at this time.

5. "ALL-OR-NONE" Law

All or none law states that, Once the threshold intensity is reached, a full – fledged action potential is produced. Further increases in the intensity of a stimulus produce no increment or other change in the action potential as long as other experimental conditions remain constant.it is applicable to a single fibre or cell only. The action potential fails to occur if the stimulus is sub threshold in magnitude, and it occurs with constant amplitude and form regardless of the strength of the stimulus if the stimulus is at or above threshold intensity. The action potential is there fore all are none in character and is said to obey the "All-or-None" Law.

6.Chronaxie & Rheobase:

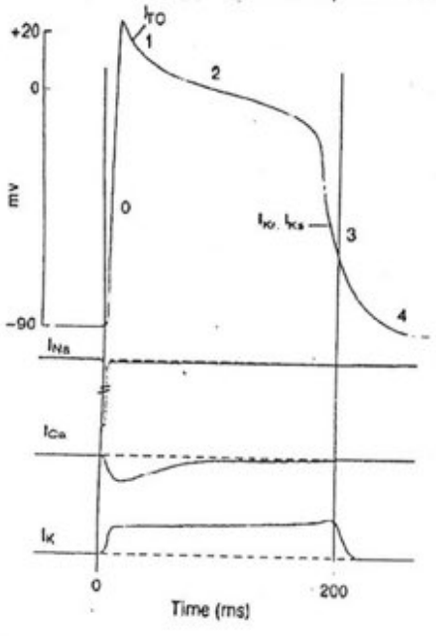
A stimulus of fixed duration is applied to a nerve and the current is increased until a response is obtained. This is the threshold intensity.

The minimum current intensity strength applied for an adequate time in a nerve fiber is called rheobase (strength of the current).Duration for which rheobase strength should be applied to produce an AP is called utilization time.

Time taken by the nerve to respond when twise rheobase intensity is applied is called chronaxie.

7. Plateau Potential:

In some instances the excitable membrane does not repolarise completely after depolarization. Instead the potential remains on a plateau near the peak of the spike for many milliseconds and then final repolarization occurs. This is called plateau type of action potential.



There are five phases-0, 1, 2, 3&4

Phase 0-initial rapid depolarization. It is due to the opening of voltage gated sodium channels and explosive entry of Na^+ in to the cell.

Phase 1- initial rapid repolarization. It is due to the closure of Na^+ channels and opening K^+ channels(K^+ efflux).

Phase 2- is the plateau phase. It is due to a slower but prolonged opening of voltage gated calcium channels through which Ca^{2+} and Na+ enter in to the cell and K^+ efflux through K^+ channels.

Phase 3- final rapid re polarization due to closure of cacium channels and delayed K^+ efflux through various type of K^+ channels.

Phase 4- resting membrane potential

Cardiac muscle exhibit plateau potential.

8. Classification of nerve fibers:

Nerve fiber types in mammalian nerve.[1]

Fiber Type	Function	Fiber Diameter (μm)	Conduction Velocity (m/s)	Spike Duration (ms)	Absolute Refractory Period (ms)
A					
a	Proprioception; somatic motor	12-20	70-120		
ß	Touch, pressure	5-12	30-70	0.4-0.5	0.4-1
	Motor to muscle spindles	3-6	15-30		
d	Pain, cold, touch	2-5	12-30		
B	Preganglionic autonomic	<3	3-15	1.2	1.2
C					
Dorsal root	Pain, temperature, some mechano-reception, reflex responses	0.4-1.2	0.5-2	2	2
Sympathetic	Postganglionic sympathetics	0.3-1.3	0.7-2.3	2	2

[1] A and B fibers are myelinated; C fibers are unmyelinated.

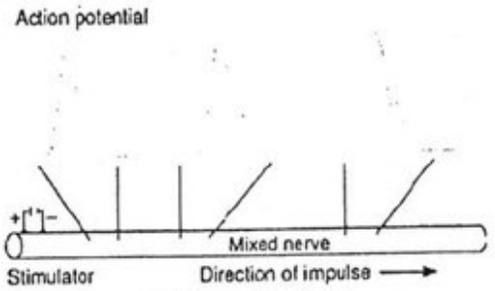
Numerical classification sometimes used for sensory neurons.

Number	Origin	Fiber Type
Ia	Muscle spindle, annulospinal ending.	.A a
Ib	Golgi tendon organ.	A a
II	Muscle spindle, flower-spray ending; touch, pressure.	A ß
III	Pain and cold receptors; some touch receptors.	A d
IV	Pain, temperature, and other receptors.	Dorsal root C

9. Compound Action Potential:

It is a property of a mixed nerve. Multipeaked action potential is compound action potential. Cause: Mixed nerve is made up of nerve fibers with different diameters and conduction velocities. When all the fibers are stimulated, the activity in fast conducting fibers reach at the recording electrode faster than that of slow fibers. If the APs are recorded farther away from the stimulating electrode, the separations between the fast and slow fiber peaks become greater. The number and size of the peaks

depends upon type of nerve fibers present in the stimulated nerve. In general, GpA fibers make maximum contribution to compound action potential and GpC fibers the least.



10.Types of Muscle Fibre:

Table 3-3. Classification of fiber types in skeletal muscles.[1]

	Type I	Type II
Other names	Slow; oxidative; red	Fast; glycolytic; white
Myosin isoenzyme ATPase rate	Slow	Fast
Ca^{2+}-pumping capacity of sarcoplasmic reticulum	Moderate	High
Diameter	Moderate	Large
Glycolytic capacity	Moderate	High
Oxidative capacity (correlates with content of mitochondria, capillary density, myoglobin content)	High	Low

Muscles containing many type I fibers are red muscles because they are darker than other muscles. They respond slowly, have a long latency, and are adapted for long, slow, posture maintaining contractions. The long muscles of back are red muscles. White muscles , which contain mostly type two fibers have short twitch durations and are specialized for fine , skilled movement. E.g.: Extra ocular muscles

11.Sarcotubular System:

Myofibrils are surrounded by structures made up of membrane that appear as vesicles and tubules under electron microscope.It is together called sarco tubular system. It has two parts

1) T-System
2) Sarcoplasmic reticulum

T-tubular system

They are inwardly directed extension of sarcolemma into muscle fiber at the junction of A and I band. Each tubule is 30 nm wide and their lumen is continuous with the ECF.They penetrate from one side of muscle fibre to the opposite side.Space inside the T-tubule is an extension of extracellular space containing ECF.In mammmalian sk.ms there is 2T tubules for each sarcomere.In lower animals like frog and in mammalian cardiac ms ther is single T-tubule for each sarcomere.MembraneT-tubule contains receptors called dihydropyridine receptors which are voltage gated calcium channels. Their function is rapid transmission of action potential from cell membrane to all myofibrils in the muscle. This receptor also serves as voltage sensor and cause release of Ca^{2+} from SR.

Sarcoplasmic reticulum

On either side of the t- tubules there are SR.SR is an extensive endoplasmic reticulum.It has 2 parts,

1.Longitudinal tubules:- that run parallel to myofibrils and surround them on all sides.

2.Terminal cisternae:-large chambers in which longitudinal tubules terminate is called terminal cisternae.They are in close contact with T system at the junction of A- I band. This contain Ca^{2+} release channel called ryanodin receptors.

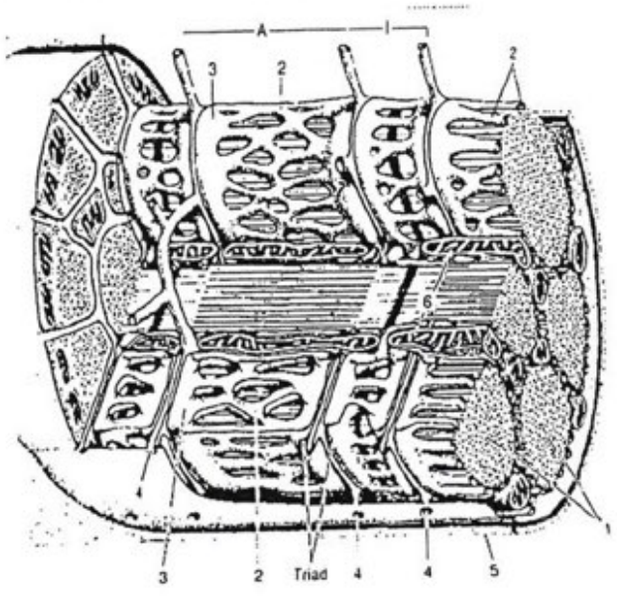
⊗Each sarcomere contain two sarco tubular system

⊗Triad- T-tubule and two terminal cisternae constitute triad

Functions of SR:

-Stores Ca^{2+} and relese during muscle contraction.

-Sequestration and storage of Ca^{2+} during muscle relaxation.A Ca^{2+} pump SERCA pump is located inthe walls of SR for pumping away of Ca^{2+} from sarcoplasm in to SR.Inside the SR is a protein called Calsequestrin,it can bind with Ca^{2+} and keep it stored.



Mammalian skeletal muscle.(1)The cut surface of the myofibrils shows the arrays of thick and thin filaments.The sarcoplasmic reticulum (2) with its terminal cisternae (3) surrounds each myofibril.The T system of tubules (4),which invaginates from the sarcolemma,contacts the myofibrils between the A and I bands twice in every sarcomere.The T system and the adjacent cisterns of the sarcoplasmic reticulm constitute a triad.A basal lamina (5) surrounds the sarcolemma.(6) mitochondria

12. Walk Over Theory: (refer essay 1,include diagrams of essay 1)

Muscle contraction is the result of the thin filament at each end of the sarcomere sliding over the thick filament towards the centre.

During resting stage, troponin I is tightly bound to actin and troponin- tropomyosin complex covers the active site of actin. This troponin-tropomyosin complex prevents the interaction between myosin head & actin. Therefore troponin & tropomyosin are together called relaxing proteins

Events leading to contraction & relaxation of SKM:

1. Discharge of motor nerve: Action potential reaches the end field nicotinic Ach receptors in the motor end plate.
2. Generation of end plate potential & AP: AP travels through the T-tubule to the interior of the muscle fiber. Depolarization of T-tubule activates the SR via dihydropyridine receptor. They are voltage gated channel and they serve as voltage sensor &cause release of Ca from SR. The receptors in the SR is called ryanodin receptors which are not voltage gated. AP causes release of Ca from SR to sarcoplasm. It is called **Ca pulse**.

Before contraction begins,myosin head binds with ATP and cleaves the ATP to ADP &P_i.but cleavage products are bound to head. In this state myosin head extends perpendicularly towards the actin filament but not attached to it and said to be in a cocked position..

When an AP comes sarcoplasmic Ca^{2+} increases. The Ca^{2+} in the sarcoplasm binds to troponin C. This leads to the weakening of the linkage between troponin I & actin.Tropomyosin moves laterally exposing the site of actin.7 active sites are exposed or uncovered. For each molecule of troponin binds to ca cross-linkages are formed between actin and myosin leading to contraction. The process by which depolarization of muscle fiber initiate contraction is called **excitation-contraction coupling** & the linkage between these excitation & contraction is calcium.

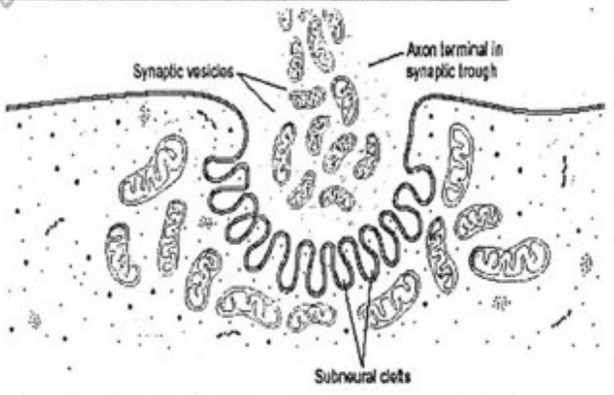
This binding simultaneously cause change in intra molecular forces between head and arm of cross bridge.This causes head to tilt towards the arm and the actin filament is dragged along with it relative to the myosin filament.This tilt of head is called power stroke for pulling the actin filament. It requires energy. Energy is already stored before contraction by cleaving ATP.Tilting of head causes release of ADP and Pi that were previously attached to the head.

A new molecule of ATP quickly binds to the myosin head. This binding causes detachment of myosin head from actin. ATP cleaved again to ADP &Pi ,this energy released cause a recocking of myosin head to its perpendicular direction and ready to bigin a new power stroke cycle.As long as Ca^{2+} remains elevated and sufficient ATP is available, the cycle is repeated.

13. Role of Calmodulin in Smooth Muscle Contraction:

In smooth muscles, Ca^{2+} binds to calmodulin, and the resulting complex activates calmodulin-dependent myosin light chain kinase. This enzyme catalyses the phosphorylation of the myosin light chain on serine residues at position 19. The phosphorylation increases the ATP activity. Relaxation of the muscle presumably occurs when the Ca^{2+}-Calmodulin complex finally dissociates.

14. Neuromuscular Junction:



It is a junction between motor nerve and skeletal muscle fibre.

Structure:

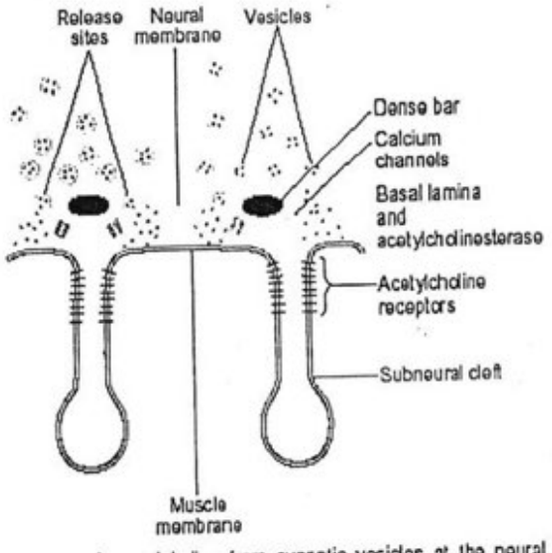
At termination, the axon supplying the skeletal muscle fibre loses its myelin sheath and divides into a number of terminal buttons or end feet which fits into depressions in the motor end plate - thickened portion of the muscle membrane at the junction. This depression in the motor end plate is called synaptic gutter.

Space between the end feet(nerve terminal) and the motor end plate(thickened muscle membrane) is called synaptic cleft. It is about 20-30 nm wide at the bottom of the gutter.There are numerous folds of muscle membrane called sub neural cleft which increases the surface area at which synaptic transmitter can act. The whole structure is known as neuromuscular or myoneural junction.

End Feet(Axon Terminal):– It contains large number of mitochondria which produces ATP for the synthesis of excitatory neuro transmitter Ach. There are $3x10^7$ vesicles per nerve terminal .Each vesicle measures 30-40 nm. Vesicle contains excitatory neuro transmitter Ach. The Ach is synthesized in the cytoplasm of nerve terminal from choline and acetate catalyzed by choline acetyl transferase found in the cytoplasm of cholinergic neurons. Then it is taken into synaptic vesicles by vesicular transporter. Inside the surface of neural membrane there are linear dense bars. On both sides of the dense bars there are voltage gated calcium channels.

In synaptic space large quantities of enzyme Acetyl choline esterase is seen It is capable of distroying Ach after it relaesed from synaptic vesicles.

Motor End Plate:–The muscle membrane forms numerous folds called sub neural clefts. There are two types of acetyl choline receptors – muscarinic receptors i.e. seen in smooth muscles and glands and –nicotinic receptors seen in NMJ, autonomic ganglia and CNS. This nicotinic receptors are located near the mouth of sub neural cleft lying immediately near the dense bar areas.Each acetyl choline receptor is a protein complex containing five sub units two alpha, one beta, one gamma and one delta. Each alpha sub units contain binding site for Ach. Binding causes conformational changes in the acetyl choline receptors which causes opening of the channels and sodium influx.



Release of acetylcholine from synaptic vesicles at the neural membrane of the neuromuscular junction. Note the proximity of the release sites in the neural membrane to the acetylcholine receptors in the muscle membrane, at the mouths of the subneural clefts.

15.Neuromuscular Transmission:

Sequence of events during N-M transmisson

- When a nerve is stimulated, impulse or action potential reaches the nerve terminal.
- Opening of the voltage gated calcium channels and large quantities of calcium diffuse from the synaptic space to the nerve terminal.
- Calcium attracts acetyl choline vesicles to the neural membrane adjacent to the dense bar.
- Vesicles then fuse with the neural membrane and empty the acetyl choline onto synaptic space by exocytosis.
- From the synaptic space, acetyl choline binds to nicotinic acetyl choline receptors in the mouth of the sub neural clefts of the motor end plate.
- Binding of ACh to the receptor opens the ACh gated Na channels and allow large no of Na influx.
- This Na influx produces a local depolarising potential-end plate potential.This local potential inturn generate AP. Normally this EPP is sufficient to depolarize the adjacent muscle membrane to the firing level.
- AP are conducted along the muscle fibre which inturn causes muscle contraction.

The released Ach continues to activate the Ach receptors as long as it persists in the synaptic space. So it should be removed rapidly. Most of the Ach is destroyed by Ach esterase present in the fine connective tissue that fills the synaptic space.

16.Diseases of Neuromuscular Junction:

Myasthenia gravis:A serious, sometimes fatal disease characterised by weakness and easy fatiguability of skeletal muscles. It is due to the formation of circulating antibodies against nicotinic acetyl cholinergic receptors in motor end plate. The antibody is produced by B-lymphocyte because of the disorder of thymus gland.Abs cause distruction and endocytosis of ACh receptors.

Clinical features:-

- Usually appears between 15&50 years.
- Females are most affected.
- Main symptom is fatigue of muscles.
- Ptosis & diplopia are the first symptoms
- Weakness of swallowing movements, speech and in movements of limbs especially shoulder girdle
- Cause of death is mainly due to respiratory paralysis.

Treatment:Drugs that inhibit Ach esterase.For e.g. Pyridox pigmine.

Lambert Eaton Syndrome:

Resembles myasthenia gravis. Here, muscular weakness is due to antibodies against calcium channel in the nerve ending at the NMJ. This leads to decreased calcium influx and decreased Ach release.

17. Antidromic and Orthodromic Conduction:

An axon can conduct in either direction. In a living animal, impulses normally pass in one direction only, i.e., from synaptic junctions or receptors along axons to their termination. Such conduction is called orthodromic. Conduction in the opposite direction(towards the cell body) is called antidromic. Since synapses, unlike axons, permit conduction in one direction only, any antidromic impulses that are set up fail to pass the first synapse they encounter and die out at that point.

18. Motor Unit (MU):

The axon of spinal motor neuron divide to branches to innervate several sk.ms fibres.Single motor neuron and muscle fibers it innervates, constitute a motor unit. It is the smallest part of the muscle that can be made to contract independently by neural stimulation.

The number of muscle fibers in the motor unit varies according to the precision of the movement. In muscles concerned with fine skilled and precise movements, the number of muscle fibers in each motor unit is less (only 3 to 6 fibers/MU) E.g.: eye muscle.Some other MU contai more muscle fibers e.g.: limb muscles (more than 200

muscles fib/MU in gastronemius muscle).Recruitment of MU–With minimum voluntary activity, a few MU discharges and with increased voluntary activity more MU discharges.

Each spinal motor neuron innervates only one kind of muscle fibre i.e.,all the muscle fibres in a motor unit are of the same type.All the muscle fibres of a motor unit contract and relax togethe,but all of them are not found together;instead they are dispersed throughout the muscle.

When a motor nerve to the SKM is cut it is LMN type of paralysis. It cause atrophy of SKM, complete paralysis of the muscle; fine, irregular contraction of muscle fiber, abnormal excitability of the muscle.

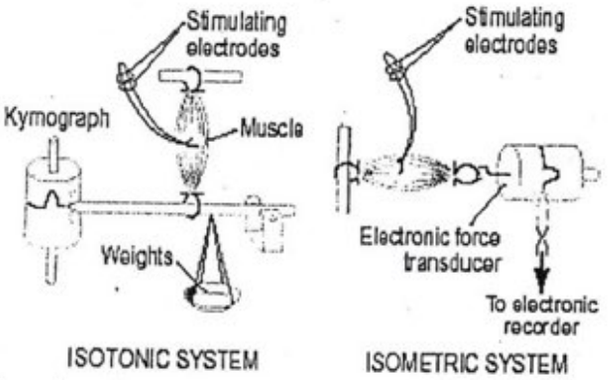
19. Isometric & Isotonic Contraction:

Isometric contraction – Means same length. There is no shortening of muscle during contraction. Tension is increased during contraction. No work is done here. Heat production is more. E.g.: muscle that maintain posture and gravity, contraction of muscle when tried to push against a wall trying to lift heavy weight

Isotonic contraction - Means same tension. Shortening of muscle during contraction is there so it does some work; heat produced is less. E.g.: lifting up a weight with the hand and shortening of biceps

CVS changes

ISOTONIC	ISOMETRIC
Increased heart rate	Increased heart rate
SBP increases moderately	BothSBP and DBP increases
DBP same or decreases	Blood flow decreases
SV increases markedly	SV changes relatively
PR decreases	PR increases



ISOTONIC SYSTEM ISOMETRIC SYSTEM

Isotonic and isometric systems for recording muscle contractions.

20. Rigor Mortis:

It is the post mortem stiffening. When muscle fibers are completely depleted of ATP and Phosphoryl creatine, they develop a state of rigidity called rigor. When this occurs after death , this condition is called rigor mortis. In rigor, all most all of the myosin heads attach to actin but in an abnormal, fixed and resistant way.

21. WallerianDegeneration or Anterograde Degeneration:

Changes in the axon distal to injury.

- up to 3 days after section, distal axon continues to conduct impulse.
- after 3 days conduction of impulse deteriorates seriously.
- after 5 days, an impulse can no longer be evoked.

Changes in the axon-

Shortly after the nerve has been cut, axon swells up, become irregular in shape & within few days, it breaks up into small fragments.

Changes in myelin sheath

Myelin sheath breaks into small fragments. it undergo hydrolysis by the enzyme released from Schwann cell & macrophages & is replaced by fatty droplets. Myelin degeneration begins by 8th day & is completed by 32 days after injury.

Changes in neurilemma-

Neurilemma remain intact.The Schwann cell increase in size & multiply in number.Schwann cells act as macrophages & remove the remnants of axon & myelin sheath.

Ultimately, a hollow tube with large number of phagocyte digesting ingested materials remain .such a tube is called a host tube.

22. Reterograde Degeneration:

Degeneration proximal to injury. Changes are similar to anterograde degeneration. Cell body enlarges, become spherical, and swells. Nissle's granules undergo degeneration. This phenomenon is called chromatolysis. In severe cases it ends in cell death.If cell survives, changes reverses after a period of time.

Physiological basis:

1.Tetanus not possible in cardiac muscle.

Tetanus to be occur, the second stimulus should fall during the contraction phase of previous one.In cardiac muscle whole systole is in ARP(Absolute refractory period).Refer shortnote-4 CVS

2.A nerve does not respond if stimulus is applied during diastole.

Refer shortnote-4.During rising and falling faces of action potential, neuron is refractory to second stimulus

3.Parathyrodectomy leads to signs of neuromuscular hyperexcitability.

Hint-C ı plays a major role in skeletal muscle relaxation

Central Nervous System

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ESSAYS

1.Properties of synapse & synaptic inhibitions

Synaptic Inhibitions:

1.postsynaptic inhibition:

It results from deivery of an inhibitory transmitter by the incoming axon which hyperpolarise the postsynaptic membrane.it is of 2 types

a.Direct inhibition:

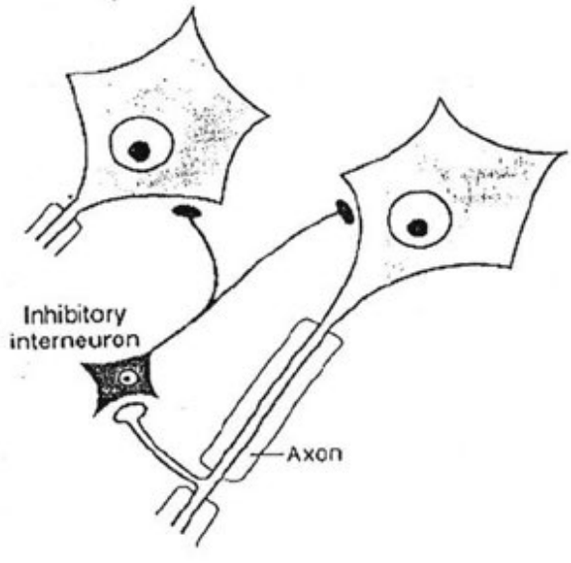
Post synaptic inhibition during the course of an IPSP is called as direct inhibition because it is not a consequence of previous discharges of postsynaptic neuron.

Afferent fibres from the muscle spindles (stretch receptors) in skeletal muscle are known to pass directly to the spinal motor neurons of the motor unit supplying the same muscle. Impulses in this afferent supply cause EPSP. At the same time, IPSP's are produced in motor neurons supplying the antagonist muscle mediated by branches of afferent fibres that end on Golgi bottle neuron.This is also called as reciprocal innervation.

b.Indirect inhibition

Inhibition due to effects of previous postsynaptic neuron discharge.It may be due to

- postsynaptic neuron c an be refractory to excitation because it has just fired and is in refractory period
- During afterhyperpolarisation
- Renshaw cell inhibition:
- **Negative feedback inhibition (Renshaw cell inhibition)**



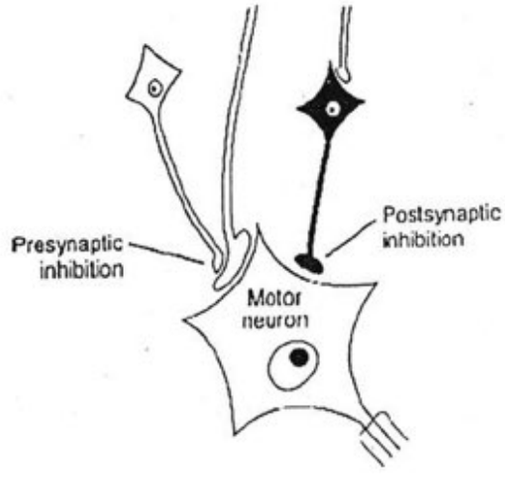
Neurons may inhibit themselves in a negative feedback fashion. Spinal motor neurons regularly give off recurrent collateral which synapses with an inhibitory interneuron that terminates on the cell body of the spinal neuron and other spinal motor neuron. Impulses generated in the motor neuron activate the inhibitory interneuron to secrete inhibitory mediator and this slows or stops the discharge of the motor neuron. This form of inhibition is regularly used to check the over discharge from neurons.

2.Presynaptic inhibition

This is a process mediated by neurons that end on excitatory endings forming axo-axonal synapses. Activation of the receptors mediating presynaptic inhibition reduces the amount of neurotransmitter released. This can be either in 3 of the ways which reduces action potential:

- Increased opening of Cl channels
- Decreased opening of K^+ channels
- Less opening of voltage gated Ca^{2+} channels

So Ca^{2+} influx is reduced and fewer transmitters released and thus the action potential is reduced. Presynaptic inhibition due to descending pathways that terminate on afferent pathways in the dorsal horn may be involved in the gating of pain transmission.



Feed forward inhibition

This type of inhibition is seen in the cerebellum. flask shaped cells called pukinje cells and small cells called basket cells in the cerebellum.The basket cell act as inhibitory interneurons.When impulses passes through the afferent nerve both basket cells and purkinje cells are stimulated.But basket cells inturn inhibit purkinje

cells.Thus duration of discharge by purkinje cell is reduced and output discharge from purkinje is controlled.This type of inhibition is feedforward inhibition.

Properties of synapse:

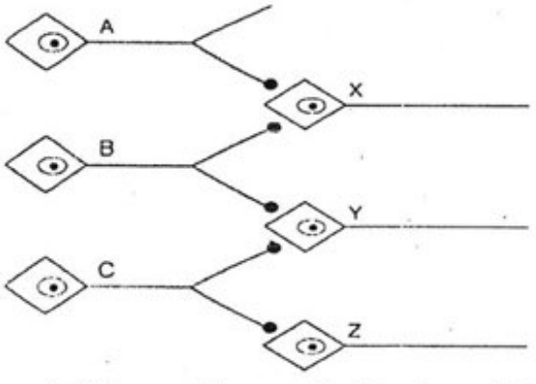
1.Synaptic delay

When an impulse reaches the presynaptic terminals there is an interval of at least 0.5 ms called as the synaptic delay before a response is obtained in the post synaptic neuron. The delay following maximal stimulation of the presynaptic neuron corresponds to the latency of the EPSP and is due to the time it takes for the synaptic mediator to be released and to act on the membrane of the postsynaptic cell.

Since the minimum time for transmission across one synapse is 0.5ms it is also possible to determine whether a given reflex pathway is monosynaptic or polysynaptic by measuring the delay in transmission from the dorsal to the ventral root across the spinal cord.

2.Summation and occlusion

In a hypothetical example, neurons A and B converge on X, and neuron B diverges on X and Y. A stimulus applied to A or to B will set up an EPSP in X. If A and B are stimulated at the same time, 2 areas of depolarization will be produced in X and their actions will sum. The resultant EPSP in X will be twice as large as that produced by stimulation of A or B alone, this effect is called as summation.



In this case Y has not fired but its excitability has been increased, and it is easier for activity in neuron C to fire Y during the EPSP. So Y is said to be in the subliminal fringe of X ie, neurons are in the subliminal fringe if they are not discharged by an afferent volley (not in the discharge zone) but do have their excitability increased.

If neuron B is stimulated repetitively X and Y will discharge as a result of temporal summation. If C is stimulated repetitively Y and Z will discharge. If B and C are fired repetitively at the same time, X Y and Z will discharge.Thus the response to stimulation of B and C together is not as great as the sum of responses to B and C separately because B and C both end on neuron Y. This decrease in expected response, due to presynaptic fibres sharing postsynaptic neurons is called occlusion.

3.Synaptic plasticity

Long term changes in synaptic function can occur as a result of continuous discharge at a synapse; ie, synaptic conduction can be strengthened or weakened on the basis of past experience.

Post tetanic potentiation

This is one form of plastic change which is the production of enhanced postsynaptic potentials in response to stimulation. The tetanising stimulation causes Ca^{2+} to accumulate in the presynaptic neuron to such a degree that the intracellular binding sites that keep cytoplasmic Ca^{2+} low are overcome.

4.Habituation

When a stimulus is benign and is repeated over and over, the response to the stimulus gradually disappears which is called habituation. This is associated with decreased release of neurotransmitter from the presynaptic terminal because of decreased intracellular Ca^{2+} due to gradual inactivation of Ca^{2+} channels. It can be either short term or prolonged.

5.Sensitization

It is the prolonged occurrence of augmented postsynaptic responses after a stimulus t which an animal has become habituated is paired once or several times with a noxious stimulus. Sensitization is due to presynaptic facilitation.

6.Long term potentiation

It resembles post tetanic potentiation but is more prolonged and can last for days. It is a rapidly developing persistent enhancement of the response to synaptic transmission produced by brief, repetitive activation of postsynaptic neurons. This is due to an increase in the intracellular Ca^{2+} in the postsynaptic neuron rather than the presynaptic neuron.

7.Long term depression

It is a condition which is opposite to that of long term potentiation. It occurs when neurons are partially depolarized by afferent input, but not as much as the approximate threshold required for permitting Ca influx. For example in cerebellum simultaneous firing of climbing and parallel fibres causes a long term depression of conduction of the parallel fibre.

2. Touch receptors & pathway:

Dorsal Column(posterior column) pathway:

These tracts are present in the posterior funiculus. Also as tract of Goll (situated medially) and tract of Burdach (situated laterally).

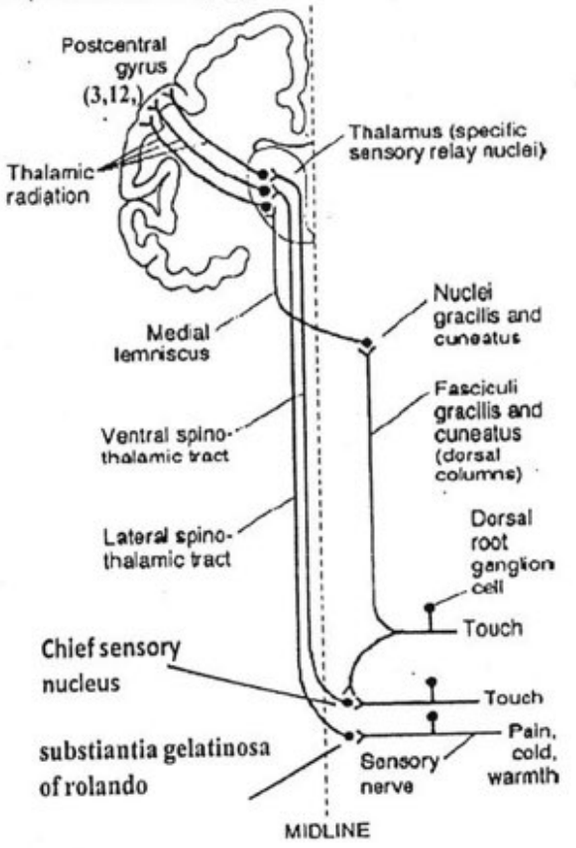
Sensations carried: epicritic sensations –

1.Fine touch
2.Tactile localization

3.Tactile discrimination
4.Stereognosis.

These tracts also carry vibration sense and kinaesthetic sense. The latter is the sense of position and movement of diff parts of the body.

Receptors: Receptors, free nerve endings, Pacinian corpuscles, Ruffini's end organ, merkel's disc (refer receptors short note), Iggodome receptors.



Course:

Fibres are mainly A-α, A-β. 1st order neurons is in the cell body of the dorsal root ganglion. Their peripheral process supplies the receptors and the central process enters the SC and constitutes the posterior column. The fibres enter the SC through the medial division of the posterior nerve root. Then enter the posterior white column of the same side and ascends in the posterior column. These synapse in the medulla with the neurons in the nucleus gracilis and nucleus cuneatus, i.e. tract of Goll with nucleus gracilis medially, and tract of Burdach with nucleus cuneatus laterally. 2nd order neuron is in the cells of nucleus gracilis and cuneatus and fibers of the second order neurons arise from fasciculus gracilis begins at the lowest level of SC (sacral segment) and carries fibres from the lower limbs while tract of Burdach is evident from mid thoracic region and they contain fibres from upper thorax and cervical segments. Fibres entering spinal cord get pushed medially as they ascend up in the spinal cord. So the fibre arrangement from the medial to lateral i.e. sacral to cervical. First order neurons are uncrossed. Second order neurons arising from nucleus gracilis and cuneatus. (They form internal arcuate fibres.) across the midline forming chief sensory decussation and ascends in the medial lemniscus to end in the ventroposterior nucleus and related specific sensory nucleus in thalamus, ascends up to cortex, passing first in the posterior limb of internal capsule, then in corona radiata to end in post central gyrus, i.e. primary sensory cortex or area 3, 1, 2.

Sensation from face:

They are carried by sensory root of trigeminal nerve. First order neuron cell ody is in the trigeminal ganglion. All the sensations are carried by ophthalmic, maxillary and mandibular branch of trigeminal nerve; i.e. by the peripheral processes of the first order neuron in the trigeminal ganglion. The central processes enter the pons through the sensory root of trigeminal nerve. Fibres end in the sensory nucleus. Sensory nucleus has 3 parts:

- Mesencephalic nucleus
- Main sensory nucleus
- Spinal nucleus

Fibres that convey sensations of touch, tactile localisation and discrimination, sense of position, movement and vibration sense end in the main sensory nucleus. Fibres arising from the main sensory nucleus cross to the opposite side and pass up along TG lemniscus to the posteroventral nucleus of thalamus. Third order neurons are present here and there; fibres pass through posterior limb of internal capsule and corona radiata and reach the sensory cortex in the post central gyrus.

Sensory fibres carrying pain and temperature from face arising from the first order neuron in the trigeminal ganglion descend from the pons through medulla and spinal cord synapsing with neurons in the spinal nucleus of trigeminal nerve. Spinal nucleus corresponds to the substantia gelatinosa. Fibres from the spinal nucleus cross to the opposite side, ascend up in the SC and medulla and reaches the trigeminal lemniscus from there to the posteroventral nucleus of thalamus and then to the sensory cortex.

Fibres convey proprioceptive impulses from muscles of mastication and ocular muscles enter the pons and ascend to the Mesencephalic nucleus (first order neuron). This is the only instance where the sensory pathway is within the brain. From the Mesencephalic nucleus, fibres leave, cross to the opposite side, ascends in TG lemniscus and ultimately relay to the sensory cortex.

Functions of dorsal column:

- Proprioception: Muscle spindle length, muscle tension, Pacinian corpuscle around joints, ligaments and capsule, synovial membrane.

Divided into 2 types:

1.Conscious: carried by dorsal column
2.Unconscious / Sub conscious: do not reach cerebral cortex

They mainly reach cerebellum via dorsal and ventral spinocerebellar tracts. They help to control muscle tone and body posture.

Position sense:

1.Static position sense which means conscious perception of orientation of different parts of the body w.r.t one another.

2.Kinesthesia /Dynamic Proprioception: Movement sensation. Receptors are: Skin receptors, joint receptors, muscle spindle, Pacinian corpuscle.

Synthetic sense:

Cutaneous sensations for which separate neural pathways are touch, warmth, cold, pain and probably itching. The combinations these sensations and patterns of stimulation and some cases cortical components are synthetic sensation.

E.g.: vibration, two point discrimination, Stereognosis.

Vibration sense carried by the dorsal column. Receptor for high frequency vibration respond up to 700 vibrations / sec. Meissner's corpuscle respond to low frequency vibration less than 200 cycles per second. These vibrations are called clutter vibrations. The pattern of rhythmic mechanical stimuli is identified as vibration sense.

Stereognosis, two point discrimination refer short notes.

Degenerations of dorsal columns is seen in conditions like poorly controlled diabetes mellitus, pernicious anaemia and some vitamin deficiency can result in impairment of vibration sense and usually accompanied by decreased Proprioception also.

NB: The Na^+ channel, BNCI is closely associated with touch receptors.

This channel is one of the when over expressed results in degeneration of neurons in which they are present.

Crude touch by anterolateral system;

a)Anterior Spinothalamic tract:

Carries the sensation of crude touch.

Receptor: Mainly Pacinian corpuscle, but some touch receptors also contribute.

Course: First order neuron is present in dorsal root ganglion. Peripheral process innervates the receptor and central process enters spinal cord through medial division of posterior nerve root. Reach the posterior horn and synapse with chief sensory nucleus neurons in the dorsal horn.

Second order neurons are present here and their fibre cross to the opposite side in the anterior white Commisure, reach anterior funiculus opposite and ascend up as anterior Spinothalamic tract.

Fibres reach medulla, then joins with LSTT to form spinal lemniscus which ascends along the brain stem, reaches thalamus and relays in posteroventral nucleus of thalamus. From there the third order neuron passes through posterior limb of internal capsule and through corona radiata to areas 3, 1, 2 of cerebral cortex.

Touch sensation has dual pathway. So lesions of ASTT causes only slight loss of touch mainly crude touch.

b)Lateral Spinothalamic tract:

It carries fibres of all types of pain,temperature,itch&tickling sensation.(discussed in essays 3&4)

3. Temperature Pathway: (Diagram refer essay 2)

It is carried by Lateral Spinothalamic tract.

Receptors:

Cold	Krause's end bulb
Warm	Ruffinis End organ

Cold receptors are stimulated by temperature [10-38°C], while warm receptors are stimulated by temperature 30->45°C

These receptors are now also described as specialized nerve endings or modified nerve endings. On the skin, separate cold sensitive and warm sensitive spots have been described. Ten times more cold spots than warm spots are present.

Afferent:

Cold	Aδ and C fibers
Warmth	C fibers

Thermal sensation is said to have different gradations.

Cold - freezing cold, cold and cool

Heat - warm, hot and burning hot

-Similarly their receptors can be described as cold receptors, warm and pain. Pain receptors are stimulated by extremes of temperature.

-More cold spots are present in finger tips, lips and less in trunk.

-Warm: mainly by C fibers, receptors may be free nerve endings also.

-If by experimental procedures, fibers are stimulated, there are 4 types of fibers.

cold pain	less than15°C
cold receptors	7-42°C
warmth receptors	30-50°C
heat pain	greater than 45°C

Mechanism of thermal sensation being elicited is believed to be due to changes in metabolic rate produced by cold or warmth condition which alters the rate of intracellular chemical reactions. Spatial summation of thermal sensation occurs when large area of skin or entire body is stimulated all at once. Signals summate and even a small change in temperature can be detected. Temp changes 100 times greater will not be detected if the skin affected is less than 1 cm sq size.

Another group of receptors:

1.VR 1 – Vanilloid receptor which responds to vanillin .Vanillins are a group of compounds that cause pain. This includes capsaicin. VR 1 responds to capsaicin and temp > 43°C and protons (K^+ etc).

2.VRL 1 – Another receptor which responds to temp >50'C but not to capsaicin. This has been isolated from C fibres and shows that there may be many type of receptors on single peripheral C fibre ending. So there may be many C fibre systems also.

3.CMR 1 – Cold and menthol sensitive receptors.

LATERAL SPINOTHALAMIC TRACT

1st order neurons in the dorsal root ganglion:

Central process enters spinal cord (SC) via lateral division of posterior nerve root. It ascends or descends for a short distance between the tip of posterior horn and periphery of the cord before ending in the cells of substantia gelatinosa of Rolando. This short tract is called Lissauer's tract.

Temperature sensation is carried by two groups of fibres – A-delta & C fibres, and they synapse with neurons in lamina 1 and 5 for A –delta and lamina 1 & 2 for C fibres, i.e. subs gelatinosa of Rolando of dorsal horn.

2nd order neurons arise from subs gelatinosa of Rolando and cross to the opposite side in anterior commissures (temp carrying fibres take a more oblique course whereas pain fibres cross to the opposite side in the same segment) reaches lateral funiculus and ascends as lateral Spinothalamic tract.

Cervical fibres are kept more medially and sacral fibres are more laterally.

In medulla LSTT is seen separate and in the pons and midbrain, it comes close to ventral STT & together they are called spinal fillet or spinal lemniscus.

The fibres that carry thermal sensations end in the reticular area of brainstem and most end in posteroventral area of thalamus.

3rd order neurons are present in thalamus; their fibres convey sensation to post central gyrus (area 3, 1, 2). Now it's said that in addition to relay in area 3, 1, 2 thermal fibres from thalamus end in ipsilateral insula of cortex, suggesting that it may be of true primary thermal receiving area.

4. Pain Pathway: (diagram refer essay 2)

Receptors:

Free unmyelinated nerve endings. They are present in superficial layer of skin mucous membrane as well as as internal tissue like periosteum, parietal pleura, pericardium, arterial walls, joint surfaces as well as tentorium and falx cerebri. The receptors are less in viscera and deeper tissues. VR 1 and VRL 1 type of receptors (refer temperature pathway)

Stimuli that excite the receptors:

·Receptors are generally called nociceptors. The stimuli may be thermal like high temperature but the threshold for activation of pain for temperature is 100 times more than that required for temperature receptors. The critical temperature for perception of pain starts at about 45°C and causes tissue damage.

•Strong electrical currents

•Mechanical stimuli like increased pressure, touch etc

•Chemicals can stimulate pain receptors and cause pain e.g.: bradykinin, acids, K^+, vanillin, proteolytic enzymes, lactic acids and substance P increases the sensitivity of pain endings but does not directly excite them.

·Ischemia of tissues can also cause pain.

Mainly mechanical and thermal stimuli result in fast pain. Mechanical, thermal and chemical stimuli result in slow pain.

Characteristics of pain

•Increasing intensity of pain causes increased pain and it spreads to adjacent area and causes tissue destruction. Threshold intensity stimulus cause pain and sub threshold causes no pain. Distraction of mind increases the threshold for pain and in severe anxiety there is reduced pain.

•Adequate stimulus: Different types of stimuli produce pain. Excessive stimulation of touch and temperature receptors can cause pain.

•Adaptation: They adapt very little and sometimes not at all and are called as slowly adapting tonic receptors. On continous stimulation pain continues as long as receptors are stimulated but degree decreases slightly.

•Hyperalgesia: Increased sensitivity of pain receptors is seen in some conditions like slow aching pain noxious pain

•Localisation: Superficial pain is better localised. Deep pain is diffused and poorly localised. Visceral pain is usually referred to other areas on the skin.

•Association with emotions: Pain initiates strong withdrawal and avoidal reflexes maybe due to connection with cingulated gyrus of limbic system. Threshold of pain sensation is the same for different individuals but the response varies from person to person and from time to time.

Strong stimulation of visceral receptors results in autonomic response like nausea, vomiting, fainting, change in heart rate etc.

Pain pathway:
Lateral Spinothalamic pathway (Refer temperature pathway)

Dual pathway

Fast pain: Aδ fibres which end mainly in lamina
Slow pain: C fibres end primarily end on neurons in lamina

After entering the spinal cord the pain signals take two pathway:

- oNeospinothalamic pathway
- oPalaespinothalmic pathway

Neospinothalamic

Stimuli are mainly mechanical and acute thermal pain. Aδ fibres end mainly in lamina. From there 2nd order neurons arise. They cross to the opposite side. They ascend in Anterolateral column and some fibres in reticular areas of brainstem. Most fibres pass to ventrobasal area of thalamus along with medial leminiscal tract and a few fibres end in posterior nuclei of thalamus. From there sensations are conveyed to the somatosensory cortex (3, 1, and 2) and some signals to the basal areas of the brain.

Palaespinothalmic

For transmission of slow chronic pain, stimuli are mainly chemical and sometimes persistent mechanical or thermal stimuli. It is an older pathway. Fibres are mainly C fibres and some Aδ fibers of spinal cord i.e., substantia gelatinosa of Rolando of spinal cord. Additional short fibre neurons end in lamina. 2nd order neurons ascend in the Anterolateral column. Only 1/4th to 1/10th of these fibres pass to the thalamus to be relayed in the cortex. The rest of the fibres end in one of the different areas:

- Reticular nuclei of medulla, pons and midbrain
- Tectal area of mesencephalon deep to superior and inferior colliculi
- Periaquedectal gray surrounding aqueduct of sylvius

Neurotransmitters:

- At the A alpha fibre ending, neurotransmitter is glutamate (excitable) and the action lasts only for a few milliseconds.
- At the C fibre ending both glutamate and substance P are generated. However action of glutamate lasts for only short time while substance P is released more slowly and its concentration may increase over a period of seconds or minutes.

Visceral Pain:

Pain sensation from visceral organs can arise due to conditions like ischemia,Obstruction of hollow viscous,Inflammation,Distension,Severe vasodilation..etc.

Characteristics of visceral pain:

- It is referred.
- It is poorly localised
- Accompanied by autonomicsymptoms like nausea,vomiting&fall of BP.
- Cause reflex spasm of abdominal skeletal muscles and make it rigid,clinically called guarding,a protective reflex

Pathway for visceral pain

Visceral afferents reach CNS via sympathetic and parasympathetic pathways. Theell bodies are located in the dorsal root and homologous cranial nerve ganglia. The sensory afferents from thoracic and abdominal viscera are carried by afferents through sympathetic nerves. **Pain afferents** enter the spinal cord through T1- L2 segments. From oesophagus, trachea, pharynx, and eye: IX, X, VII, V cranial nerves. Structures within the pelvis: parasympathetic fibers. The visceral sensations travel along the same pathway as Spinothalamic tract as thalamic radiations and cortical receiving areas are intermixed with somatic sensory areas. Some P substance containing afferents make connections via collaterals to the post ganglionic sympathetic nerves in the collateral sympathetic ganglia like inferior mesenteric ganglion. These connections play a part in reflex control of viscera independent of CNS.

Localisation of Visceral pain:

1.True Visceral Pathway: via pain sensory fibers within autonomic nerve bundles. (Referred pain).

2.Parietal pathway conducted directly into local SN from parietal peritoneum, pleura, and pericardium. Stimulation causes localized pain over painful area.

Pain can be perceived even after complete removal of the somatosensory area. This may b because conscious perception of pain may be possible with lower brain system. Meaningful interception of pain and exact localisation of pain sensory cortex.

3.Cauterization of specific pain areas in intralaminar nuclei in thalamus – selective surgical method which often relieves suffering type of pain- Acute pain is intact.

4.Post rhizotomy- section of dorsal nerve root carrying pain fibers from affected areas

5.Medullary tractectomy at the level of medulla

6.Mesencephalic tractectomy at the level of mid brain.

7.Gyrectomy: post central gyrus is removed.

8.Peripheral nerve section: sectioning of nerve fibers carrying pain from the affected areas.

Pain modulation:

Central Analgesic System:

The pain control system which is activated by brain to suppress the impact of pain signals to the nervous system. The endogenous pain inhibiting systems have 2 major sites of action:

- The descending pain inhibiting / descending analgesic system:
- At the SC level

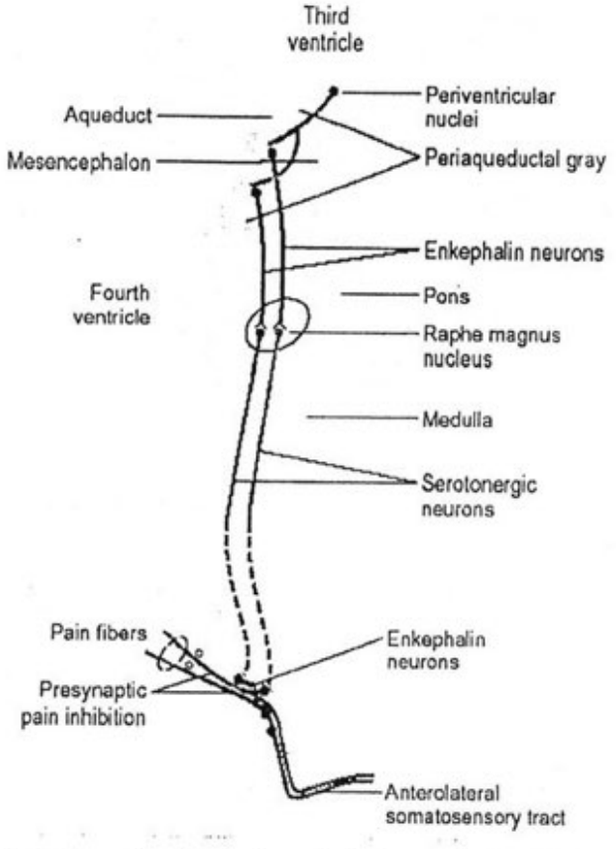
3 important components are:

1.Periaquedectal grey and periventricular areas of mesencephalon and upper pons, surrounding the aqueductus sylvius and portions of III, IV ventricles.

2.Raphe magnus nucleus, nucleus reticularis paragigantocellullaris.

3.Pain inhibiting complex located in the dorsal horn of spinal cord.

Reticular formation, thalamus and cerebral cortex cause conscious perception of pain. Intralaminar nuclei of thalamus, reticular area of brain stem in these areas electrical stimulation causes strong arousal effect on nervous activity through out brain principal arousal system. Quality of pain interpreted by cerebral cortex.



Analgesia system of the brain and spinal cord, showing (1) inhibition of incoming pain signals at the cord level and (2) presence of *enkephalin-secreting neurons* that suppress pain signals in both the cord and the brain stem.

Surgical interception of pain pathways:

1.Prefrontal lobotomy:

The deep connections between the prefrontal areas and the rest of the brain are cut off. The patient feels the pain and is not concerned about it. The procedure involves extensive personality changes and social behavioural changes and toilet habits. Usually done only in terminally ill patients with unbearable pain like advances cancer.

Less severe procedures are:

2.Anterolateral caudotomy:

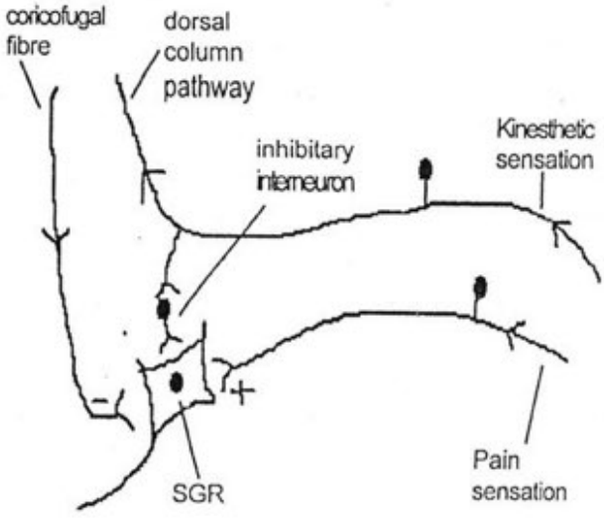
Caudotomy in the thoracic region, SC o the opposite side is partially cut in the Anterolateral quadrant to selectively interrupt the Anterolateral sensory pathway. Caudotomy may not always relieve the pain for two reasons:

- Many pain fibers from the upper half of the body cross to the opposite side only at the higher levels in the brain. So they are not transacted with caudotomy
- The pain frequently returns several months later partly as a result of sensitization of other pathways which are normally

Gate controlled Theory of Pain:

Mechanical stimulation of injured area sometimes relieve pain.After a hit if we rub or massage that area the intensity of pain decreases.This is due to stimulation of mechanoreceptors in the area,which exerts a suppressor effect on pain sensation.

The first order neuron of the pain pathway ends in the SGR.The dorsal column pathway has collterals to the dorsal horn cells.These collaterals end in certain interneurons in the dorsal horn which release enkephalin at their endings.



As the touch receptors are stimulated by rubbing the affected area, impulses are carried through the collaterals

to activate the interneuron which releases enkephalin. This enkephalin binds with the receptors in the membrane of primary nerve endings in the pain pathway and depolarizes it. The amplitude of action potential is reduced when it reaches the nerve endings due to presynaptic inhibition by the collateral. The transmission of pain signals to the second order neurons in SGR is inhibited. Thus the gate ie., SGR controls pain sensation to large extent.,

Brain opiate systems: Endorphins and enkephalins: Morphine given intrathecally is effective in causing extreme degrees of analgesia.

Receptors for morphine are opiod peptide. They have these sites of action:

- Peripherally at the site of injury
- In the dorsal horn
- More rostral areas in the brain stem

Opiod peptides are produced in the dorsal root ganglion cells that migrate peripherally and centrally along the nerve fibres. In the periphery inflammation causes production of opiod peptides by the immune cells. These opiod peptides act on the receptors in the afferent nerve fibre to reduce pain or cause absence of pain by inhibiting the release of Substance P. In the dorsal horn the opiod peptides could act presynaptically to decrease release of Substance P. The nature of these endings is not yet clear.

Injection of morphine to PAG activates descending pathways and causes inhibition of transmission of primary pain afferents i the dorsal horn. Action of serotonin is unsettled.

5. Pyramidal System & Lesions:

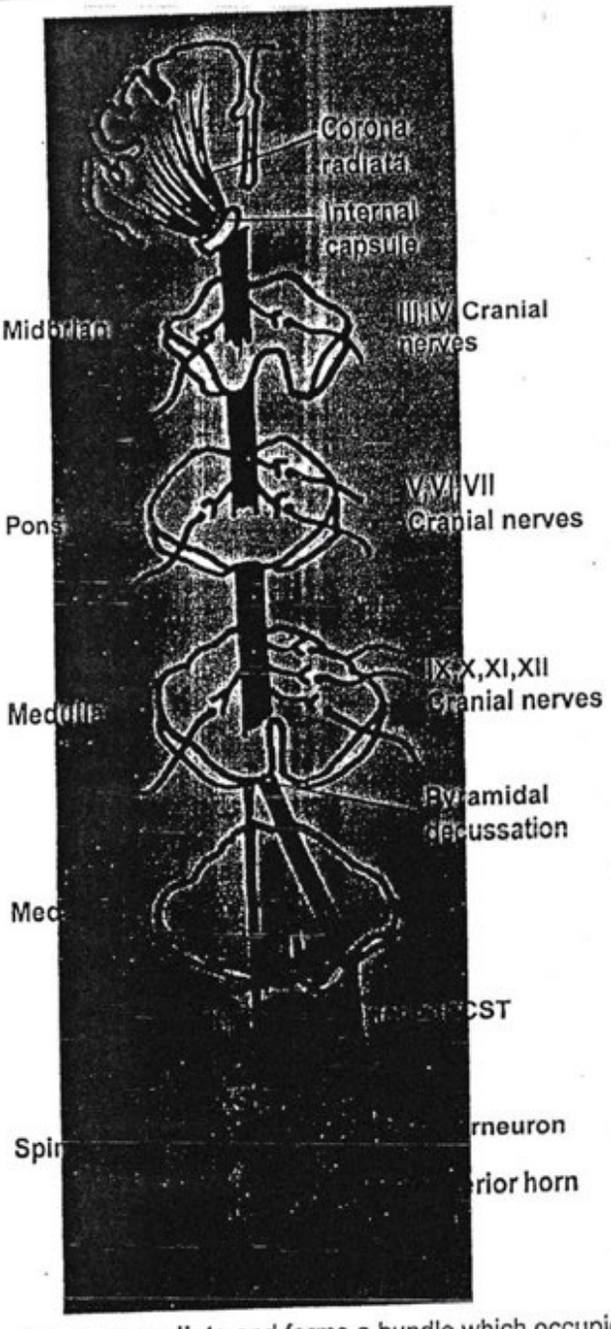
It is the most important output pathway from motor cortex, the largest tract starting from motor cortex reaching the last segment of spinal cord and present only in higher animals where cerebrum has developed.

Origin:

- Fibres arise from 5th layer, inner pyramidal cell layer of cerebral cortex
- 30% fibers arise from primary motor cortex
- 40% fibers arise from somatosensory areas in post central gyrus
- 30% arise from premotor and supplementary motor area
- More than 1 million fibers are in a slowly conducting pathway
- Most of the fibers are small diameter (less than 4 µm) slowly conducting fibers. Large Myelinated fibers called betz cells with a diameter of 16µm and a transmission velocity of 70m/s arising from giant pyramidal cells constitute 3% of total corticospinal tract fibers.

Course:

- 80% of pyramidal tract fibres arise from motor areas and 20% from sensory areas of cortex. Fibres converge



to **corona radiata**, and forms a bundle which occupies the genu and anterior 2/3rd of the **posterior limb of internal capsule.** Fibres from the head area are seen anteriorly and fibres from foot area posteriorly. The fibres of the pyramidal tract pass down through the brainstem, i.e., **midbrain, pons and medulla.** In the midbrain it occupies the crus cerebra. In the pons, the pyramidal tract splits into discrete bundles due to the prescence of pontine nuclei. After passing pons, it again forms a bundle and occupies the pyramids of medulla (ventral bulges) and hence this tract is called **pyramidal tract.** Fibres to the muscles of head and neck refion cross to the opposite side to end in the corresponding cranial nerve nuclei in brainstem. Motor nuclei of the cranial nerves in which these axons terminate are that of III, IV, V, VI, VII, IX, X, XI and XII cranial nerves. These fibres of the pyramidal tract are called **corticonuclear or**

corticobulbar fibres.The rest form **corticospinal** fibres.The lowest motor neurons of cranial nerves convey impulses that control precise,voluntary movements of eyes,tongue and neck and cordinate the activities of muscles of mastication,facial expression,and speech.

In the medulla,80% of fibres pass to opposite side (contralateral) as **pyramidal decussation** and 20% pass uncrossed(ipsilateral).The crossed fibres occupy the lateral funiculus of spinal cord and go as the **lateral corticospinal tract.**20% of uncrossed fibres in the spinal cord forms the **anterior corticospinal tract.**These fibres also cross to opposite side at different levels in spinal cord via the anterior white commissure before they end in spinal motor neurons.Only the largest Corticospinal fibres end directly in the α-motor neurons or γ– motor neurons.*The right cerebral cortex controls muscle of the left side and vice versa.*

•Pyramidal tract was the nerve tract to be discovered. All fibres are present at birth but Myelination is complete only at about 2 years.

Function:

1.The pyramidal tract fibres arising from bets cells are probably concerned with skilled movements and smaller fibres with gross movement.

2.LCST convey motor impulses to spinal cord for initiation and carrying out skilled voluntary activity of distal limb especially fine gesture movement of hand and fingers (along with rubrospinal tract as it lies close to LCST)

3.ACST is concerned with control of muscles of trunk and proximal position of limbs that carry postural adjustments and gross movements

4.Effect on alpha motor neuron may be excitatory or inhibitory depending on the neuron where it is ending. If it ends on or then the effect is excitatory, if on interneuron then the effect is excitatory or inhibitory.

5.Some of the fibres transmit information from brain to afferent neurons, so it can affect afferent system activity.

6.Role in sensory motor co-ordination: In lesions of somatosensory area, hand eye co-ordination & executing learned skilled activity like eating with knife and fork etc is lost.

7.Corticobulbar system: Voluntary control of muscles of pharynx, larynx, palate, upper and lower face, jaw, eye etc

8.Some neurons in 5 & 7 area play an important role in hand head eye co-ordination.

Lesions:

The main function of pyramidal system is that it forms 1⁰ pathways for the initiation of skilled voluntary movements. Destruction of the system causes considerable loss of voluntary activity, actually paresis (weakness) rather than paralysis is caused by pure pyramidal tract lesion. Also the affected muscles are hypotonic in pure pyramidal lesions.

In lower animals like cats and dogs, complete destruction of pyramidal system, still activities like walking, running etc are possible. In birds where pyramidal tract is not developed, activities like flying and nest building are carried out due to lower motor centres like basal ganglia.

Experimentally, section of pyramids in primates produces selective destruction of LCST and causes loss of fine voluntary movements. In human beings, commonest site of lesion is internal capsule. Thrombosis, haemorrhage of lenticulcstriate branch of MCA can cause IC lesions and lesion of pyramidal tract.

When corticospinal fibers are alone affected, there is initially weakness of contra lateral side of body. Rapid improvement occurs resulting in residual impairment of fine rapid movements as in picking up an object. Mild weakness of hip flexion and shoulder abduction are also seen.

Hemiplegia: Paralysis of one half of the body; loss of voluntary activity on that half.

Site of lesion: Cerebral cortex, IC, midbrain, pons, medulla, spinal cord

Commonest site: IC

Lesion on one side causes paralysis on opposite side. Para pyramidal tract lesion produces flaccidity and hypotonia; but in IC lesion, usually both pyramidal and extra pyramidal fibers are affected as they are closely packed in IC and lesion at this level produces Hypertonia and spastic paralysis.(as both pyramidal and extra pyramidal fibers)

Following lesion 2 stages occur

1) Acute stage: Initially a stage of shock. Condition resembles spinal shock. There is temporary depressant effect on anterior horn cells (neuronal shock). This stage is characterized by hypotonia, absent reflexes (superficial and deep), flaccid paralysis of opposite side especially faces, leg, arms and finger movements.

Movements which involve both sides of the body such as respiration, movement of head, trunk and abdomen are generally retained because the nervous pathways controlling these are predominantly under sub cortical control and are represented bilaterally. Corticonuclear fibers may escape injury, and then eyeball movements are intact. Lasts for few days; 2-3 weeks.

2) Chronic UMN stage: Characteristic features are seen. Occur few days- 2-3 weeks, after lesion. Also regarded as recovery stage. Reflex activity return to affected side and muscles become spastic. UMN features develop. If we try to extend the limb, great resistance is encountered initially, suddenly the limb gives way and extends. Loss of inhibitory influences from higher centres is the cause of spastic paralysis.There is increase tone in antigravity muscles and flexors of UL and extensors of LL.The limbs may be placed or fixed in abnormal position.For UL,adduction at shoulders,elbow semiflexed,forearm

pronated,wrist and fingers flexed and passive movements difficult.For LL,hip adduction,knee extended ankle plantar flexion.

Deep reflexes: Knee jerk, ankle jerk- hyper reflexia.

Clonus may be exhibited:Consist of rhythmic contraction of flexor or extensor muscle in response to sudden passive stretch.

Superficial reflexes like abdominal, cremasteric and anal reflexes are lost.

Plantar reflex: Extensor plantar response, Babinski's sign is obtained

Babinski's sign- Refer S.N.

Spasticity is due to accessory pathways (non pyramidal). Normally inhibit vestibular/ reticular brain stem motor nuclei and when these nuclei become inhibited, they become spontaneously active and cause excessive spastic tone in the involved muscle.

In course of time, considerable improvement can occur. Patient may walk with a limb and gait is called spastic/ hemiplegic/ circumduction gait drags the affected feat as if glued to the ground. A good deal of power returns to arm and face. Some semi voluntary movement can be reflexely aroused by forceful voluntary movement on normal side.

Flaccid paralysis

Usually in UMN lesion, lower part of face is involved. Upper part escapes due to bilateral representation of the upper part. Mouth opens. There will be muscle wasting due to disuse atrophy.

In case of cortical lesion, damage to area 4 can cause monoplegia.

Corona radiate: monoplegia. Aphasia, Jacksonian epilepsy

Lesion at thalamus: C/L hemiplegia and sensory abnormalities

Lesion at mid brain: i/l G III & IV palsy with C/L hemiplegia.

Lesion of Pons (above facial N nucleus): UMN (G VII) & C/L hemiplegia

Below facial N nucleus: LMN (G VII) & C/L hemiplegia

Lesion at medulla: More fatal since all centres are located there.

Bulbar Palsy

Lesion of 9, 10, 11 & 12 cranial nerve. Results in palatal, pharyngeal and tongue weakness causing dysphonia, dysarthria and dysphagia.

Pseudo bulbar palsy

Bilateral lesion of 9, 10, 11 & 12 CN causes loss of voluntary palatal and pharyngeal movements, but gag reflex is preserved. Tongue is spastic, jaw jerk is brisk.

6. Effect of Transection of spinal cord.

1.Complete Transection:

Causes:

- Gun shot injury
- Dislocation of spinal cord due to fall from great height or any other trauma.
- Acute inflammation of spinal cord- transverse myelitis.
- Tumours of spinal cord

Commonest site of involvement: Mid thoracic region.

Effect depends on the site of injury

Acute complete Transection:

Stage1: Stage of spinal shock:

Feels though cut into 2.Complete paralysis of muscles below the level of lesion. If the lesion is in higher cervical segments: Quadriplegia. If the effect is in the mid thoracic region paralysis of lower half of the body: Paraplegia

Features:

- Muscle tone is lost below the level of Transection: hypotonia.
- Flaccid paralysis
- All reflexes below the level are lost
- All sensation below the level are lost
- At the onset, BP falls constantly& drastically- mean BP even goes down to 40mm Hg
- Vasomotor paralysis because sympathetic activity becomes almost blocked. Higher the level of Transection, greater the fall in BP.
- Venous return is decreased, cardiac output decreases
- Paralysed limbs cold and blue.
- Prone to develop bed sores
- Sweat secretion is abolished, skin becomes cold and dry
- Muscles of bladder and rectum become paralysed. Bladder becomes toneless. There will be retention of urine and faeces. Urine dribbles through sphincters. Overflow incontinence.

Cause of spinal Shock: Uncertain

Normal activity of spinal neuron depends on continued tonic excitation by discharge of nerve fibres from higher centres, especially, reticulospinal, vestibulospinal, corticospinal tracts. Cessation of these impulses in descending pathway may be the reason.

Duration of spinal shock is proportionate to the degree of encephalisation of motor function in various species. In human it takes a minimum of 2 weeks.

If no complication occurs it passes on to the next stage. If complications like infection, malnutrition etc occurs it lasts longer or passes directly to third stage

of sympathetic fibres from lateral horn which causes dilatation of blood vessels below the level-fall in BP

- ❖ Spinothalamic sensations are not lost on the same side because they cross over.

➢Opposite side (contra lateral):

- ❖ Complete loss of pain, temperature and crude touch. Interruption of Spinothalamic tract fibres which have already crossed.

No loss of posterior column sensation.

2.Changes below the level of lesion:

➢Complete loss of all sensations, damage to posterior nerve root and posterior horn cells of corresponding segment.

➢Complete LMN paralysis in the segment. Damage of anterior horn cells

➢Flaccid paralysis

➢Loss of all reflexes

➢Later wasting of muscles

➢Vasomotor paralysis

3.Changes above the level of lesion:

➢Band of cutaneous hyperaesthesia on the same side.

7. Basal Ganglia:

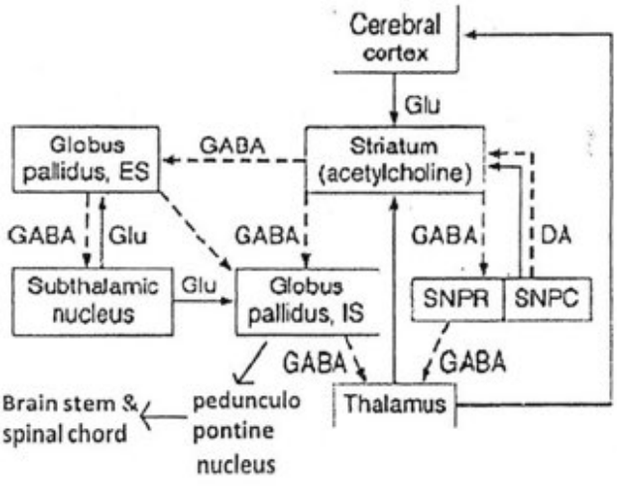
The term basal ganglia is generally applied to 5 structures on each side of the brain

- •Caudate nucleus
- •Putamen

Globus pallidus (internal and external segment)

- •Subthalamic nucleus
- •Substantia nigra (pars compacta and pars reticulate)

Caudate nucleus and putamen together called as striatum. Putamen and globus pallidus together called as lenticular nucleus.



Connections:

Afferent connections

a)Corticostriate projection from all parts of the cerebral cortex.

b)Projection fibres from the centromedian nucleus of the thalamus to the striatum (thalamostriate fibres).

Internuclear connection

a)Dopaminergic nigrostriatal projection from the pars compacta of the substantia nigra to striatum

b)GABAergic fibres from the striatum to the pars reticularis of substantia nigra

c)The caudate nucleus and putamen(striatum) projects to both segments of globus pallidus.

d)The external segment of globus pallidus projects to the subthalamic nucleus, which in turn projects to both segments of the globus pallidus and the substantia nigra.

Efferent connection

a)The principle output from the basal ganglia is from the internal segment of the globus pallidus via the thalamic fasciculus the ventral lateral, ventral anterior and centromedian nucleus of the thalamus. From the thalamic nucleus, fibres project to the prefrontal and premotor cortex.

b)The substantia nigra also projects to the thalamus.

However the main feature of the connections of the basal ganglia is that:

Direct pathway

Cerebral cortex
↓
Striatum
↓
Internal segment of globus pallidus
↓
Thalamus
↓
Cerebral cortex

Indirect pathway

Cerebral cortex
↓
Striatum
↓
External segment of internal capsule
↓
Subthalamic nucleus
↓
Internal segment of globus pallidus
↓
Thalamus
↓
Cerebral cortex

Functions:

- **Basal ganglia is involved in the planning and programming** of movement or more broadly in the processes in which an abstract thought is converted into voluntary action. It helps to coordinate a series of actions which will result in a final complex end result such as running away from seeing a lion.
- Basal ganglia also plays a role in some **cognitive processes**, and particularly in the region of caudate nucleus. Lesions in the head of the left but not the right caudate nucleus results in dysarthric form of aphasia.
- To determine the **nature of writing** like writing in large font on a black board and in small font in a notebook
- Normal **associated unconscious movement** such as swinging of the hands when walking.
- Together with cerebellum, it plays a role in the **maintainence of balance**
- Basal ganglia play an important role in the **expression of emotional aspects** of mind. In the lesion of basal ganglia, the patient has a mask like face that is quite expressionless.
- The interaction between nuclei of basal ganglia results in a balance in the movement so that there is no spasticity or rigidity.

Diseases of Basal ganglia:

Disease processes affecting the basal gaglia in humans produce marked and characteristic **abnormalities of motor function**. Disorders of movement associated with diseases of the basal ganglia in humans is generally of two types

Hyperkinetic (excessive and abnormal movement):

- Chorea: rapid, involuntary, dancing movement
- Athetosis: continuous, slow, writhing movement
- Ballism: Flailing, intense, and violent movement

Hypokinetic:

- Akinesia: Difficulty in initiating movement and decreased spontaneous movement
- Bradykinesia: Slowness of movement

Huntington's disease

- This disease is characterised by hyperkinetic choriform movements that gradually increase until they incapacitate the patient.
- Speech becomes slurred and incomprehensible.
- There is progressive dementia followed by death usually within 10-15 years after the onset of symptoms
- The initial event in Huntington's disease is selective degeneration of the striatal GABAergic and cholinergic neurons that project to the putamen. Since this pathway is inhibitory and its loss permits the hyperkinetic features of the disease to develop.
- Huntington's disease is inherited as an autosomal dominant disorder and its onset is usually between the ages of 30 and 50.
- The gene responsible for the disease is located on the short arm of chromosome 4 which codes for a protein called as Huntington which when abnormal is coded in large number and results in the disease.Huntingtons disease is characterised by trinucleotide expansion(CAG)

Parkinson's disease (paralysis agitans)

This disease has both hyperkinetic and Hypokinetic features:

Causes

- In earlier times parkinsonism was a common late complication of a type of influenza that was epidemic.
- It occurs today in idiopathic form in elderly individuals.
- There is a steady loss of dopamine and dopamine receptors with age in the basal ganglia and it is apparently an acceleration of these losses that precipitates Parkinsonism.
- It is also seen as a complication of treatment with the phenothiazine group of tranquiliser drugs that block D2 dopamine receptors.
- Also produced by injection of MPTP. MPTP is metabolised by the enzyme monoamine oxidase in various brain cells to produce a potent oxidant MPP. In primates, MPP is removed slowly and is taken up by dopaminergic neurons in the substantia niagra, which it destroys without affecting other dopaminergic neurons to any appreciable degree.

Features

- The Hypokinetic features of Parkinson's disease are Akinesia and Bradykinesia and the hyperkinetic features are rigidity and tremor
- There is marked absence of motor activity and difficulty in initiating voluntary movement.
- Parkinsonism shows characteristic feature of fine tremor; ie, tremor at rest due to increased motor neuron discharge to both agonist and antagonist muscle.
- There is a decrease in associated movements
- Normal, unconscious movement such as swinging of arms during walking is lost.
- Facial expressions related to the emotional content of thought and speech and the multiple fidgety actions and gestures are lost; ie, the patient has a mask like face.
- There is difficulty in initiating movement such as walking but once started it is easier to run than walk
- The patient has festinent type gait(shifting gait)
- Writing becomes smaller and smaller (micrographia)
- The rigidity is different from spasticity because there is increased motor neuron discharge to both agonist and antagonist muscle.
- Lead pipe rigidity: passive motion of an extremity meets with a plastic, dead feeling resistance like bending a lead pipe.
- Cog wheel rigidity: there is a series of catches during passive movement.

Treatment.

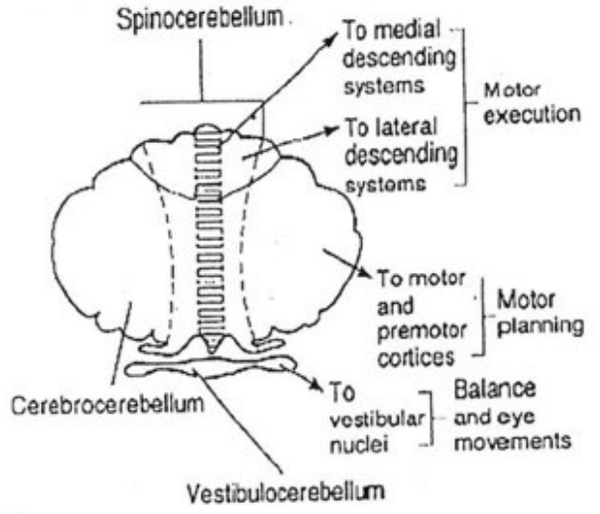
- Improvement is seen with administration of L-Dopa. Unlike dopamine this dopamine precursor crosses the blood brain barrier and helps repair the dopamine deficiency.
- Implantation of tissue from the basal ganglia of foetuses
- Transplantation of adrenal medulla to the ventricular surface of the caudate nucleus.
- Bromocriptine and other synthetic dopamine agonists that penetrate brain tissue
- Deprenyl, a drug that inhibits monoamine oxidase appears to slow the progress of the disease.

8.Cerebellum:Functions,Functional Divisions,Connections and lesions:

Located in posterior cranial fossa behind brainstem
On each side connected to brainstem by 3 cerebellar peduncles
•Superior →midbrain
•Middle →pons
•Inferior → medulla

Anatomical divisions
•Anterior lobe
•Posterior lobe
•Flocculonodular lobe

Physical division	Functional division
Archicerebellum	Vestibulocerebellum
Paleocerebellum	Spinocerebellum
Neocerebellum	Cerebrocerebellum



It has
•Outer grey matter divided into 3 layers
•Molecular – stellate and basket cells
•Purkinje
•Granular – Golgi and granule cells
•Inner white matter

Deep nuclei
•Dentate
•Emboliform
•Globose
•Fastigial

Connections:
Cerebellar afferents
•Climbing olivocerebellar tract fibers
Project to dendrite of Purkinje cell and intertwine like plant.
Each Purkinje cell has 1 climbing fiber makes 3000 synapses
Stimulation causes strong and prolonged AP
Gives a branch to the deep nuclei
Inferior olivary nucleus→crosses→inferior cerebellar peduncle→spinocerebellum, Cerebrocerebellum, globose, emboliform, dentate,
Inferior olivary nucleus receives proprioceptive impulse from all part of the body.
•Mossy fibers
All other afferent entering cerebellum end in synaptic glomerulus
Collaterals to cerebellar nuclei and Golgi cells
One mossy fiber to 1000 granule cells
Stimulation causes weak short AP

Function of principal afferent systems to the cerebellum.

Afferent Tracts	Transmits
Vestibulocerebellar	Vestibular impulses from labyrinths direct and via vestibular nuclei
Dorsal spinocerebellar	Proprioceptive and exteroceptive impulses from body
Ventral spinocerebellar	Proprioceptive and exteroceptive impulses from body
Cuneocerebellar	Proprioceptive impulses, especially from head and neck
Tectocerebellar	Auditory and visual impulses via inferior and superior colliculi
Pontocerebellar	Impulses from motor and other parts of cerebral cortex via pontine nuclei
Olivocerebellar	Proprioceptive input from whole body via relay in inferior olive

Purkinje cells large cells middle layer
oExtrinsic arborisation in molecular layer
oAxons extend → deep cerebellar nucleus only output from cerebellar cortex
oInhibitory neurotransmitter GABA
Granule cells small cells in granule layer send axon to molecular layer where it bifurcates into "T"
oMakes contact with stellate, basket, purkinje cells
oExcitatory neurotransmitter glutamate
oReceives excitatory input from mossy fibres
Basket cells in molecular layer
oDendrites contact with parallel fibres of granular cells excitatory input
oAxons form basket around body and axon hillock of purkinje

- oInhibitory neurotransmitter GABA
- oFeedforward inhibition
- oSharpens signals

Stellate cells more superficial in molecular layer
- oInput via axon end on purkinje
- oAxons on purkinje inhibit(GABA)

Golgi cells large cells in granular layer
- oDendrites project in granular layer
- oInput from parallel fibres
- oMany mossy fiber collateral
- oOutput → granule cells (inhibitory GABA)

Deep nuclei
- oExcitatory input from climbing and mossy fibres
- oInhibitory from purkinje cells
- oOutput from deep cerebellar nucleus→ thalamus and brainstem always excitatory
- oEntire cerebellum concerned with modulation output of deep cerebellar nucleus

Efferents:

Most of the output from vestibulocerebellum→Brainstem
Deep nuclei only output for spinocerebellum, Cerebrocerebellum
Medial spinocerebellum→ fastigial→ brainstem
Lateralspinocerebellum→globose, emboliform→ brainstem Cerebrocerebellum→ dentate nucleus → thalamus

Vestibulocerebellum

Cerebellovestibular
vestibulocerebellum→uncrossed→inferior cerebellar peduncle→vestibular nucleus
Fastigiovestibular
Fastigioreticular

Spinocerebellum

Afferents ventral and lateral spinocerebellar, tectoccerebellar, cuneocerebellar, pontocerebellar
Fastigiobulbar fastigial nucleus→ uncrossed→inferior cerebellar peduncle→reticular formation→reticulospinal tract
Cerebelloreticular emboliform and globose nucleus uncrossed →superior cerebellar peduncle → reticular formation → reticulospinal tract
Cerebelloolivary emboliform and globose nucleus uncrossed →superior cerebellar peduncle →inferior olivary nucleus → olivospinal

Cerebrocerebellum

Dentatothalamic→superiorcerebellar peduncle→crosses→thalamus→motor cortex
Dentatorubral dentate nucleus→ superior cerebellar peduncle →crosses→red nucleus
Rubrothalamic thalamus → cortex
Rubroreticular reticular formation
Rubrospinal spinal cord
Cerebellum controls the same side of the body.

Functions:

1.Control of posture and equilibrium

Loss of flocculonodular lobe causes disturbance of equilibrium and posture. It is much more if involve rapid changes in direction.
Vestibular apparatus is important in maintaining balance between agonist and antagonist and anticipatory correction of posture during rapid movement
Flocculonodular lobe is concerned with vestibulocular reflex

2.Muscle tone

Spinocerebellum influences reticulospinal tract regulates stretch reflex and muscle tone.
In humans hypotonia is character of cerbellar lesion than hypertonia.

3.coordination of voluntary movement

Coordination of rate, range, force, timing and direction
Done by

•Error detection and correction

Cerebellum receives afferents from cortex receive copy of intended movement.Spinocerebellar tract receives proprioceptive information from muscle and joint about the actual movement..Spinocerebellum compares actual plan to performance.
Corrective signals are sent to the cortex.

•Damping/breaking action

All movements are pendular movements. Momentum develops and should come to a stop.
Because of all this all movement have tendency to overshoot.
Cerebellum via learned movement stop at intended point(lesion causes intentional tremor)

•Control ballistic movements

In very alternate raid movements in skilled work like typing cycling it is impossible for feedback.
Entire movement is a preplanned set in motion to go a certain distance and stop.

•Planning sequential movements

Plan and perform intricate sequential movements Eg hands, fingers, vocalization.
Planning begins in premotor cortex and somatosensory areas→cerebellum and back. Both help in planning sequence of movements.

•Timing functions

Cerebrocerbellum provides timing function for cerebellar movements. From rapidly changing spatial temporal

changes and changing visual field can predict when we reach an object

•Learning of skilled movements

Concerned with learned adjustment, makes coordination easier when task is performed repeatedly.

Basic motor skills related to inferior olivary nucleus and climbing fibers.

Lesions of cerebellum:

Manifestation is proportional to extend of lesion.

Basal defects in cerebellar lesion are hypotonia and loss of influence of cerebellum on cerebral cortex.Muscle atrophy,sensory changes and paralysis are not present in cerebellar lesions.

The classical manifestation are:

1.Atonia or Hypotonia

2.Asthenia is weakness and easy fatigability

3.Ataxia or incoordination

4.Disequilibrium

•Ataxia is incoordination due to errors in rate,range,force,and direction of movement

•Past-pointing or dymetria-overshooting to one side when finger nose test is performed

•Intension tremor:characteristic of cerbellar lesion

•Cerebellar Nystagmus-oscillatory movements of eye ball.

•Rebound phenomenon& pendular knee jerk -absence of braking action.

•Dysdiadokokinesia-lack of coordnition of motor activity

•Staggering gait -ataxia

•Slurring speech-ataxia

9. Functions of hypothalamus

1) Regulation of Autonomic functions:

Sherrington referred hypothalamus as head ganglion of ANS. Stimulation of lateral and posterior part of hypothalamus resulted in

i) Sympathetic stimulation

ii) Increase in adrenal medullary secretion.

Increase inHR,BP, VC, pupillary dilatation, piloerection etc result. Stimulation of anterior HT results in parasympathetic effects.Increase in GI and bladder contractions, cardiac inhibition.

2) Neurosecretory function

a) Posterior pituitary secretion

Vasopressin and oxytocin: Synthesized in cell bodies of magnocellular neurons in supraoptic and paraventricular nuclei and transported through hypothalamohypophyseal tract: posterior lobe of pituitary. They are neural hormones.

b) Control of anterior pituitary secretion

A number of releasing and inhibiting hormones is synthesized in the Neurosecretory cells of hypothalamus whose endings are in the region of median eminence. These hormones reach anterior pituitary through hypophyseal portal circulation and either promotes or inhibits release of anterior pituitary hormones.

There are six hypophysiotropic hormones

1.Corticotrophin releasing hormone(CRH)

2.Thyroropin releasing hormone (TRH)

3.Growth hormone releasing hormone (GHRH)

4.Growth hormone inhibiting hormone (GHIH)

5.Gonadotropin releasing hormone (GnRH)

6.Prolactin inhibiting hormone PIH

PRL is the only hormone which increases following sectioning of pituitary stalk, because action of HT on PRL is mainly inhibitory. Multiple neuroendocrine functions of HT help to adjust endocrine secretions to the demands of changing internal and external environment. Most common endocrine symptom of hypothalamic disease is precocious puberty. Lesions interrupt the pathway that keeps the GnRH secretions in check.

3) Regulation of food intake

Body weight depends upon the balance between caloric intake and the utilization of calories. Food intake is regulated not only on the basis of meal to meal, but also in a way to maintain body weight at a set point. Hypothalamic regulation of appetite for food depends primarily on interaction between two areas.

1)A lateral feeding centre

2)A medial satiety centre.

Lateral feeding centre:Feeding centre is composed of adrenergic neurons. Stimulation causes eating behaviour in animals and lesions of it causes anorexia.

Medial satiety centre: In ventromedial nucleus. Stimulation causes cessation of eating.

Lesion causes hyperphagia. If food supply is abundant, syndrome of hypothalamic obesity occurs.

Normally satiety centre is not tonically activeThere are receptors in the satiety centre which can respond to glucose level in the satiety centre called glucosats. Feeding centre is chronically active and its activity is transiently inhibited by the activity of satiety centre after the ingestion of food.

Agents that increase food intake (Orexigenic)

•Neuropeptide Y: The cell bodies of neurons secreting this are located in the arcuate nucleus.

•Orexin A & Orexin B: Lateral hypothalamus

•Melanin concentrating hormone (MCH)

•Ghrelin

•Agouti Gene Related Protein (AGRP)

Agents that decrease food intake (Antiorexigenic)

•Cocaine and amphetamine regulated transcript (CART)

•á MSH (MC4 receptor-Effect on appetite)AGRP binds with MC4 receptor and inhibits the action of á MSH on MC4-R
•CRH
•Leptin
•POMC (Proopiomelanocortin)

Other factors determining food intake

1. ***Lipostatic hypothesis*** -

It states that adipose tissue produces a humoral signal which is proportional to amount of fat acting on HT and decrease food intake& increases energy output.The humoral signal are called Leptins.Leptin is a product of ob gene and produced primarily by fat cells.Leptin receptors are present in HT. Stimulation of these receptors inhibit increased food intake.Leptin increases activity of POMC secreting neurons & decreases the activity of Neuropeptide Y secreting hormones.

2. ***Glucostatic hypothesis-***

Activity of satiety centre in ventromedian nucleus of HT is governed by glucose utilization of its cells.VM nucleus has neurons which acts as glucostat. If glucose utilization is low their activity is decreased and the feeding centre remains unchecked and individual feels hungry. If utilisation is high activity of satiety centre is increased and feeding centre is inhibited and individual feels satisfied.

Cells of VM nucleus acts as glucostat-

1.On I.V administration of 2- deoxy glucose there is decreased glucose utilization and increased food intake.
2.During hypoglycaemia there is decreased amount of glucose reaching glucostat cells and there for appetite.
3.Polyphagia in diabetes mellitus – due to insulin deficiency low cellular utilization of glucose.

3. ***Gut Peptide*** -

Food in GIT causes release of one or more polypeptides which acts on HT to inhibit food intake.
Peptides which inhibit food intake are:
•Peptide YY
•Gastrin releasing peptide (GRP)
•Glucagon
•CCK
•Somatostatin

Ghrelin is 28 amino acid polypeptide. Principal site of production is stomach. Secretion decreases after food intake and increases after fasting. Arcuate nucleus lying outside blood brain barrier is site of peripheral action of Ghrelin.

Other agents which increase food intake.

1.GIT distension
2.cultural aspects
3.conditioned reflexes
4. Presence of brown fat.

4) Thermostat:

Fall of body temperature above a set point decreases appetite and decrease from set point increases appetite.

5) Regulation of thirst:

Water intake is increased by –
❖Increase in osmotic pr.
❖Decreased ECF volume
❖Psychological Functions

A thirst centre is locared in the lateral hypothalamus.Stimulation of this area causes the animal to drink water .Lesion cause decrease in thirst.This area contains osmoreceptors and these are stimulated by an increase in osmotic pressure of body fluids and i itiate thirst.Thirst centre is composed of cholinergic neurons.

Supraoptic neucleus of hypothalamus secretes ADH which causes increased reabsorption of water from the collecting tubules.Stimuli are increase with increase in osmotic pressure and decrease with increase in ECf volume.

Other factors regulating water intake:

1.Psychological and social factors
2.Degeneration of pharyngeal mucosa
3.Pharyngeal/gastro intestinal metering: drinking stops even before water is absorbed into body.

6) Regulation of body temperature:

Centre for heat loss is located in anterior part of hypothalamus. Electrical stimulation of this area leads to vasodilation, sweating etc which promotes heat loss. Centre for heat conservation is located in posterior part of hypothalamus and its stimulation causes shivering & vasoconstriction.

Lesion in Ant nuclei: animal not able to lose heat
Lesion in posterior nuclei: animal not able to conserve heat.When HT is removed animal becomes poikilothermic.

7) Circadian Rhythm & biological clock:

Rhythmical fluctuations in functioning of living cell is Circadian Rhythm. It is also defined as diurnal variation of body function within an interval of 24hrs. Normally it entrains the person to day and night cycle. If they are not entrained they will progressively go out of phase of day night cycle. Located in paired suprachiasmatic nucleus and receives information about light dark cycle, via retinohypothalamic fibres. The rhythm is due to 24 hr cyclical changes in hypothalamic signals. They include rhythm in secretion of ACTH & other pituitary hormones.

Sleep/wake cycle is controlled by secretion of melatonin. A nocturnal peak in secretion of melatonin is a signal entraining other cells of body.

8) Sleep:

Diencephalic sleep zone - posterior & anterior HT nuclei (intralaminar nuclei) medullary synchronising zone - reticular formation in medulla. Basal forebrain sleep zone – part of it lies in supra optic nucleus. Once it is stimulated it will produce sleep.

Diagonal band of broca – in them low frequency causes sleep and high frequency causes arousal. Slow wave sleep is under HT control and lesions of HT will cause somnolence.

9) Emotional &Behavioural changes:

Along with limbic system HT plays an important role in emotional and behavioural changes e.g.: sexual behaviour, rage, motivation etc.

10) Functioning of CVS:

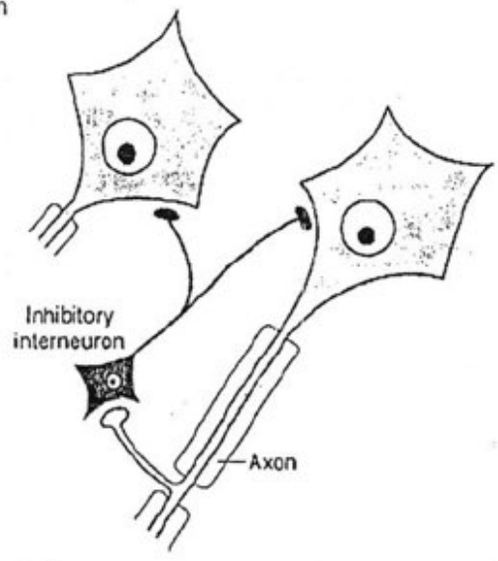
There are descending tracts from cerebral cortex to vasomotor centre which relay in hypothalamus. They are responsible for CVS changes.

SHORT NOTES

1.Presynaptic&Postsynaptic inhibition: (refer essay 1)

2. Renshaw cell Inhibition:

Neurons may inhibit themselves in a negative feedback. Each spinal motor neuron regularly gives off a recurrent collateral that synapse with inhibitory interneuron termed as Renshaw cell which terminate with the cell body of spinal neuron and also on the spinal motor neuron. Therefore activity in the Renshaw cell brings about feedback inhibition of the same neuron. This is the mechanism by which a motor neuron can exert control over its own activity. This is seen in cerebral cortex, limbic system



3. Subliminal Fringe: refer essay 1

4.Summation & Occlusion:refer essay 1

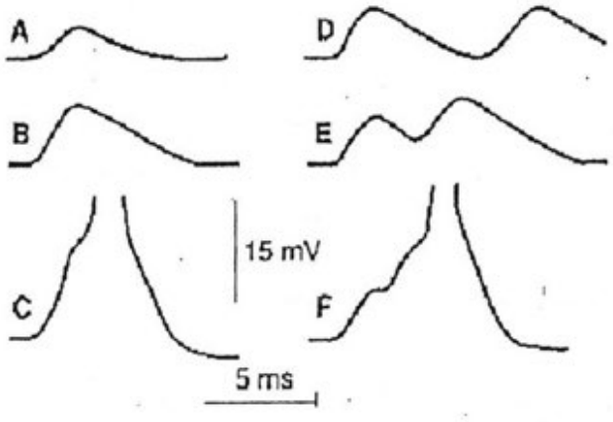
5. EPSP and IPSP

EPSP:

Single stimulus applied to the sensory nerves does not lead to the production of a propagated action potential in the post synaptic neuron. Instead the stimulation produces either a transient partial depolarization or a transient hyper polarization.

The initial depolarizing response produced by a single stimulus to the proper input begins about 0.5 ms after the afferent impulse enters the spinal cord. It reaches its peak 11.5 ms later and then declines exponentially. During this potential, the excitability of neuron to other stimulus is increased and consequently the potential is called EPSP.

EPSP is due to depolarization of the post synaptic cell membrane immediately under the presynaptic ending. The excitatory transmitter opens Na^+ or Ca^{2+} ion channels in the post synaptic membrane, producing an inward current. The area of current flow thus created is so small that it does not drain off enough positive charge to depolarize the whole membrane. Instead an EPSP is inscribed. The EPSP due to activity in one synaptic knob is small, but summation can take place. Longer the time constant for EPSP, greater the opportunity for summation. EPSP is directly proportional to the size of strength of the afferent stimulus.



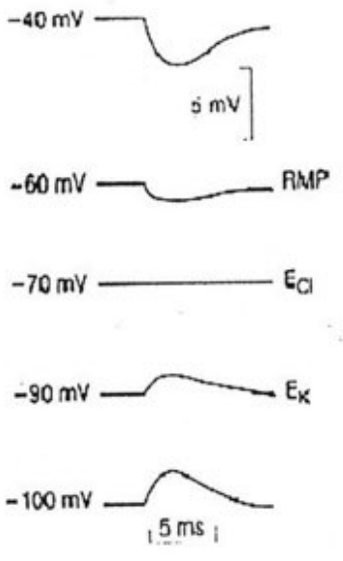
Spatial summation (A-C) and temporal summation (D-F) of EPSPs.records are potential changes recorded with one electrode inside the post synaptic cell.A-C:Afferent volleys of increasing strength were delivered.More and more synaptic knobs were activated and in C,the firing level was reached and an action potential generated.D-F:Two different volleys of the same strength were delivered,but the time interval between them was shortened.In F, the firing level was reached and an action potential

IPSP

Stimulation of some inputs produces hyperpolarizing responses. They are called inhibitory post synaptic potential. They peak 1-1.5 ms after the stimulus and decrease exponentially with a time constant (1/e or 1/2.718 of the maximum) of about 3 ms. during this potential the excitability of the neuron to other stimuli is decreased. Consequently it is called IPSP. Spatial summation as well as temporal summation occurs.

An IPSP can be produced by a localized increase in Cl^- transport. When a synaptic knob becomes active, the released transmitter triggers the opening of Cl^- channels in the area of the post synaptic membrane under the knob. Cl^- moves down its concentration gradient. The net effect is the transfer of negative charge into the cell, so that the membrane potential increases. The decreased excitability of the nerve cell during the IPSP is due to movement of the membrane potential away from the firing level. Consequently, more excitatory (depolarizing) activity is necessary to reach the firing level.

IPSPs can also be produced by opening of K^+ channels with movement of K^+ out of the post synaptic cell. In addition they can be produced by closure of Na^+ or Ca^{2+} channels.



IPSP due to increased Cl^- influx produced by stimulation when the membrane potential is set at various values with a voltage clamp. RMP, resting membrane potential of this neuron. Note that when the voltage is set at E_{Cl} the IPSP disappears and that at higher membrane voltages it becomes positive.

6. Classification & properties of receptors:

Classification:

According to the type of stimulus:

1. Mechanoreceptor: mechanical stimulus like touch pressure
2. Chemoreceptor: Chemoreceptors for taste, smell, osmoreceptors
3. Thermoreceptors: thermal-degree of warmth
4. Nociceptors-Noxious stimuli, damaging body tissue. E.g.: pain
5. Photoreceptors: Electromagnetic stimulation. Light. E.g.: rods and cones

According to type of receptors:

1. Teleceptors: Concerned with sensory perception at a distance. E.g.: Hearing, vision, smell
2. Exteroceptors: Concerned with perception of external environment near at hand. E.g. Touch, pressure, pain, temperature
3. Interceptors: Respond to changes within the body itself.

Its different types are:

- Proprioceptors:
  - a) Muscle Spindle
  - b) Joint receptors
  - c) Golgi tendon organ
  - d) vestibular receptors

These gives information about changes of position of the body in space specially tension of muscles at given moment.

- Visceroceptors:
  - a) Baroreceptors
  - b) Osmoreceptors
  - c) Chemo receptors

General/Anatomical Classification:

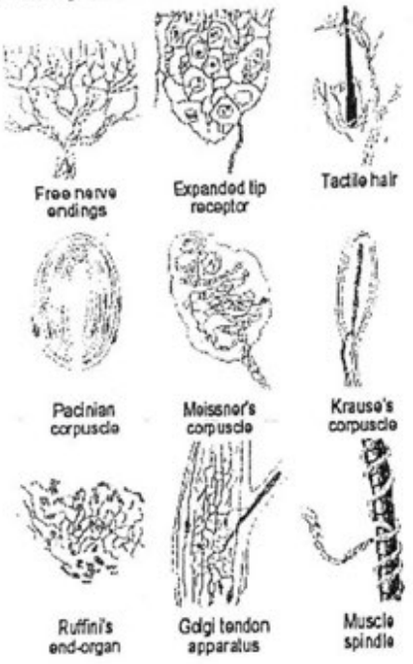
Receptors are situated very close to the CNS and the information is carried by the CNS to brain. They are especially for one type of sensory stimulation.

1. Special senses: vision, hearing, smell, taste etc
2. Superficial/cutaneous: Information carried by cutaneous branches of spinal branches. E.g.: Touch, pressure, cold, warmth
3. Deep Senses: Carried by deep muscular branches of spinal nerves from deep body tissue.
4. Visceral senses: Concerned with perception of internal environment and carried by autonomic nerves also. E.g.: Pain from the visceral structures.

Merkels Disc:

Expanded nerve terminal concerned with perception of touch supplied by A α of sensory nerve fibres. They transmit an initially strong but partially adapting signal and then a continuing weaker signal that adapts only slowly. Therefore they are responsible for giving steady state signals and allow determining continuous touch of

objects against the skin. Found in finger tips, lips, mouth. Also in hairy skin around the base of hair follicle.



Meissners Corpuscle:

Again form encapsulated ending. Maximum density in the skin of fingertips, hand, foot, nipples and in non hairy parts of skin

Paccinian Corpuscles:

Unmyelinated nerve terminals of Aβ fibres surrounded by concentric ring of connective tissue lamellae. Myelination starts within the corpuscle. First node of Ranvier is within Pacinian corpuscle. It resembles the cut section of an onion. Found in large numbers in skin, sub cutaneous tissue and mesentery. It's rapidly adapting.

Ruffini's end organ:

Encapsulated and expanded ending. Present in deep layers of skin and connective tissue. Slowly adapting, respond to heavily prolonged touch and pressure.

Krause's end bulb:

Encapsulated nerve ending in skin. Occurs in papillae of lips and conjunctiva.

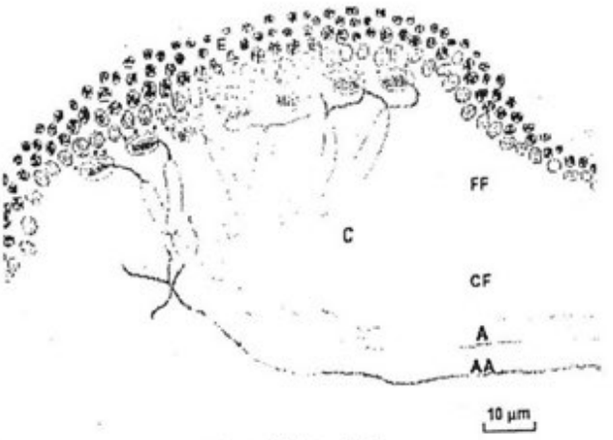
Hair end organ: Hair on the body and a nerve fibre entwining its base. Adapts readily. It is a touch receptor.

Detects:

- Movement of objects on the surface of the body
- Initial contact with the body

Iggodome receptor:

Merkel's disc grouped together which projects upwards against the underside of epithelium of the skin. Extremely sensitive receptor helps in localising touch sensation to specific surface areas of the body and in determining the texture of touch.



Iggo dome receptor. Note the multiple numbers of Merkel's discs connecting to a single large myelinated fiber and abutting tightly the undersurface of the epithelium.

Naked nerve endings: Terminal branches of nerve fibres, Aα or C. Concerned with pain. Also convey sensation of temperature and touch. Pain receptors show no adaptation.

Thermoreceptors: Warmth-Dorsal root C fibres .Cold by Aδ and also by C fibres. If the skin is mapped mm by mm by a fine hair, the sensation of touch is evoked from spots overlying the touch receptors. It has been established that large areas of skin have all four cutaneous sensations with no visually recognisable specialised receptors. This indicates that the receptors are probably the naked free nerve endings and transmission of sensation is by peripheral nerve fibres.

Properties of receptor function:

1.Law of Adequate Stimulus: Each receptor is highly specific responding to the adequate stimulus maximally even though it can be sometimes stimulated by other stimuli when applied in high strength. Rods and cones-light, muscle spindle-stretch.

2.Adaptation/Desensitisation of Receptors: When a stimulus of constant strength is applied to a receptor, the frequency of AP in a sensory neuron decreases over a period of time i.e. the receptor gets accustomed to the stimulus. The degree to which adaptation occurs varies from one sense organ to other and the mechanism of adaptation is also different in different receptors. Generally the mechanism may be a receptor phenomenon. The adaptation occurs due to a receptor phenomenon.

In the case of Pacinian corpuscle adaptation occurs in 2 ways. Pacinian corpuscle is a viscoelastic structure. When a distorting force is suddenly applied to one side of the corpuscle, the force is transmitted to inside and the Unmyelinated nerve ending is stimulated and the generator potential is produced which is transmitted along the nerve fibre. AP is produced which reaches the CNS.

Immediately after this, i.e. few hundredth of a second, the fluid within the Pacinian corpuscle gets redistributed and the receptor potential is no longer generated.

Because the adaptation of Pacinian corpuscle occurs due to the accommodation of nerve fibre within Pacinian corpuscle i.e. even if the central nerve fibre gets distorted, the tip of the nerve fibre gradually become accommodated to the stimulus which results from progressive Inactivation of Na^+ channels in the nerve membrane. Depending on the adaptation there are there are 2 types of receptors.

1.Rapidly adapting/Phasic receptors:

Also termed as Rate/Phasic receptors. They are stimulated when the strength of the stimulus changes and these receptors cannot be used to transmit continuous signal. E.g.: Touch receptors like Pacinian corpuscle, Meissners corpuscle. Merkels disc and Ruffini's end organ adapt more slowly. Olfactory receptors are also example.

2.Slowly adapting /Tonic:

They continue to transmit impulses as long as the stimulus is present. This adaptation appears to have some value to the individual. Eg: The light touch would be distracting if it were persistent one does not feel the contact of the clothes he wears. E.g.: Muscle spindle, Golgi tendon organ, Baroreceptors, Chemoreceptor etc. The slow adaptation of muscle spindle is needed to maintain the body posture. Similarly the input from the Nociceptors provides a warning effect. They would lose some of their values if these receptors were rapidly adapting.

3.Muller's doctrine of specific nerve energies:

This comes under coding of sensory information. This is by different mechanism. In general, the AP are parallel in all neurons. For e.g.: the AP produced in a nerve fibre from a touch receptor is essentially identical to that produced in a nerve fibre from a warm receptor. There are different mechanisms:

- Impulse generated in a receptor depends upon the part of the brain they ultimately activate.
- In addition, there are separate pathways from the sense organs to the cerebral cortex and they are developed early in the life.

When the nerve pathway from a particular sense organ is stimulated, the sensation is evoked for which the receptor is specialised no matter how or where along the pathway, the activity is initiated. This principle first established by Muller and is called as **Muller's doctrine of specific nerve energies**. E.g.: If a Pacinian corpuscle in the hand is stimulated or arm is stimulated by pressure at the elbow or by irritation from a tumour in the brachial plexus, the sensation experienced is that for touch sensation.

4.Law of Projection:

No matter where a particular sensory pathway is stimulated along its course from a receptor to the cortex the conscious sensation produced is referred to the location of the receptor. E.g.: In humans during the neurosurgical procedure in conscious patients, this was illustrated. When the cortical receiving area for impulses from the left hand is stimulated, patient receives sensation in the hand.

Phantom Limb:

Another example is the amputated limb. Some of the patients may complain pain and proprioceptive sensation in absent limb(unusual limb).It is referred to as Phantom Limb. The nerve endings were cut at the time of amputation. This neuromass may discharge properly. Some sensation may again stimulate the neuromass. Impulses previously came from the amputated limb and the sensation produced projected is located previously.

5.Law of intensity discrimination:

2 ways by which we can differentiate the intensity whether the touch is light/heavy; pain is mild, moderate/ severe; they are the2 mechanisms by which information about the intensity of the stimulus is transmitted to the brain.

- Variation in the frequency of AP generated in the given receptor
- By variation in the number of receptor getting activated.

The magnitude of sensation felt is proportional to the log of intensity of stimulus. This is the **Weber Fechner law**

A power function more accurately describes this relation:

$$R=KS^a$$

R: Sensation felt

S: Intensity of stimulus .K and A are constants

6.Sensory units:

Sensory axon and its peripheral branches. Number of branches may be there for cutaneous sensation. Receptive field of a sensory unit is the area from which a stimulus produces response in that unit. In cornea and adjacent sclera. Area supplied by a single sensory unit is 50-200 mm^2. Area supplied by one sensory unit overlaps and interdigitates the area supplied by the other.

7.Recruitment of Sensory units:

As the strength of the stimulus is increased, it tends to spread around a large area and activate receptors in the surrounding area. If the stimulus is weak it activates receptors with higher threshold also. If the strength of the stimulus is more, more and more units get activated, i.e. more afferent pathways get activated. Receptors of the sensory unit also get activated.

7.Law of projection&phantom limb:

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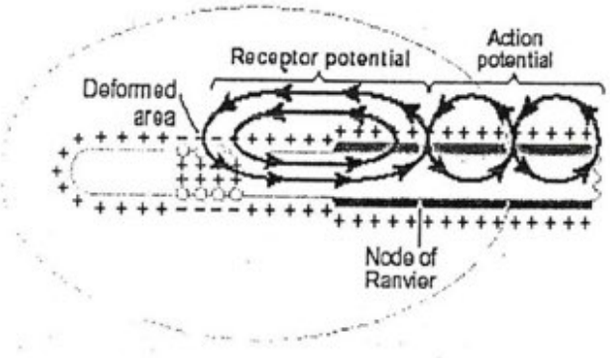
8. Generator potential:

When a stimulus is applied, certain changes occur in the receptor leading to the production of AP in the sensory neurons. Different receptors can be excited in different ways.eg: Mechanical, chemical, thermal stimuli. In all instances, the basic cause for the change in membrane potential is due to the change in the membrane permeability which causes diffusion of ions across the membrane and non propagated depolarising potential which resembles EPSP is produced. This is called **Receptor Potential** or **Generator Potential**. The receptor in turn induces a local circuit of current flow which spreads along the nerve fibres. At the first node of Ranvier, AP is generated. It is transmitted through the nerve fibre to CNS.

Thus at the node, the graded response is converted to AP and the frequency is proportional to the strength of the stimulus. The mechanism by which receptor generates AP in the sensory neuron varies with size of the sense organ. In the skin, Pacinian corpuscle has been studied in great detail.



Excitation of a sensory nerve fiber by a receptor potential produced in a pacinian corpuscle.

Pacinian corpuscle can be isolated and subjected to micro dissection and can be studied using micro electrodes. The recording electrode can be placed over the sensory neuron as it leaves the corpuscle. Another electrode can be placed over the sensory neuron as it leaves the corpuscle. Another electrode can be placed at unmyelinated nerve ending. When a small amount of pressure is applied to the Pacinian corpuscle, a non propagated depolarising potential is recorded. This is the generator potential or receptor potential .As the pressure is increased, the magnitude of receptor potential is also increased. When it is about 10mV, a propagated AP is produced in the sensory nerve. The relation is that as the intensity of stimulus is increased, (here pressure) the generator potential increases in magnitude and the frequency of AP is increased.

When pressure is applied to the Pacinian corpuscle, deformities in the centre lead to changes in membrane permeability, which causes opening of Na^+ channels, and generator potential. Magnitude depends on the number of Na^+ channels opened.

Sources of GP: By micro dissection, it has been shown that initially receptor potential is produced which on reaching firing level produces the propagating AP.

After removing the connective tissue First node of Ranvier blocked by pressure when the sensory neuron is cut and allowed to degenerate

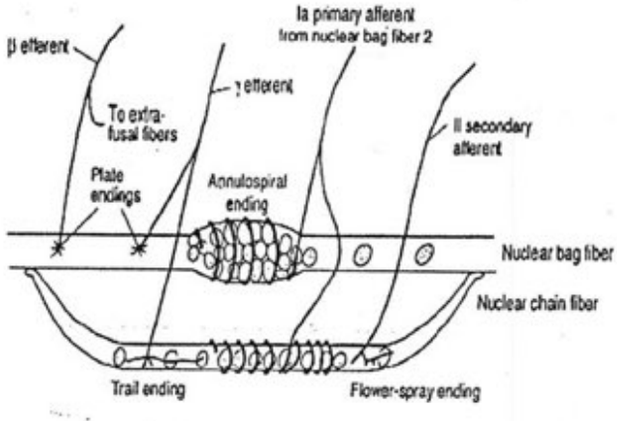
Lamellae, if we apply pressure we get or giving narcotics.GP is unaffected. No AP and stress is given, no GP and AP.

Graded response first and then AP

Thus it is concluded that the generator potential produced in the unmyelinated nerve ending and AP at first node of Ranvier in Pacinian corpuscle.

9. Structure of Muscle Spindle:

Muscle spindle is a small (3-10mm long) encapsulated spindle like structurelocated within fleshy parts of muscle. Ends of spindle capsule is attached to tedons at either end of muscle or to connective tissue of the sarrounding extrafusal fibres



Each Muscle spindle has 3 elements

1. A group of special intrafusal muscle fibres with contractile ends and a non contractile center.
2. Large myelinated afferent nerves (Type Ia and II) originating in the central portion of the intrafusal fibres
3. Small myelinated afferent nerves (γ) supplying the polar contractile regions of the intrafusal fibres.

Intrafusal fibres

- Intrafusal fibres are positioned parallel to extrafusal fibres (the regular ccntractile units of muscle)
- Intrafusal fibres have contractile ends and a non contractile center.
- Intrafusal fibres are purely sensory in function, they do not contribute to contractile force of the muscle.

There are 2 types of Intrafusal fibres

1) Nuclear Bag fibres
   - Contain many nuclei in a central dilated area
   - Subtypes - Dynamic and Static
   - Each spindle has about 2 or 3 Nuclear Bag fibres
2) Nuclear Chain fibres
   - Thinner and shorter and lacks a definite bag and have nuclei throughout the receptor area
   - each spindle has about 5 of these fibres

Afferent nerves

2 types of sensory endings in each spindle

1. Single 1° endings (Group Ia) - 17μm, 70-120m/sec
2. Upto 8 2° endings (Group II) - 8μm, 30-70m/sec

- The Ia fibres wraps around the ceter of dynamic & static nuclear bag fibres (annulospiral endings)
- Group II are located adjacent to the nuclear chain fibres (do not innervate dynamic nuclear bag fibres)→
- when the muscle spindle is stretched → central portion of spindle is stretched →depolarise the afferent nerve endings → Receptor pottential is generated → Action pottential in the sensory fibres is propotional to the degree of stretching.

- when the spindle is relaxed → cessation of the afferent activity (loading the spindle)
- Ia afferents are very sensitive to the velocity of change in muscle length during stretcg (dynamic response) - provide information about speed of movement

- Tonic activity of Group Ia and Group II provide information on steady sate length of muscle (static response)

- Ia afferent dischage most rapidly while the muscle is being stretched (dynamic response) and less rapidly during sustained stretch (static response)

- Group II discharge during sustained stretch (sstatic response)

- Group II fibres make only a small contribution to stretch reflex.

- Most Group II fibres terminate on multiple interneurons that cause muscle contraction by polysynaptic pathway

Dynamic stretch reflex

caused by rapid stretch → stimulation of Ia → instantaneous strong reflex → reflex function to oppose sudden change in muscle length

Static stretch reflex

elicited by continuous static receptor signals → Ia & II endings → reflex causes degree of muscle contrction to remain reasonably constant.

Efferent nerves

- Spindles have a motor supply of their own.

- These nerves are γ motor neurons

2types

- Dynamics (γ_d) - supply the dynamic nuclear bag fibres (plate ending)

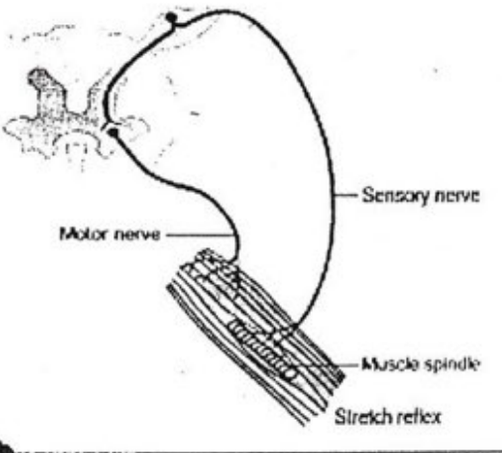
- Static (γ_s) supply the static nuclear bag fibres & nuclear chain fibres(trail ending).

10. Monosynaptic reflex:

If the reflex arc has an afferent nerve connecting directly with only one synapse in the centre; reflex pathway is monosynaptic. Stretch reflex is the typical e.g.: When a skeletal muscle with an intact nerve supply is stretched, it contracts

Stimulus → Stretch on the muscle
Sense organ → Muscle spindle
Afferent nerve → dorsal root ganglion
Centre → Spinal cord α motor neuron or brainstem nucleus

Efferent nerve → Á motor neuron supplying the same muscle
Effect → Contraction of the muscle being stretched



Clinical example:

•**Knee jerk**: Tapping the patellar tendon elicits the knee jerk stretch reflex.On tapping,quadriceps muscle is stretched,results in reflex contraction.It seen as a forward movement of leg.

•**Triceps Jerk**: Stretching of Triceps by tapping the olecranon process which receives the insertion of the muscle, will extend the elbow.

physiological importance:stretchb reflex is responsible for maintaining muscle tone&thus maintain posture and equilibrium of body.

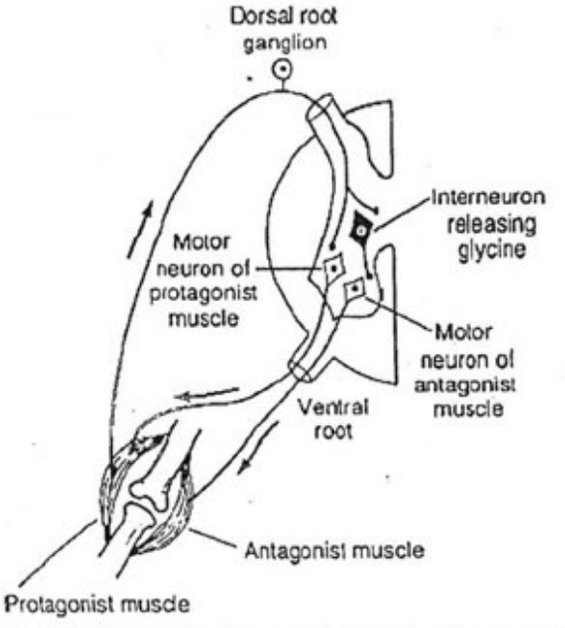
Reaction time: Time between the application of stimulus and the response is called Reaction Time. Time for knee Jerk is 19-24 ms.

Central Delay: Time taken for the reflex activity to traverse the spinal cord.0.6-0.9 ms for knee jerk. Minimum synaptic delay is 0.9, i.e. only 1 synapse in knee jerk.

11. Reciprocal innervation:

• Its an example for a **bisynaptic reflex**

When a stretch reflex occurs, the muscles that antagonise the action of the muscle involved (antagonists) relax. This is phenomenon is said to be due to **reciprocal innervation**. Impulse in I a fibre from the muscle spindle of the protagonist muscle cause **post synaptic inhibition** of the motor neurons to the **antagonists**. The pathway mediating this effect is bisynaptic. A collateral from each I a fibres passes in the spinal cord to an inhibitory interneuron(Golgi bottle neuron) that synapses directly on one of the motor neurons supplying the antagonist muscles.



(also refer figure of reciprocal inhibition in short note 11)

12. Inverse stretch reflex:

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 ceases and the muscle relaxes.** This relaxation in response to strong stretch is called the Inverse stretch reflex or **autogenic inhibition**.

The receptor for the inverse stretch reflex is in the **Golgi tendon organ.**Afferent fibres go to inhibitory interneuron ,which inhibits the α motor neuron so that its firing is decreased.GTO acts as a transducer regulating tension of muscle.

Muscle spindles are excitatory to muscle tone,whereas GTO are inhibitory to muscle tone.

Since the Golgi tendon organ, unlike the spindles are in series with the muscle fibres, they are stimulated by both passive stretch and active contraction of the muscle. The threshold of the Golgi tendon organs is low. The degree of stimulation by passive stretch is not great, because the more elastic muscle fibres take much of the stretch and this is why it takes a strong stretch to produce relaxation. However discharge is regularly produced by contraction of the muscle, and the Golgi tendon organ thus functions as a transducer in a feedback circuit that regulates muscle force in a fashion analogue to the spindle feedback circuit that regulates muscle length.

GTO decides tension in the muscle &mucle spindle regulateslength of muscle.Moderate stretch producing contraction and stronger stretch producing relaxation;this can be better studied in case of **hypertonia like Clasp-knife rigidity.Ankle clonus** is a neurological sign that elicited in the gastrocnemius muscle in hypertonia.

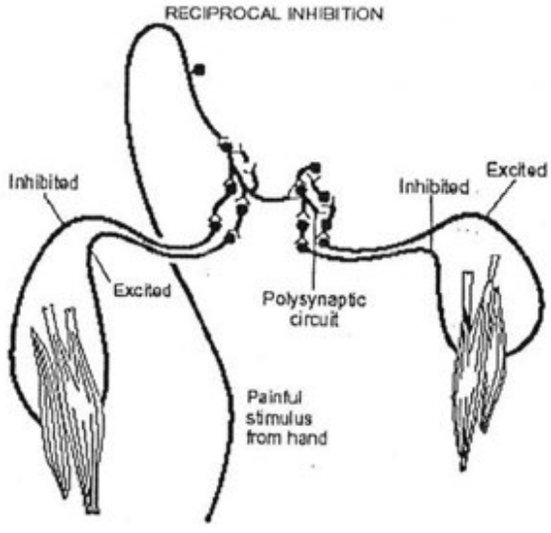
13.Withdrawal Reflex:

•its an example for a **polysynaptic reflex.**

•It occurs as a result of **noxious or painful stimulation** of skin, sub cutaneous tissue or muscle. The response is usually flexion, contraction of flexor group of muscles, relaxation of extensor group of muscles so that the stimulated limb is withdrawn. **Centre is the spinal cord and there are large number of synapses** response also varies depending on the strength, duration and site of application of stimulus.When a strong stimulus is applied to a limb, there is flexion and withdrawal of that limb and simultaneously

•In **spinal animals**, when a hind limb of an animal is stimulated with a strong stimulus, that limb is withdrawn, and then opposite hind limb is extended, ipsilateral forelimb extended and contra lateral forelimb flexed.

•A strong stimulus cause spread of excitatory impulse up and down the spinal cord stimulating more and more motor neurons. This is termed as **irradiation of stimulus** and there is increased number of active motor neuron. This is also termed as **recruitment of motor neurons.**



Flexor reflex, crossed extensor reflex, and reciprocal inhibition.

Importance:

It is a protective reflex. Occur only with nociceptive stimuli, stimuli that are noxious, potentiallyharmful to the animal.The flexion of stimulated limb gets it away from the source of irritation. Extension of the other limb supports the body.

Withdrawal reflexes are **stronger** than the other. They block the spinal pathways from any other reflex activity taking place at the moment.

•**Local Sign:** The dependence of the exact response on the location of the stimulus is called Local Sign. For e.g.: medial aspect of the limb is stimulated, the response includes some abduction with flexion. When the lateral side is stimulated, adduction and extension result. The reflex response in each case generally serve to effectively remove the limb from irritating stimulus.

14. Properties of reflexes:

1.Adequate stimulus:

All reflexes are evoked by a stimulus. The stimulus that triggers the reflex is very precise. That stimulus is called adequate stimulus for that reflex.

2.Final Common pathway:

The Alpha motor neuron that supply the extra fusal fibres in the skeletal muscle are the efferent of many reflex arcs. All neural influences affecting the muscle contraction ultimately passes through the alpha motor neuron to the muscle. They are known as final common pathway. Numerous inputs converge on the alpha motor neuron, one from the same spinal level, and second from the levels of spinal cord via interneuron, both excitatory and inhibitory reflexes are reaching alpha motor neuron, third from multiple long tracts descending from the brain. They always converge on the alpha motor neuron determining the activity of the final common pathway.

3.Central excitatory states and inhibitory states:

Spinal cord shows prolonged changes in the response due to activity of reverbatory circuit .The prolonged state in which excitatory influences exceeds the inhibitory influences is the central inhibitory state. For e.g.: after complete transection of spinal cord, initially there is a state of spinal shock. After there is the return of reflexes. During that period if a mild noxious stimulus is given, it may cause withdrawal reflex and some autonomic changes occur. Urination, defecation ,sweating and there may be changes in BP. This is known as Mass reflex which occurs when the central excitatory state is marked.

4.Habituation & Sensitisation:

By experience, the reflex activity can be modified. If the stimulus is benign/harmless and if repeated at frequent intervals, response declines after sometime and finally disappears. This response is termed as habituation. Sensitisation is the opposite response, i.e. the facilitation of synaptic conduction is a response that can be produced by noxious stimulus. This effect can last for hours and days. It is important in learning and memory.

5.Reaction time:

Time required for the production of reflex action after application of stimulus. Time for synaptic delay, time to cross the central synapse and time to pass through efferent nerve are included in this.

6.Summation:

- Spatial: If a number of sub threshold stimuli are applied simultaneously-evokes response.
- Temporal: Increasing the frequency of sub threshold stimuli within short intervals: evokes response.

7.Occlusion:

Simultaneous stimulation of 2 afferent nerves produces a response smaller than the sum total effect of separate stimulation. This is due to the convergence of neurons in afferent pathway.

8.Subliminal fringe:

It is due to the divergence of the neurons, i.e. the stimulus applied to an afferent nerve build up threshold excitatory state in certain neurons and excitatory state of adjacent neurons is increased and the neuron is said to be in the subliminal fringe of others. In this case, when the 2 adjacent nerves are simultaneously stimulated, the effect produced is more than that of additive effect.

9.Recruitment:

When the threshold stimulus is applied for prolonged period, due to the activity of more motor units supplying the muscle,response occurs.

10.Irradiation:

Increased strength of stimulus: Central excitatory state spreads to greater number of neurons resulting in greater muscle activity.

11.After discharge:

Even after the application of stimulus, the reflex action of muscle continues.After discharge is possible only in the case of polysynaptic reflexes.

12.One way conduction:

Always going to the receptors from the afferent nerve and from there to the centre, then through efferent nerve to effector organ.

13.Reciprocal Innervations:

When the flexors are activated, the extensor group of muscle get inhibited. This is seen in Stretch reflex.

14.Rebound phenomenon:

During activation of a reflex, if an inhibiting stimulus is applied to the afferent nerve and if the inhibitory stimulus is removed, there is augmentation of reflex response.

15.Fractionation:

Muscle contraction induced by direct stimulation of the motor neuron will always be greater than the reflex contraction of the same muscle induced by the stimulation of afferent nerve. This is because, if the afferent nerve is stimulated, it activates only a fraction of motor units supplying the muscle.

16.Fatigue:

Can occur due to repeated activation of reflex. In fatigue, there is lengthening of the reaction time and also the strength of the response also decreases and the reflexes are susceptible.

17.Local sign: Mainly in withdrawal reflexes.

15. Adequate Stimulus:

It comes in 2 places:

1.Receptors: Each receptor is highly specific responding to the adequate stimulus maximally even though it can be sometimes stimulated by other stimuli when applied in high strength. E.g.: Receptors in retina are maximum sensitive to light. Application of high pressure to eyeball can also stimulate the retina, but the threshold is very high. So light is the adequate stimulus.

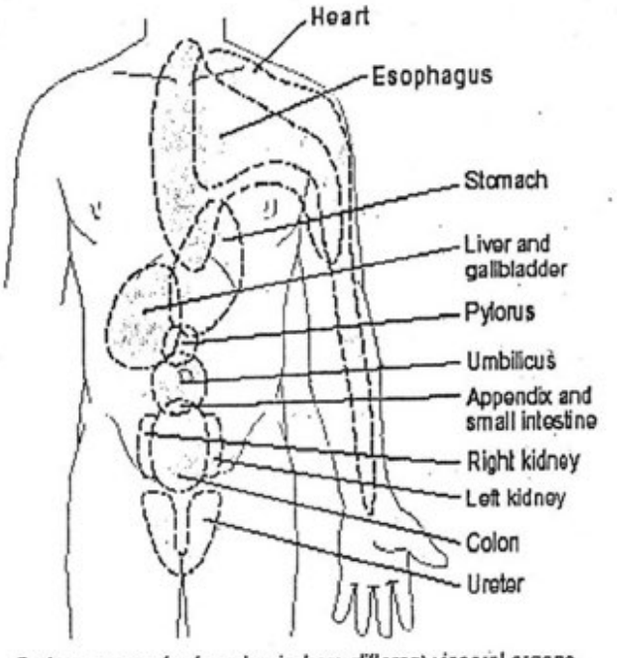
2.Reflexes: The stimulus that triggers a reflex is generally very precise. This stimulus is called the adequate stimulus for the particular reflex. A dramatic example is the stretch reflex in the dog. This spinal reflex is adequately stimulated by multiple linear touch stimuli such as those produced by an insect crawling across the skin. The response is vigorous scratching of the area stimulated. If the multiple touch stimuli are widely separated or not in a line, the adequate stimulus is not produced and no scratching occurs.

16. Referred Pain:

It is a characteristic of visceral pain and an aid to the diagnosis of visceral diseases. It is a pain felt in an area away from the site of its origin. Here the pain due to the irritation of viscous is felt in some somatic structure that may be considerable distance away. Deep pains may sometimes be referred.

E.g.:

- Cardiac pain-to inner aspect of left arm
- Diaphragmatic pain: To the shoulder especially to the tip of the shoulder
- Maxillary sinus to the near by teeth
- Gall bladder to the epigastrium
- Ureteric pain to testicle
- Appendicitis to umbilicus



Surface areas of referred pain from different visceral organs.

Mechanism of referred pain:

1.Dermatomal rule:

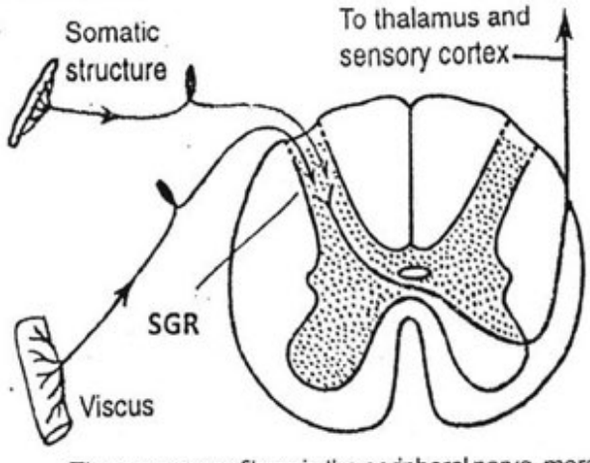
The visceral pain is referred to a structure that has developed from the same embryonic segment or dermatome as the structure from which the pain originates (both develop from the same dermatome)e.g.: Diaphragm.During embryonic development, diaphragm migrates from chest to abdomen, but retains its nerve

supply arising from C2 to C4.So diaphragmatic pain is referred to skin of the shoulder which is supplied by same segments.

Similarly the head and arm have the same segmental origin. The testicle has migrated from the primitive urogenital ridge from which kidney and ureter have developed. As a result Ureteric pain is referred to testicle. The main cause of referred pain appears to be plasticity in CNS, coupled with convergence of peripheral and visceral pain fibres ,on the same second order neuron that project to brain.

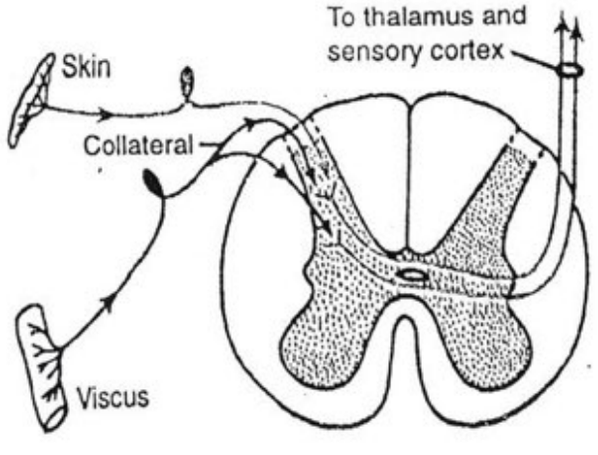
Theories of Referred Pain:

1.Convergence:



There are many fibres in the peripheral nerve, more than there are axons in the LSTT. So considerable degree of convergence of peripheral sensory nerve fibre and visceral pain fibre occur in the same dorsal horn. 2nd order neuron that project to the brain. The peripheral and visceral nerves converge in lamina I to VI of ipsilateral dorsal horn, i.e. since somatic pain pathway is mostly stimulated pain arising from the viscera may be interpreted by the brain as that arising from the somatic structure. In the case of prolonged visceral stimulus hat facilitate the peripheral nerve ending and that stimulate the 2nd order neuron.

2.Facilitation:



Fibres from the visceral organ give collaterals to the neurons of the pain pathway. So the 2nd order neuron of pain pathway comes in the subliminal fringe of visceral afferent pathway. When visceral sensation is activated, because of subliminal fringe effect, excitability of dorsal horn neurons that receive pain impulses from somatic structures is increased. Therefore minimal activity in somatic pain pathway which in the normal case usually dies out in the spinal cord is facilitated and causes strong pain.

17. Fast and Slow Pain

Fast Pain:

It is seen as a sharp localized sensation. It is due to the activity in A δ fibers. It is followed by slow pain or 2nd pain, which is seen as dull, intense diffuse and unpleasant feeling due to activity in C pain fibers.

fast pain is elicited by mechanical and thermal stimuli. A δ fibers release Glutamate

Slow Pain:

The slow pain is also described as slow warning pain. It is due to tissue destruction. It is similar to pain produced by intense heat. It is more diffuse in character. C fibers release substance P

- Aching pain is usually a deeply situated pain originating from muscles mainly.
- Throbbing pain: Pain increases with every pulsation or heart beat. May be seen associated with an abscess close to the bursting point with an intense head ache.
- Colicky pain: Appears usually at regular interval. It is due to smooth muscle spasms. e.g.:uretery colic, intestinal colic.

18.Two Point Discrimination & Stereognosis:

Two Point Discrimination:

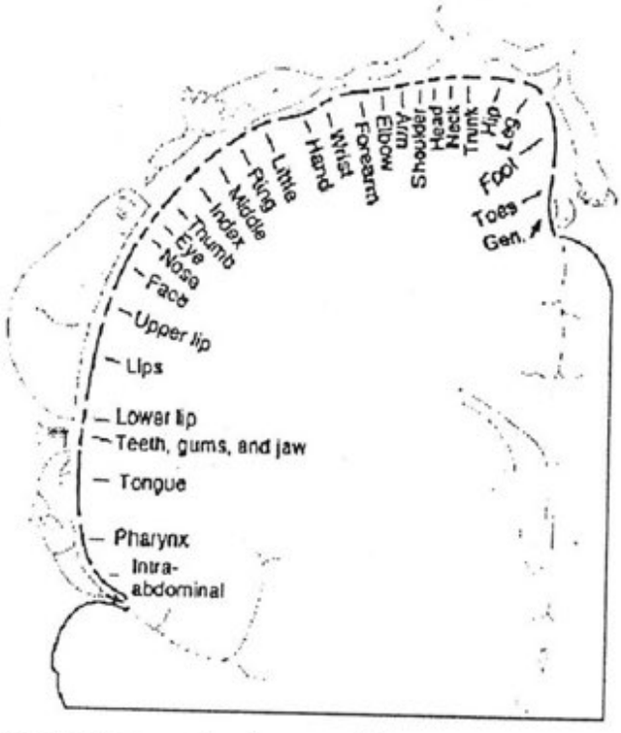
The minimal distance by which 2 touch stimuli must be separated to be perceived as separate called the two point discimination. It depends on touch plus the cortical component of identifying one or two stimuli. Its magnitude varies from place to place and is smallest where the touch receptors are most abundant. Points on the back for instance must be separated by 65 mm or more before they can be distinguished as separate, where as on fingers ,two stimuli can be resolved if they are separated by as little as 3mm.On the hands the magnitude of two point discrimination threshold is also small. However the peripheral neural basis of discriminating two points is not completely understood; and in view of the extensive interdigitation and overlapping of the sensory units, it is probably complex.

Stereognosis:

The ability to identify objects by handling them without looking at them is called Stereognosis. The ability

depends on the relatively intact touch and pressure sensation and is compromised when the dorsal column is damaged. It has a large cortical component. So impaired Stereognosis is an early sign of damage to the cerebral cortex and sometimes occur in the absence of any detectable defect in touch and pressure sensation. When there is lesion in the parietal lobe posterior to post central gyrus.

19.Sensory & Motor Homunculus:

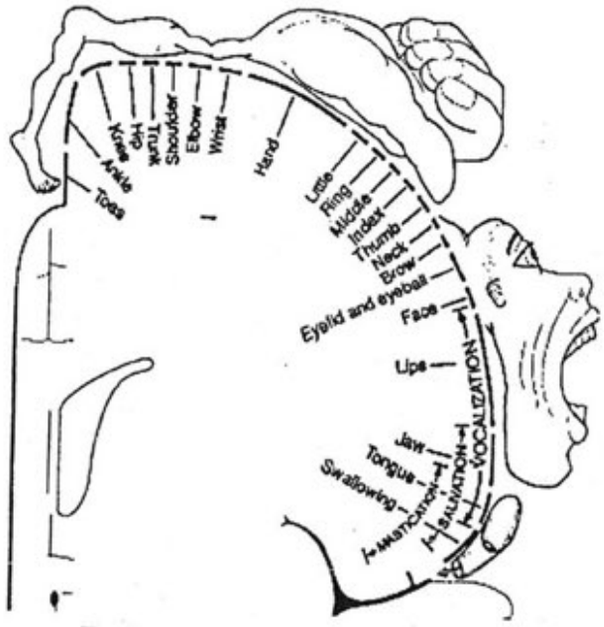


Sensory homunculus drawn overlying a coronal section through the post central gyrus.

Sensory homunculus: Different parts of the body have different representation. A map of body represented in the cortex: Sensory Homunculus by Penfield & Rasmussen. Important features:

- Body is represented upside down in Post central gyrus.
- One half of the body is represented in the sensory area of cerebral cortex of opposite side, i.e. sensations from right side of the body are represented in the left SI. This is because of the crossing of fibres in different levels.
- There is discrete point to point localisation of the peripheral parts of the body. If any point in the SI cortex is stimulated, it gives rise to sensations projected to the corresponding sides of the body.
- Large areas of representation are present for thumbs, face, lips and less for trunk and feet. Representation corresponds to the number of receptors in that particular area. More sensitive areas have larger areas of representation.
- Plasticity of neurons: If the nerve of the right hand is destroyed, and there is a sensory loss of the palm, then the corresponding area of sensory homunculus becomes useless and with passage of time, impulses from the neighbouring neurons project to the palm area of left SI. So that this area regains some activity.

Motor Homunculus:



The body is represented in the precentral gyrus with feet at the top and face at bottom. Face area represented bilaterally. But rest of the body parts-unilateral; i.e. cortical motor area controls the musculature of opposite half of the body. The cortical representation of each body part is proportional to the skill with which the part is used. Large areas of representation are present for lips, hands, thumb and the muscles concerned with the movement of pharynx, larynx, lips, tongue, feet, etc. Map of the representation of body in motor cortex-motor homunculus. Axial musculature and proximal portion of the body anterior end of precentral gyrus and distal portion: posterior edge of precentral gyrus. More than half is concerned with muscles of hand and muscles of speech. MI is organised in terms of movement rather than individual muscle. Cells arranged in columns and they receive fairly extensive input from peripheral areas in which they exert movement. This helps in feed back control

20.Difference between UMN and LMN lesions

UMN Lesions

- Destruction of upper motor neuron; neurons of brain and SC that activate the α motor neuron ,i.e. fibers of corticospinal and corticobulbar tract
- 3 types of UMN to be considered
  1. Lesion in the posture regulating pathway leads to spastic paralysis

2.Lesion of corticospinal and corticobulbar tract leads to paresis and hypotonia

3.Cerebellar lesion produces incoordination

- It involves a group of muscle
- Voluntary movements lost
- Paralysis of movements rather than muscles
- Hypertonia
- Spastic paralysis; spasticity and clasp knife rigidity
- Deep reflexes are hyperactive or exaggerated
- Superficial reflexes are absent except plantar
- Babinski's sign +ve
- Disuse Atrophy only is present, slight muscle wasting
- No electrical reaction of degeneration
- Effects of lesion of UMN are due to interruption of pyramidal and extra pyramidal system. Classical signs are weakness which predominantly affects fine distal movements, hip flexion, shoulder abduction, increased tendon reflexes, extensor plantar response. Babinski's sign +ve due to damage to lateral CST. It is believed to be flexor withdrawal reflex normally held in check by CST, useful in locating disease process but physiological significance is unknown

LMN lesions

- Lesions of spinal motor neuron and homologous cranial motor neurons that innervates the muscle, anterior motor neurons and below that level
- Voluntary movements and total reflexes lost
- Muscles either 1 or group is affected
- Hypotonia or atonia
- Flaccidity and flaccid paralysis
- Deep reflexes are diminished or absent
- Plantar reflex is normal flexor response if innervation is intact
- Muscle wasting and atrophy is marked because normal contraction is not possible
- Reaction of degeneration present
- Weakness, muscle wasting, hypotonia, weakness of muscle fibers. Repeated discharge in anterior motor neuron

21. Babinski's Sign:

It is the extensor plantar response. When the sole of the foot is struck with a sharp/blunt object from the heel around the lateral edge of sole towards medial side, dorsiflexion of big toe and fanning of other toes occurs. This is called Babinski's sign. This is a sign of Pyramidal tract lesion and UMN lesion. The normal response is flexor plantar response of toes. In some hemiplegia, the reaction may be extensive, associated with dorsiflexion, flexion of knee, flexion of hip etc. In children below 2 yrs, Babinski's sign is positive; because Myelination and proper functioning of pyramidal tract is completed by 2 yrs. Causes of +ve Babinski's sign are children less than 2 years,deep sleep,chain stoke breathing,hypoxia etc.

22. Extra pyramidal tract

All the descendimg tracts other than pyramidal tracts are called extrapyramidal tracts.It is important to note that the pyramidal tract in medulla contains not only cortical fibres or cortico bulbar fibres,but also fibres that terminate on brain stem neurons like that of reticular formation,inferior olivary nucleus etc.,which are extrapyramidal fibres.

Extrapyramidal fibres arise from cerebral cortex and from subcortical structures like basal ganglia,brainstem,reticular formation,red nucleus,tectal nucleus,vestibular nucleus and olivary nucleus.

Cortically originating extrapyramidal fibres

-Facilitatory fibres which stimulate muscle tone and stretch reflexes.

-Inhibitory fibres which inhibit or suppress motor activity or reflexes.

Cortically originating extrapyramidal fibres do not go directly to the α motor neuron;instead ,relay in reticular formation directly or indirectly through the basal ganglia.Thus,reticular formation forms the most omportant relay and integrating centre for extrapyramidal influences.

Reticulospinal tract

Fibres arising from reticular formation descend as anterior and lateral reticulospinal tract.These fibreas end in different levels of spinal cord in the γ motor neuron which supply the muscle spindle.These reticular formation consists of 2 parts;the bulboreticular facilitatory area capable of spontaneous firing of impulses and caudal inhibitory area arising from inhibitory suppressor strip of cerebral cortex or from basal ganglia which inhibit the firing of impulses.Normally there is balance between the facilitatory and inhibitory areas.The slow steam of facilitatory impulses maintains the muscle tone.

Lateral vestibulospinal tract

Arising from lateral vestibular nucleus of same side. Descends on same side. Ends in α motor neuron directly or through interneuron at various levels of spinal cord, make connections with lamina 7 and 9. It is a facilitatory pathway. Increases muscle tone of extensor muscles especially those that maintain posture.they inhibit the activity of flexor muscles.

Medial vestibulospinal tract

Arises from medial and inferior nuclei on both sides; descends in anterior funiculus, terminate in lamina 7 and 8 of anterior horn. Tract descends up to mid thoracic level. Vestibular nuclei function in close association with pontine reticular nuclei. It regulates the tone of anti gravity muscle. Impulses from cerebellum form vestibular apparatus influence the neurons of spinal cord through this pathway.They increases muscle tone of extensor muscles especially those that maintain posture.they inhibit the activity of flexor muscles

Rubrospinal tract.

Fibres decscending from the red nucleus of midbrain form the rubrospinal tract. Red nucleus has

connections with cerebellum,cerebral cortex,reticular formation.Descending fibres araising from both magnocellular which contains large neurons and parvocellular which contains small neurons.The rubrospinal tract end in α motor neuron,γ motor neuron or interneuron.But they mainly end in α motor neuron supplying the flexor muscles.It serves as an accessory path for transmission of discrete signals in motor cortex of spinal cord. When corticospinal tract is damaged, discrete movements can still occur. Fine movements of fingers and hands are considerably impaired.Rubrospinal tract facilitate the activityof flexor muscles,and inhibit the activity of extensor muscles.So it is antagonist to vestibulospinal tract.

Tectospinal tract

Fibers arise from superior colliculus in the mid brain, crosses to opposite side (Maynard's decussation) in the tegmentum and descends through reticular formation in the spinal cord, terminates in the anterior horn, lamina 5, 7, 8, either directly or indirectly. So receives impulses from retina. This tract indirectly connects retina with spinal motor neuron and co-ordinates retinal impulses with body movements.

Olivospinal tract

Fibers arise from inferior olivary nucleus of medulla, descends in lateral funiculus up to cervical region. It is less developed and less important in mammals.

Medial longitudinal fasciculus

Great physiological importance. Extends from midbrain to medulla, up to upper part of spinal cord. Composed of fibers which connect cranial nuclei of 3, 4 and 6 nuclei with one another and also with vestibular nucleus and anterior horn cells of cervical segments of spinal cord. Extends up to upper thoracic segments. It receives fibers from labyrinth, auditory pathways and cerebellum through the vestibular nucleus and superior colliculus.

The bundle co ordinates reflex movements of ocular and neck muscles in response to labrynthine, visual and auditory stimuli. Co-ordination of head and eye movements depends upon signals from vestibular apparatus. Turning movements of head in co-ordination with direction of gaze and visual axis.

Inter segmental bundles

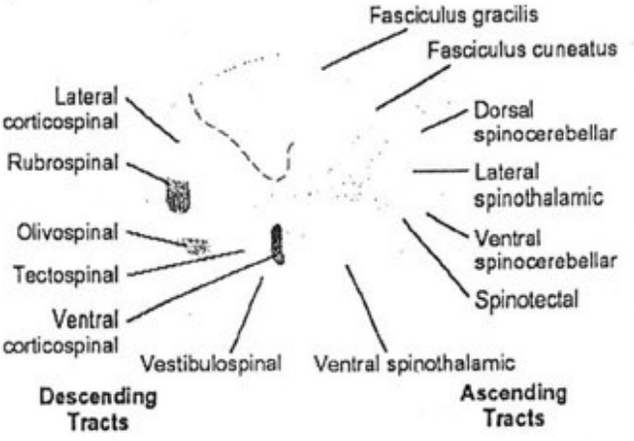
Lateral – lateral funiculus
Anterior – anterior funiculus
Posterior– posterior funiculus

They link the spinal segments at different levels. They arise in the grey matter of spinal cord. They ascend or descend for varying distance and may end on neurons of same side or opposite side of lower or higher level.

Functions of extra pyramidal tracts

1) Control of posture
2) Initiation of movements, especially those which affect postural mechanisms like sitting, standing, turning over, complex volitional movements which require postural adjustments and fine distal movements.

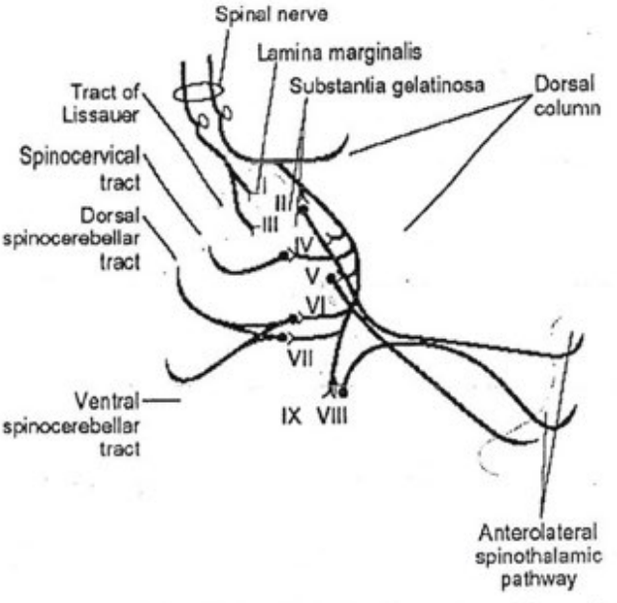
Disease or lesion of extra pyramidal tract causes difficulty in initiating the voluntary movements. Impairment of orienting and balancing reflexes by alteration in muscle tone and by appearance of involuntary movement. Muscle power is rarely weakened.



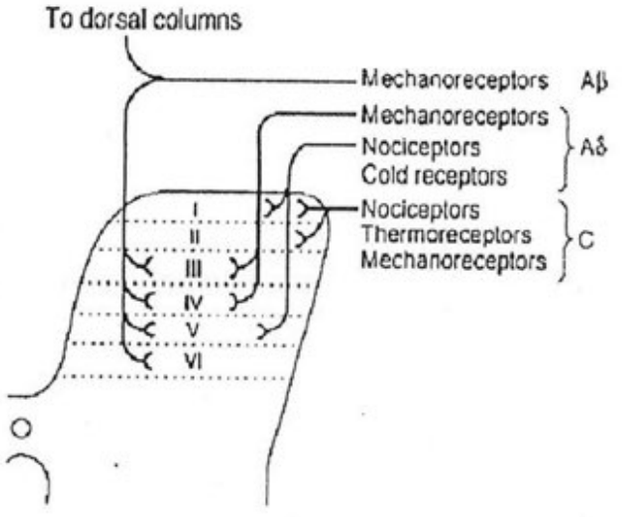
Cross section of the spinal cord, showing principal ascending tracts on the right and principal descending tracts on the left.

23. Cell groups in grey matter of spinal cord:

Posterior horn: There are 3 types of areas
i) Substantia gelatinosa seen at the tip of posterior horn
ii) Clarke's column at the base of posterior horn
iii) Chief sensory nucleus between i and ii



Cross section of the spinal cord, showing the anatomy of the cord gray matter and of ascending sensory tracts in the white columns of the spinal cord.



Anterior horn: Contains 2 types of motor neurons.
i) α motor neuron (large)
ii) γ motor neuron (small) which supply the muscle spindle

Axons pass through anterior nerve root and enter the sympathetic ganglion chain. In the sympathetic ganglion chain; they synapse with post ganglionic sympathetic neurons. The axons in turn enter into the grey ramus communicans.

Another classification based on the histological characteristics → Rexed's lamina

Posterior horn	:	lamina 1 to VI
Lateral horn	:	lamina VII
Ventral horn		lamina VIII, IX
Around central canal		lamina X

3 types of primary afferent fibers mediate cutaneous sensations:

- Aα, Aβ :Are large myelinated fibers that transmit impulses generated by mechanical stimuli
- Aδ :Carries impulses from cold receptors, nociceptors, mechanoreceptors(some) and fast pain fibers also.
- C :Small unmediated C fibers are concerned with pain and temperature.

24.Brown Sequard syndrome: refer essay 6

25. Decerebrate rigidity:

In experimental animals in which the hindbrain and spinal cord are isolated from the rest of the brain by transaction of the brainstem at the superior border of pons, the most prominent feature is marked spasticity of the body musculature. The pattern of spasticity is called Decerebrate rigidity.It is a release phenomenon.

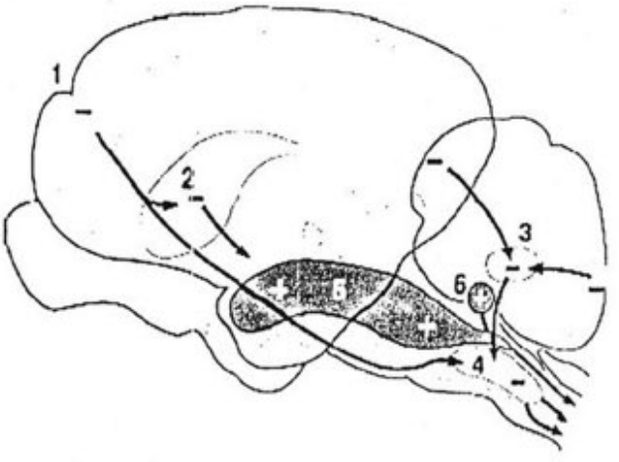
Mechanism of Decerebrate rigidity:-

Due to diffused facilitation of stretch reflexes. Facilitation is due to 2 factors:

1.Decreased inhibition of stretch reflex from higher centres
2.Increased release of spinal γ motor neuron by extrapyramidal discharge.

Significance of Decerebrate Rigidity

Marked increase in muscle tone of extensor group of muscle,called decerebrate rigidity.In cats and dogs, the spasticity produced by decerebration is most marked in the extensor muscles. Sherrington pointed out that these are the muscles with which the cat and dog resist gravity; the Decerebrate posture in these animals is, as he put it, "a caricature of the normal standing position". What has been uncovered by decerebration, then, are the tonic, static postural reflex mechanisms that support the animal against gravity. Additional evidences that this correct interpretation of the phenomenon comes from the observation that decerebration in sloth produce rigidity in flexion. In humans, the pattern in true Decerebrate rigidity is extension in all four limbs, similar to those in cats and dogs. Apparently, human beings are not far enough removed from their quadruped ancestor to have changed the pattern in their upper extremities even though the main antigravity muscles in the upright posture is are flexors. However it is rare in humans, and the defects it produce are incompatible with life.



areas in cats brain where stimulation produces facilitation (+) or inhibition (-) of stretch reflexes. 1, motor cortex;2,basal ganglia; 3, cerebellum; 4,reticular inhibitory area; 5,reticular facilitatory area;6, vestibular nuclei.

26. Chorea, Athetosis, ballism: Refer essay 7:

27. Huntingtons disease: Refer essay 7

28. Parkinsons disease: Refer essay 7

29.Lead pipe & Cog wheel rigidity:

Refer essay 7

30.Lesions of cerebellum: Refer essay 6

31.Function of cerebellum:refer essay 6

32.Regulation of food intake-Refer essay 9

33. Conditioned reflex

It is a reflex response to a stimulus that previously elicited little or no response, acquired by repeatedly pairing the stimulus with another stimulus that normally produces the response. This is a form of associative learning. (a stimulus studied in association with another).

Broadly conditioned reflex can be divided into 2:

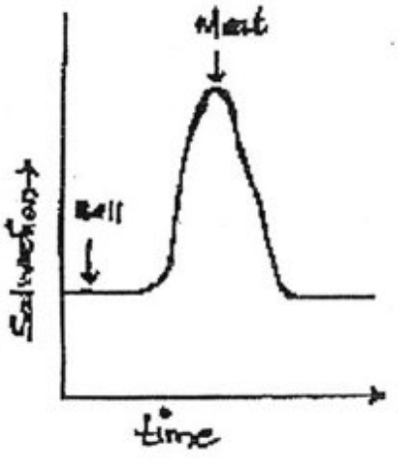
1.Type 1/classical/pavlovian conditioning:

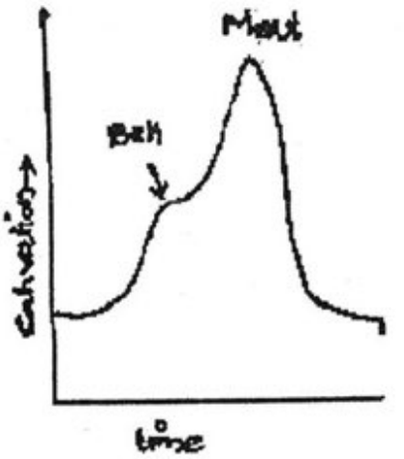
Pavlov's experiment: Here conditioned reflexes in dogs were studied. A bell was rung just before the meat was placed in the dog's mouth. It was done in a quiet room and repeatedly no of times until the animal would salivate. When the bell was rung even though no meat was placed in the mouth, dog learnt to associate bell ringing with meat. Unconditioned stimulus: meat in the mouth which produces particular innate response (salivation).

Conditioned stimulus: ringing of bell. Bell ringing which was a neutral /indifferent stimulus became a conditioned stimulus followed by repeated pairing and periodic reinforcement.

Conditions to be satisfied:

- Animal should be alert, healthy and free from any disturbances.
- Conditioned stimulus should precede the unconditioned stimulus.
- Repeated pairing is neeessary.
- Periodic reinforcement is necessary.





•Types of conditioned stimuli	•Conditioned reflex response
1.Auditory	1.Somatic
2.Visual	2.Visceral
3.Olfactory	3.Neural
4.Tactile	4.Defence
5.Thermal	5.Alimentary
6.Kinesthetic	
7.Electrical	

Biofeedback:

Conditioning of visceral response. Changes include alteration in BP and heart rate. Condition decreases BP which has been advocated for the treatment of hypertension, but the depressor response is small. Biofeedback requires considerable training. Biofeedback is claimed to be responsible for relieving migraine, headache and other forms of pain. It produces a sense of well being which is considered to be a form of conventional medical therapy.

Temporal Conditioning:

Time interval can be considered as a conditioned stimulus. A dog is fed at regular intervals of 3 hrs. After few trials, salivation occurs every 3 hrs though no food is administered. Disappearance of a stimulus can also be a conditioned stimulus. Ringing of bell is stopped and food is administered. After several experiments cessation of bell alone can produce salivation. Stopping of bell act as conditioned stimulus.

Defense conditioned reflex:

Withdrawal of a limb occurs when a faradic shock is applied to limb.Here the faradic shock is the unconditioned stimulus. Then touching the back is combined with this and a reflex is established. Then

touching the back without applying will cause withdrawal of the limb.

Higher Order Conditioning:

2nd order conditioning:

After establishing a conditioned reflex with a conditioned stimulus, yet another conditioned stimulus is added. E.g.: flash a light, then ring a bell, put meat in mouth, response is salivation. After several repetition, flashing the light alone produce salivation. Alimentary reflexes have been established up to 2nd order.

3rd order conditioning:

Sound of bubbling water→ringing bell→touching back→faradic shock→withdrawal of limb. After repetition, bubbling of water alone produces withdrawal of limb. Defence conditioned reflexes have been established up to 3rd order conditioning.

Properties of conditioned reflex:

1. Specificity-A response occurs only to that particular conditioned stimulus for which that conditioned reflex is established and not for other.

2. Generalization-Stimulus very close to conditioned stimulus can also produce a response. If a defense conditioned response has been established with touching of back as conditioned stimulus, touching the body very close by will also produces a response. For alimentary conditioned reflexes, a frequency close to conditional frequency can produce a response.

3. Summation-Adding of effects occurs if 2 conditioned stimulus each producing a response are combined.

4. Inhibition-

Can be:

a)External- conditioned reflex can be inhibited by some kind of external stimulation. E.g.: a loud noise or a stranger entering the experiment room.

b)internal is of 4 types:

- extinction
- conditioned inhibition
- inhibition of delay
- differential inhibition/discrimination conditioning

Extinction:

If conditioned reflex is repeated several times without unconditioned stimulus the response becomes weaker and finally extinct. This is due to inhibition of cortical elements of reflex arc. After extinction an external stimulus can temporarily obscure the inhibition. This is called disinhibition or inhibition of inhibition.

Conditioned Inhibition:

If salivary reflex is established to the beat of metronome, later a bell is rung along with metronome not followed by feeding. After few trials metronome alone will produce salivation. Bell and metronome cause no salivation. Here bell is conditioned inhibitor producing negative conditioned reflex. Conditioned salivary reflex is established by ringing a bell for 5 sec, so that salivation occurs after 5 sec. After that duration of bell is prolonged for 10 sec, but salivation does not occur at 5 sec but at 10 sec, this is inhibition of DELAY.

Differential Inhibition:

After generalization of a tone (tone A and tone B) tone A is always reinforced and tone B is never reinforced. Then A will produce a response and B will never and tone B will acquire an inhibitory property. The animal is able to differentiate between 2 stimuli of similar nature.

Experimental neurosis:

When stimuli are close to each other the animal is not able to differentiate between the stimuli. It becomes confined, upset and shows behavioral changes and tries to escape.

Physiological basis of conditioned reflex:

1.Due to establishment of new functional connections in nervous system.

E.g.: In salivary conditioned reflex with sound as conditioned reflex, connections develop between auditory cortex and salivary centre. With light as conditioned reflex connections develop between occipital lobe and salivary centre.

Analyzer:

The peripheral end organ, afferent pathway and cortical sensory centre together are called analyzer by Pavlov.

E.g.: Auditory analyzer: organ of corti, auditory pathway, temporal cortex

Visual analyzer: rods and cones, optic pathway, occipital cortex.

Cerebral cortex is essential for conditioned reflex. But simple less precise conditioned reflex are seen in decorticate animals due to sub cortical connections.

2.Alternate Theory: No new neural connections are developed, but in the existing path neurotransmitter in the synapse are secreted more resulting in the effect.

2. Type II / Instrumental / operant / konorskian conditioning: In this the animal is asked to perform special tasks or operate on the environment to obtain a reward or to avoid punishment. The unconditioned stimulus is pleasant /unpleasant environment.eg:rat presses a lever, a pellet of food becomes available and the animal learns to press the lever and food becomes available. Drug addiction is an example of this reflex.

Conditioned avoidance reflex / Conditioned Escape reflex:

There are conditioned motor responses that permit an animal to avoid an unpleasant animal. E.g.: pressing a bar can avoid electric shock to feet.

Food aversion Conditioning:

If a tasty food given to an animal is combined with an injection, which causes nausea and vomiting the animal develops an aversion to food. It acts as a defense against poisonous material. Can occur in humans also. It

is a very strong stimulus, sometimes learned with single pairing of conditioned stimulus and unconditioned stimulus and develops when the conditioned and unconditioned stimulus are separated by an hour or more unlike other responses.

Significance of conditioned reflex:

1. It forms an imp part in the behavior of animals as these reflexes guide the animal in the choice of its own.
2. Conditioned reflex forms an imp basis of learning. Simple acts like cycling, car driving to complex skills in certain occupation on learning become conditioned reflex. Conditioned reflexes play dominant role in education and training of the child.
3. Many day to day activities are conditioned reflexes. Rising from bed, meal times, going to places of work, sleep are conditioned reflexes.
4 They form the basis of training of animals to perform tricks
5. Psychiatric disorders and drug addictions are related to conditioned reflexes.Both classical and instrumental conditioning are helpful in the study of brain functioning, especially learning and behavioral pattern.

34. Wernicke's & Broca's area:

Broca's area (area 44);

It is the motor centre of speech.Located in the posterior part of inferior frontal gyrus of dominant hemisphere.Function is to transform neural word into articulatory sequence so that the word can be uttered in the form of spoken language.Also ordering the words into sentences so that the resulting statements have meaning with grammer.Lesions leads to motor aphasia.Here patient cannot express his ideas in spoken words.

Wernicke's area (area 22,39):

It is the sensory centre of speech.It is located in the temporal lobe at the posteroinferior end of superior temporal gyrus of the dominant hemisphere. Function is to transform sensory input (auditory and visual) into neural word and project into Broca's area through arcuate fascicles.Lesion of this area leads to sensory aphasia.Here comprehension is impaired for spoken and written language.

35. Different types of aphasia:

Aphasia are abnormalities of language functions that are not due to defects of vision or hearing or to motor paralysis.They are caused by lesion in the dominant hemisphere. Common cause is embolism of cerebral blood vessels

1.Sensory aphasia/fluent aphasia:

Lesion is in the Wernicke's area(area 22). Here comprehension is impaired for spoken and written language. Speech is fluent sometimes excessive full of **neologism**(non sense, invented word), **jargon**(extreme neologism) and **paraphasia**(compensation of forgotten word by the use descriptive phrase)

Speech contains large number of prepositions and adjectives, but few nouns or verbs. Output is voluminous but uninformative.

Causes of Wernicke's aphasia:

- Embolus in inferior division of MCA
- Intracellular haemorrhage
- Venous infarction
- Neoplasm
- Severe head trauma

A coexisting right hemianopia or superior quandrantanopia

conduction aphasia

A form of fluent aphasia is a condition in which patient can speak relatively well and have good auditory comprehension but can not put parts words together or conjure up words.It is due to lesion of the arcuate fasciculus connecting Wernicke's and Broca's areas.It may also be due to lesion in and around the auditory cortex (areas 40,41&42)

2.Non fluent/Motor Aphasia:

Lesion is in the Broca's area. Here comprehension is normal, but defective formulation of words .In severe lesion, whole language is cut short to few words. These patients are often frustrated and depressed.

Causes:

- Occlusion of superior division of MCA
- Tumour
- Intra cerebral/subdural haemorrhage
- Abscess

Additional neurological defects are right facial weakness, right hemi paresis, hemiplegia etc

3.Global aphasia: Here speech output is not fluent and comprehension is impaired. It is due to combined lesion of both Broca's and Wernicke's area. Most patients initially mute or say only a few words.

Causes:

- Lesion of entire MCA in the distribution of left hemisphere coexisting right hemi plegia, right hemi sensory loss and right homonymous hemianopia.

Anomic aphasia

When the lesion is in the angular gyrus without affecting Wernicke's or Broca's areas. There is no difficulty with speech or understanding auditory informations,instead there is trouble understanding written languages or pictures ,because visual informations are not processed and transmitted to Wernicke's area.

36. ARAS

Ascending reticular system → complex polysynaptic pathway from pons→thalamus

2 types

- Specific carries specific sensations like dorsal column,

auditory, visual

•Nonspecific receives collaterals from specific pathway concerned with arousal and alertness

Part of reticular activating bypass thalamus project to cortex.Part ends in intralaminar and related nuclei project to neocortex.

Function:

•Produces consciousness, active, alert state which is responsible for wakefulness and alertness.

•Lesion causes prolonged sleep.

37. EEG waves :

Electroencephalogram is a record of the electrical activity of cortical neural units.The instrunent used to record electrical activity of brain is called electroencephalograph.

• α waves: Rhythmical waves. Frequency between 8 and 13 Hz.Amplitude: 50 μV. Found in the EEG's of almost all normal adults people when they are awake and in a quiet resting state of cerebration

Found in the EEGs of adult human who are awake but at rest with mind wandering and eyes closed. This pattern is most marked in the parietal and occipital lobes and associated with decreased level of attention.

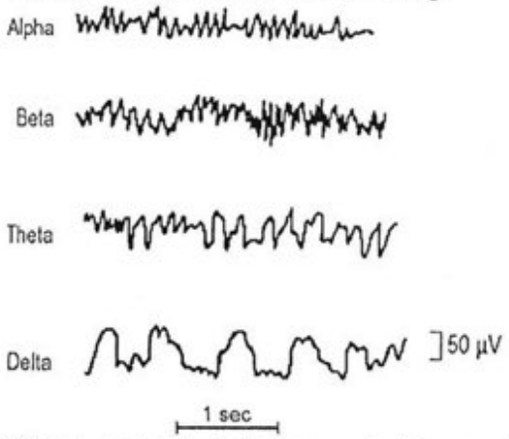
• β waves: Frequency: 14- 30 Hz. Recorded mainly from frontal and parietal regions during specific activation of these parts of the brain.

α block: when attention is focused on something, the α rhythm is replaced by β rhythm. this phenomenon is known as α block. This can be achieved by any forms of sensory stimulation or mental concentration.This is also called arousal/alerting response because it is associated with aroused,alert state.

• θ waves: Frequency: 4-7 Hz; Amplitude 10 μV. Recorded from children and is generated from hippocampus.

• δ waves: frequency <4 Hz; Amplitude 20-200 V. Usually appear during sleep in adults.

• γ waves: 30- 80 Hz: seen in patients aroused from sleep & focuses attention on something.



Different types of *brain waves* in the normal electro-encephalogram.

38. REM and NREM sleep

NREM sleep

Initially there is considerable tone in postural muscles, but later muscle tone decreases. Eye begins rolling movements until they finally stop in stage 4 with eyes turned upwards. When awakened, person does not report of dreaming.

Stages of NREM sleep:

Stage I : Very light sleep

Person is easily aroused by moderate stimulus. EEG shows low amplitude, high frequency waves. a theta rhythm (4-7 Hz) can be seen

Stage 2 : light sleep

There is further lack of sensitivity to arousal and activation.EEG characterized by presence of sleep spindle. These are burst of á like 10-14 Hz; 50μv waves. occasional high voltage biphasic waves called 'k-complexes' are also seen

Stage 3 : sleep deepens.

EEG-lower frequency, a high amplitude delta rhythm (0.5-4 Hz) dominates the EEG complex.

Stage 4 : Deep sleep.

EEG maximal slowing with large waves. Characteristic of deep sleep is pattern of rhythmic slow waves indicating marked synchronization. Activation and arousal occurs only with marked stimulation. When awakened person does not report of dreaming.

REM sleep-

Also called fast wave sleep and there is greatest relaxation and difficulty in arousal. Cannot be easily aroused by sensory stimuli. Skeletal muscle tone decrease markedly. Rapid eye movements occur in eyes. Heart rate and respiratory rate becomes irregular-character of dreaming stage. When awakened person report 80-90 %of the time that they have been dreaming.Rapid low voltage EEG activity which resembles that seen in awake,arouse state&stage1 NREM

During REM sleep brain is highly active and overall brain metabolism may increase. So its called PARADOX sleep. It is a paradox that a person can still be asleep despite marked activity in the brain.

Concomitants of REM sleep:

- •Tooth grinding (bruxism) in children.
- •Clittoral engorgement
- •Penile erection.

Another characteristic of REM sleep is presence of large Phasic potentials in groups of 3-5 that originate in pons and travel to lateral geniculate body and from there to occipital cortex and therefore it is called as ponto geniculo occipital spikes.

In experimental animals completely deprived of REM sleep loss of weight in spite of increased calorie intake and finally die. This indicate that REM sleep play an imp role in homeostasis.

39.Temperatureregulation:-

Mechanisms

- In the body,heat is produced by muscular exercise, assimilation of food, and all the vital processes that contribute to the basal metabolic rate.
- It is lost from the body in the form of radiation, conduction and vaporization of water in the respiratory passages and on the skin.
- Small amount of water is removed in the urine and faeces also.
- The balance between the heat production and heat loss determines the body temperature. Because the speed of chemical reactions varies with the temperature and because the enzyme systems of the body have narrow temperature ranges in which their function is optimal, normal body functions depends upon a relatively constant body temperature.
- Reptiles, amphibian and fish the temp adjusting mechanisms are relatively rudimentary and they are called as cold blooded (poikilothermic) because their body temperature fluctuates over a considerable range.
- In birds and mammals, also called as warm blooded (homeothermic) animals, a group of reflexes operate to maintain the body temperature within a narrow range in spite of wide fluctuations in the environmental temp.
- The centre for temperature regulation is hypothalamus.

Normal body temperature

In humans the normal value for oral temperature is 37° C (98.6° F).

Various parts of the body are at different temperatures, the extremities are generally cooler than rest of the body.

The temperature of the scrotum is carefully regulated at 32° C (less than that of body temp to facilitate spermiogenesis).

Axillary temp - 0.5° C lower than oral temp

Rectal temp - 0.5° C more than oral temp

Heat production

- BMR
- Footd intake
- Muscular activity

  major factor incresing body temp
- Calorigenic hormones
- Environmental temp
- Sympethetic discharge

  increase heat production by release of calorigenic hormones
- Brown fat

Heat loss

Radiation and conduction	: 70%
Vaporization of sweat	: 27%
Respiration	: 2%
Urination & defeacation	: 1%

- Conduction: Heat exchange between objects or substances at different temperatures that are in contact with one another. The amount of heat transferred is proportionate to the temperature difference between the objects in contact. Conduction is aided by convection, the movement of molecules away from the area of contact. Convection is greatly aided if the object moves past the medium or the medium moves pass the object ex: if a subject swims through water
- Radiation: Transfer of heat by infrared electromagnetic radiation from one object to another at a different temperature with which it is not in contact. It is because of radiation an individual can feel chilly in a room with cold walls even though the room is relatively warm
- Vaporization of water:

  Insensible Perspiration

  Sweating

The other process of transferring heat from the body in humans and other animals that sweat,is vaporisation of H_2O on skin and mucous membranes of mouth and respiratory passages.

Vaporization of 1g of water removes about 0.6kcal of heat. A certain amount of water is vaporised at all the time. During muscular exertion in a hot environment sweat secretion reaches values as high as 1600mL/h. Heat loss by vaporization of water therefore varies from 30 to over 900kcal/h.

- Some mammals loss heat **by panting.This rapid,shallow breathing geatly increases the amount of H_2O vaporisation in the mouth and respiratory passages and therefore the amount of heat lost**

Temperature regulating mechanisms

Thermoregulatory centres

- Hypothalamus is the chief centre for temp regulation
- Heat production and lose is adjusted by centres in hypothalamus,acts as a thermostat
- for heat loss - anterior part of Hypothalamus which respond to increase in body temperature
- for heat gain - posterior part of Hypothalamus which respond to decrease in body temperature

Response when Exposed to cold

1.Decrease in heat loss

- Generalized vasoconstriction by stimulation of sympathetic centres in posterior Hypothalamus
- Decreased sweating
- Curling up to decrease surface area of exposure
- Piloerection or Horripilation

2.Increased heat prodution

- Incresed apeti
- Increased muscular activity(voluntarly or involuntaryly as shivering)
- Increased secretion of calorigenic hormones

• Curling up is a common reaction to cold in animals as it decreases the body surface exposed to the environment. Shivering is an involuntary response of the skeletal muscles, but cold also causes semiconscious increase in motor activity. Eg: foot stamping and dancing up and down in a cold day. Increased catecholamine secretion is an important endocrine response to cold.

• Thermoregulatory adjustments involve local responses as well as more general reflex responses. When cutaneous blood vessels are cooled they become more sensitive to catecholamines and the arterioles and venules constrict. This local effect of cold directs blood away from the skin.

• Another heat conserving mechanism is heat transfer from arterial to venous blood in limbs. The deep veins (venae comitantes) run alongside the arteries supplying the limbs and heat is transferred from the warm arterial blood going to the limbs to the cold venous blood coming form the extremities. This mechanism is known as counter current exchange. This keeps tips of the extremities cold but conserves body heat.

Exposure to Extreme Heat

- Heat exhaustion
  peripheral vasodilation,BP falls, Profuse sweating
- Dehydration exhaustion
  If fluid lost not replaced, signs of cardiac insufficiency occur
- Heat cramps
  Due to loss of large amount electolytes, severe painful muscle contractures
- Heatstroke
  In dry skin individuals, very high temp cause damage of brain tissues

40. Vestibular Apparatus:

• Part of inner ear Concerned with maintenance of posture and equilibrium

• Consists mainly of 3 semicircular canals and 2 large chambers: utricle and saccule.

Semicircular canals(scc):

- anterior(superior)
- posterior(inferior)
- Horizontal(lateral)

Oriented at right angles to one another, so arranged in all the 3 planes of space.

Position: When head bent forward at 30 degrees, lateral SCC horizontal to earth's surface, Anterior SCC in a vertical plane project forward and posterior semicircular canal in a vertical plane project backward & 45° outward.

Two lateral canals function together, i.e. they form a synergistic pair.

Anterior canal of one side is parallel to posterior canal of opposite side & they function together.

Semicircular canals of one side are mirror image of other 3 such synergistic pairs.

Receptors:

Crista ampullaris seen in ampullary region of SCC. In the ampulla, there is a ridge on the inner wall & on it there are hair cells & the sustentacular cells & these are surmounted by loose gelatinous matrix called cupula. Processes of hair cells are embedded in cupula.

Cupula:

Extend from Crista to roof of ampulla. It closes off the ampulla

- Partitions the cavity into 2- one facing utricle & other facing SCC.
- Cupula is flexible & can move away from or towards utricle depending most on of endolymph present inside.
- Bases of hair cells are in contact with vestibular division of VIIIth nerve.

Macula:

In utricle & saccule, receptor is macula (otolith organ). It is a small sensory area, 2 mm in diameter present on the inner wall of utricle & saccule.

Utricle: macula lies horizontally on the floor with hairs vertical.

Saccule: macula is semi vertical with hairs horizontal.

In the macula, there are thousands of hair cells & sustentacular cells surmounted by otolith membrane. Embedded in it are crystals of $CaCO_3$ (otoliths/otoconia) which is denser than the endolymph. Processes of hair cells are embedded in otolith membrane. Weight of otoconia bends cilia in the direction of gravitational pull even at rest. Nerve fibres from base join these from cristae.

Hair cell

Each hair cell is embedded in an epithelial mass of supporting cells. From upper end 50-150 stereocilia arise & the largest is known as kinocilium. Stereocilia decrease progressively in height from kinocilium to the other end. Very fine processes called tip links tie the tips of each stereocilium to the side of its higher neighbour & finally to kinocilium. There are two types of hair cells:type I & type II.

Type I:flask shaped/bottle shaped.The afferent nerve ending forms a cup around greater part of sensory cell body(calyx).EFF synapses on calyx.

Type II:cylindrical,receive several afferents

RMP

When stereocilia & kinocilium bend in the direction of kinocilium, tip links stretched ⟶ opens ion channels in taller neighbors. K^+ from endolymph enter ⟶ depolarization ⟶ membrane potential becomes -50 mv. When stereocilia bend in opposite

direction away from kinocilium reduces tension on tip links, closes ion channels, there is hyperpolarisation.

Under resting condition also, there is a tonic discharge. SCC responds only to rotational acceleration or deceleration not to linear acceleration. Therefore, hair cells in cristae are called as rotary or rotatory receptors. Rotational acceleration in a particular plane causes more stimulation of SCC. SCC is filled with endolymph which is more viscous than water. When a person begins to rotate his head, SCC in that plane rotate with the head, but endolymph lags behind because of inertia & there is a relative flow of fluid in the opposite direction. Endolymph pushes cupula to the opposite side & deforms it. Bend cilia to one side ⟶ depolarization of hair cells on same side. Afferent nerve discharge rate increases on same side. Opposite changes occur in the corresponding SCC on the other side causing hyperpolarisation on opposite side. When constant speed of rotation: - fluid spin at the same rate & same direction as SCC. So cupula returns to upright position. Hair cells return to RMP. Rate of discharge in afferent nerve same as rest. During deceleration, effects are opposite to those in acceleration. Movement of SCC stops ⟶ endolymph continues to move in direction. Cupula is deformed away from kinocilium ⟶ hyperpolarisation on same side which inhibits discharge in hair cells. When momentum is overcome, endolymph stops moving, cupula returns to resting position. Similar changes occur when there is a change in the rate of movement.

Pattern of stimulation varies with direction as well as plane of rotation. From this pattern, direction of head rotation can be detected by CNS. This helps to make appropriate adjustments in posture and eye position. Linear acceleration fails to displace cupula.

Utricle respond to horizontal acceleration and saccule responds to vertical acceleration. Otoliths are denser than endolymph. Macula discharges tonically because of pull of gravity on otoliths.

When body accelerates in any direction, otoliths displaced in opposite direction and this distorts hair processes and stimulates the nerve fibers. So the rate of discharge in the afferent nerve fibers also increased. Hair cells oriented in different direction in each macula. Different pattern of excitation for each position of head and from this pattern the CNS get information of the head's orientation in space at rest (static equilibrium) and also during linear acceleration. In turn, the appropriate postural muscles are stimulated through connection with vestibular nucleus and cerebellum to maintain proper equilibrium.

Vestibular Pathway:

Receptors are hair cells in cristae of SCC, macula of utricle and saccule. Vestibular apparatus is supplied by Vestibular nerve. Cell bodies of these neurons are located in vestibular ganglion.

Peripheral processes connect with sensory hair cells and central processes enter medulla and end in vestibular nuclei of same side.

Few fibers go directly to flocculonodular lobe of cerebellum through the inferior cerebellar peduncle. These fibres coordinate activities of cerebellum with rest of equilibrium mechanism.

Vestibular nuclei have 4 parts

- ✓ Superior
- ✓ Inferior
- ✓ Medial
- ✓ Lateral

Afferents and efferents:

Superior and medial divisions recieve afferent from SCC and cerebellum.From here fibres ascend as medial longitudinal bundle and end in motor nuclei of 3rd,4th and 6th nerve of both sidesand concerned with vestibulo occular reflex,coordination of eye,head and neck movements.

Lateral division of vestibular nuclei(Dicter's nuclei) recieve afferent mainly from utricle and sacule.The efferent arising from this nuclei project down the lateral vestibulospinal tract that descends down the spinal cord mainly an uncrossed tract and end in anterior horn cell of different segment of spinal cord.Majority end in interneuron,some directly on α motor neuron supplying the extensors and some end in γ motor.Through this tract inner ear and cerebellum facilitate the activity of extensors and inhibit the activity of flexors to maintain balance.From Dicter's nuclei efferents also project to cerebellum and reticular formation.

Inferior nucleus get afferent mainly from utricle and sacule and small amount from criste and cerebellum.Efferents project to spinal cord.They help to integrate labrinthine,cerebellar and reticular activity.They contribute to lateral and medial vestibulospinal tract and medial longitudinal fasciculus.

Some fibres from vestibular nuclei ascends in medial lemniscus to opposite thalamus.From here they are relayed to primary somatosensory cortex.Fibres from vestibular nuclei pass to cerebellum of both sides via inferior cerebellar peduncle.

Fibers from utricle and saccule end predominantly in lateral division of vestibular nuclei.

From there they descend in anterior and lateral vestibulospinal tract and from there mostly in α motor neurons. They control tone of muscles in maintaining posture and equilibrium mainly the antigravity muscles. Some fibers from lateral nuclei project to cerebellum (vestibulocerebellar). Some fibers project to reticular formation- vestibuloreticulospinal tract. Fibers from semicircular canals end in superior and medial vestibular nuclei and end in the motor nuclei of cranial nerve III, IV, and VI [concerned with control of eye movement]. Some

fibers are relayed to the 1° somatosensory cortex through thalamus.

Functions of vestibular apparatus:

•Hair cells in cristae are concerned with angular acceleration:

During rest, otoconia of macula are pulled down by gravity and the hair cells are intensely stimulated and this helps to maintain posture at rest – static equilibrium. Macula stimulated by linear acceleration change in position stimulates hair cells and impulses are send to postural muscles.SCC can also predict disequilibrium and sends impulses immediately to CNS and the CNS in turn makes anticipatory correction that the person does not fall off balance. Done through vestibulo ocular reflex, tonic labyrinthine reflexes, labyrinthine righting reflexes etc which maintain body posture and movement.

• Concerned with control of eye movement through vestibulo ocular reflexes. Signals transmitted through MLF. Cause corrective movement of eye when head rotates so that vision can be fixed on a fixed image when head rotates.

Vestibulo ocular reflex:

When a person rotates head, it is difficult to fix eyes on a specific object. The vestibulo ocular reflex helps in fixation of image even during rotation. When rotation starts, eyes move slowly in opposite direction. But when limit of movement is reached, it quickly snaps back to new fixation point. Then again slowly move in opposite direction. This involuntary jerky oscillation of the eye with a slow deviation to one side [opposite to head movement] and quick movement [in the direction of head rotation] is called nystagmus. It is a reflex movement. It has

- •A slow component
- •A fast component

Direction of eye movement in nystagmus is identified by the direction of quick component, its direction of head rotation in VOR. In normal persons, nystagmus is seen only in head rotation. If it occurs in rest, it is a manifestation of ataxia and can occur in vestibular, cerebellar lesion and weakness of extra ocular muscles.

Post rotatory nystagmus

- •Occurs immediately after stoppage of rotation
- •Stoppage of rotation : cupula moves in opposite direction
- •Quick component occurs in opposite direction

Labyrinthine abnormalities

Marier's syndrome

- ➢ Recurrent attacks of vertigo
- ➢ Tinnitus
- ➢ Progressive deafness

Cause:

- •Dilatation of membranous labyrinth
- •Hyper secretion of endolymph
- •Inflammation of vestibular part of VIII nerve
- •Middle ear infection.

Motion sickness

May be seen in all types of travel to which the person is not adapted. Caused by excessive vestibular stimulation or hypersensitivity of neuroepithelium of vestibular apparatus. Nausea, vomiting, sweating, vertigo, pallor & BP changes occur.

Space motion sickness

- ➢ Nausea, vomiting and vertigo.
- ➢ Occurs in astronauts
  - o When they just enter space due to absence of gravitational pull
  - o Wear off after a few days.
  - o Can reccur on re-entry as gravity increases.

Tests for labyrinthine function

❖ **Calorie stimulation test:** water that is hotter or colder than body temperature is instilled into external ear. Due to temperature difference, convection currents are set up in endolymph which stimulates SCC, cupula deformed, hair cells stimulated and we get nystagmus, vertigo even in normal patient selectively for each ear. When irrigating ear canals in the treatment of eye infection, fluid used should be at body temperature.

❖ **Barany's chair test:**

- o Person sits on a special chair and rotated. Nystagmus develops.
- o Both produce nystagmus in normal person and altered response in dysfunction.

Effects of labyrinthectomy:

✓ **Unilateral:** Effects are due to unbalanced discharge from normal side alone. Lower animals show abnormal body posture. Postural changes much less in humans. But distressing symptoms occur like nausea, vomiting, diarrhoea which aggravates during movement. Show deviation of eyes and also nystagmus.Later compensation occurs and symptoms disappear in 1-2 months.

✓ **Bilateral:**

- oSymptoms absent
- oDefects in orientation present. If vision is normal, this can be compensated

But driving, diving etc can be very dangerous.

Vision

Prepared by
MARTIN.P.S
SHABEER.P

ESSAYS

1. Visual pathway and defects:

Receptors are the rods and cones. They connect with the peripheral process of bipolar cells in retina. Their central processes connect to the dendrites of ganglion cells. Axons converge at the optic disk to form the optic nerve. Fibers from the macula form a separate bundle called papillomacular bundle. The fibers from the 4 quadrants of retina maintain their relative position. The macular fibers occupy the central part of the nerve. The 2 optic nerves meet at the optic chiasma situated above the diaphrama sella and pituitary gland. The fibers of nasal half cross to the opposite side and join the fibers from opposite temporal retina to form the optic tract (temporal fibers don't cross). Therefore optic tract contain fibers from temporal half of same side + from that of nasal half of opposite side. The optic tract end in the lateral geniculate body, from here fibers reach the visual cortex via the optic radiations or the geniculocalcarine fibers. Primary visual cortex is located in the lingual gyrus .Also some fibers pass to other areas of brain i.e. some end in the superior colliculus of midbrain and control rapid directional movement of eye. Some reach the pretectal nucleus and are responsible for visual reflexes. Some pass from the optic chiasma to the supra chiasmatic nucleus of hypothalamus and regulate endocrine and circadian rhythm. Some also reach the ventrolateral geniculate body and control body behavior.

Lateral geniculate body

Each LGB has 6 layers and axons of ganglion cells project into it with great spatial representation. Layer 1 and 2 has large cells called magnocellular cells and receive fibers from the giant ganglion cells (type Y- responsible for detection of movement, depth and flicker). Layer 3 to 6 (parvocellular layer) receive fibers from the small ganglion cells (Type X –responsible for color vision, shape, texture and fine details) of retina.

Layer 1, 4 and 6= fibers from contra lateral eye
Layer 2, 3 and 5= fibers from ipsilateral eye

Functions of LGB

Relay information from optic tract to cortex via optic radiation.
Gates transmission of signals to visual center.

Primary visual cortex

Lies in the calcarine fissure area extending forwards from the occipital pole on the medial aspect of each occipital lobe (area 17). The lateral geniculate body projects a point to point representation to the cortex. Signals from the macular area terminate at the occipital pole. Signals from more peripheral parts of retina terminate at or in concentric semicircles anterior to pole. Upper portions are represented superiorly and lower portions inferiorly. Macula is represented by a large area.

Functions of primary visual cortex

Segregates information about color from that concerned with form and movement sense.
Combines the input of 2 eyes by means of ocular dominance Coolum.
Converts the visual world into short line segments of various orientations.

Secondary visual areas

The primary visual areas project to other parts of brain area 18, 19 etc. They continue to processes information started by area 17. They help in the appreciation of movement also.

Effect of lesion of optic pathway

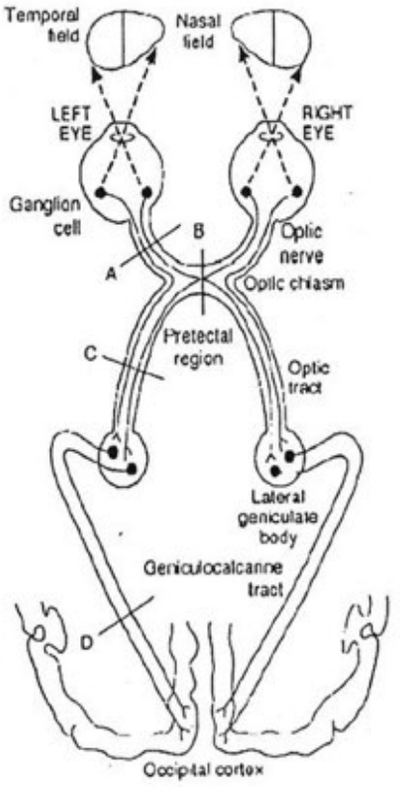
- Lesion of one optic nerve causes blindness in that eye. This usually happens in case of increased intra cranial tension, injury to optic nerve etc.
- Lesion of optic chaisma can be due to aneurysm of internal carotid artery pituitary tumors etc. this can lead to heteronymous hemianopia.Is of 2 types. Eg:, such as pituitary tumors expanding out of sella turcica (lesion of central part of optic chiasma), cause destruction of the fibers from both nasal hemiretinas. This causes blindness in temporal fields of both eyes. Also called bitemporal hemianopia. Lesion of outer margins of optic chaisma causes blindness in nasal fields of both the eyes. This is called binasal hemianopia.
- Lesion of optic tract can lead to homonymous hemianopia. Eg., lesion of right optic tract causes blindness in nasal field of right eye and temporal field of left eye. Lesion of left optic tract causes blindness in nasal field of left eye and temporal field of right eye. Since the blindness is in the same side of both visual field (left or right) it is called homonymous.
- Lesion of optic radiation is similar to lesion of optic tract. It is accompanied by macular sparing.
- Lesion of visual cortex. In the occipital cortex, representation of vision has 2 aspects:-peripheral vision and macular vision. Macular sparing is the loss of peripheral vision with intact macular vision. It is due to

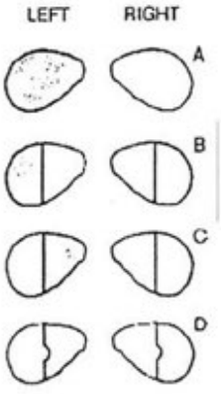
1.macular representation in the visual cotex is separate from that of peripheral field.

2. macula has got large area of representation in visual cortex

3. this area is supplied by both posterior and middle cerebral artery, both arteries may not be simultaneouly blocked to effect the macula vision.

Optic pathway and lesions





A. BLINDNESS OF LEFT EYE
B. BITEMPORAL HEMIANOPIA
C. RIGHT HOMONYMOUS HEMIANOPIA
D. RIGHT HMONYMOUS HEMIANOPIA WITH MACULAR SPARING

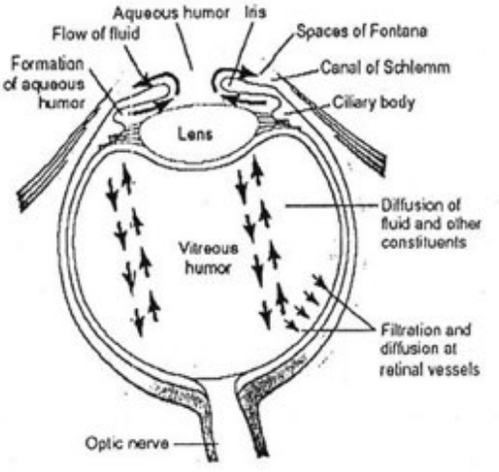
Visual pathways. Transection of the pathways at the locations indicated by the letters causes the visual field defects shown in the diagrams below.

2. Aqueous humor – production, circulating, properties and functions

Aqueous humor is clear, transparent fluid secreted by cilliary processes which are linear folded projections from the cilliary body into the posterior chamber. Folded architecture helps to increase surface area (6cm² in each eye). It is a large area compared to the size of cilliary body. The surfaces of these processes are covered by highly secretory epithelial cells and immediately beneath it is the vascular area separated by stroma contains collagen and mucopolysaccharides. Its secretion takes place by actively and passively.

Mechanism of production

Lipid soluble substances will be transported by diffusion, water soluble substances having larger size and higher charge are transported by active diffusion. First there is active secretion of Na^+ into the space between epithelial cells. The Na^+ ions pull the Cl^- ions and HCO_3^- along with them to maintain electrical neutrality. All these ions are derived by osmosis from blood into the spaces. This solution is washed out from spaces into anterior chamber of eye. Apart from ions amino acids, ascorbic acid, and glucose are also transported by active or facilitated diffusion. Production and reabsorbtion of aqueous humor is a continuous process. This balance regulates volume and pressure of intra ocular fluid.



Formation and flow of fluid in the eye.

Circulation

After the aqueous humor is formed by the cilliary process, it first flows through the pupil into the anterior compartment of eye. From here it flows anterior to the lens and then into the angle between cornea and iris. Through a meshwork of canaliculi it finally enters into canal of Schlemm. It empties into an extra ocular vein. Canal of Schlemm is a thin walled vein that extends circumferentially all the way around the eye. Its endothelial membrane is porous. It allows large proteins as well as

7510848413
9495362264

small particulate matter to pass from anterior chamber into the canal of Schlemm. Even though the canal is a venous blood vessel, so much aqueous humor flows into it that it is filled only with aqueous humor than blood. The small veins from the canal of Schlemm drain to large veins of eye also contain aqueous humor usually. Therefore they are called aqueous veins.

Properties

Clear colorless transparent fluid present in the anterior and posterior chambers of eye. Volume in anterior chamber= 0.25ml and that of posterior chamber=0.06ml. It has a refractive index of 1.34. It is alkaline (7.5 to 7.6 pH). Rate of secretion = 2-3 micro liters / min. contains all the diffusible substances of plasma.Concentration of glucose and proteins are less.

Function

Main carrier of metabolites to lens and cornea.Regulates intra ocular pressure.Maintain shape and transparency of eye. When turbid it interferes with vision, removes the waste products.

SHORT NOTES

1.Glaucoma

It is a degenarative diseaseof retinal gangion cell, usually associated with raised intra occular tension, which leads to compression of retinal artery . Retina doesn't get enough nutrition thus leading to permanent atrophy of retinal nerves and optic nerve leading to blindness. This is called glaucoma. Thus increased intra ocular pressure is only a cause of glaucoma.Other causes are:

- Unknown in most of the cases, some may be due to infection, truama to eye, prolonged use steroids.
- More often it is due to decreased out flow rather than due to increased formation of aqueos humor.

Classification (2 types)

- Closed angle glaucoma is due to closure of iridocornealangle due to forward movement of iris. sudden painful condition with mydiasis, nausea and vomiting.
- Open angle glaucoma is due to decreased permeability of trabeacular opening leads to loss of peripheral vision.

Diagnosis

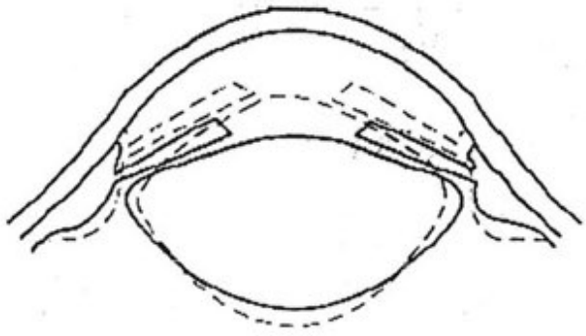
- tonometry- measuring intra occular pressure
- by measuring visual field.
- ophthalmoscopic examination.

Treatment

- Agents which decrease the formation of aqueous humor. ie acetazolamide, beta adrenergic blockers etc.
- Pilocarpin: parasympathomemetic drug, causes the constriction of sphincter pupulae (miosis) thus increasing the angle space.
- If still not cured then surgery:to open the spaces of trabeaculae or make channels to allow fluid to flow directly from the fluid space of eyeball to subconjuctival space. prostaglandin analouges.

2.Accommodation:

In an optically normal eye (emmetropic eye), the parallel rays from a distant object are brought to a sharp focus on the retina. The rays from a near object are divergent and will focus behind the retina causing blurring. But usually this does not occur because of accommodation mechanism. Bulging of anterior part of lens occurs because the lens substance is malleable and the lens capsule is elastic.



At rest the suspensory ligament is taut, the traction on the lens capsule causes flattening of the anterior surface of the lens (anterior surface more elastic). The lens ligaments are attached laterally to the circular ciliary muscles. Circular muscle fibers are arranged circularly all around the ligament attachment so when the ciliary muscles contract, a sphincter like action occurs and decreases the diameter of the circle of ligaments leading to their shortening and less pull on the lens capsule. Because of the elasticity of the lens it becomes more convex and it is the anterior surface which becomes more convex. This causes the divergent objects to be focused sharply on the retina. Purkinji sanson images, phacoscope data and slit lamp photography has proved that it is the anterior surface of the lens which under goes changes and not the posterior surface.Ciliary muscles have parasympathetic innervation. Blurring of image is the stimulus. Blurring causes stimulation of (pathway)

neural pathway

Rods and cones → bipolar neurons → optic chiasma → occipital cortex → via association fibers → to frontal eye field area 8 → via corticonuclear fibers to Edinger Westphal's nucleus → occulomotor nerve → ciliary ganglion → short ciliary nerves → ciliary muscles (increases anterior curvature of lens)

Accommodation is also accompanied by

a) Pupilary constriction: it reduces spherical and chromatic aberration, increases depth of focus and also increases visual acuity.

b) Convergence of the eye balls= by action of medial rectus.The three part response –accommodation, convergences of visual axis and papillary constriction- is called **near response.**

Neural pathway (stimulus= blurring of image)

Rods and cones ⟶ bipolar neurons ⟶ opticnerve ⟶ optic chiasma ⟶ occipitalcortex via association fibers to frontal eye field area(8)⟶ via corticoneuclear fibers to edinger westphal's nucleus and occulomotor nucleus⟶ occulomotor nerve ⟶ ciliary muscles, sphincter pupulae(constiction pupil) and medial rectus (covergence of eye ball).

Abnormalities of accommodation:

1) **Argyll Robertson pupil**: occurs when there is a lesion at pretectal nucleus (point where fibres of light reflex leave the optic tract to pretectal nucleus), usually associated with neurosyphillis, since it involve pretectal nucleus , both direct and indirect light reflex will be absent but accommodation reflex(AR) is still trere. here pupils are constricted with unequal size and irregular margin.

2) lesion beyond lateral geniculate body AR and VISION are lost, pupillary reflex is present.

3) lesion of EW nucleus: both AR and PR lost

3.Pupillary Reflexes:

When light is directed to one eye,the pupil of that eye constricts (direct light reflex).The pupil of other eye also constricts (indirect or consensual light reflex). Latent period of this reflex is 0.18 seconds, but synaptic delay of one synapse is only 0.05 seconds, therefore it is a multi synaptic pathway. With weak stimuli response is slow constriction of short duration, but with stronger stimulus the response is brisk with longer duration.

Receptors are the rods and cones.

Pathway :

Rods and cones ⟶ optic nerve⟶ optic tract leave the optic tract before reaching lateral geniculate body and reaches the pretectal nucleus in the midbrain. Next order neurons arise from here and half of the fibers reach edinger westphal's nucleus of the same side and the other half to the opposite side. Next order neurons from EW nuclues. Travel through the occulomotor nerve⟶ ciliary ganglion⟶ short ciliary nerves⟶ sphincter pupulae⟶ constriction of pupil.

Cause of indirect light reflex

- Fibers from each optic nerve enter both optic tract(due to partial crossing over at the optic chiasma)
- Fibers of each optic tract end in both pretectal nucleus.
- Fibers from each pretectal nucleus reach the EW nucleus of both sides.

Any reflex which changes the shape of pupil can be called pupillary reflex, therefore technically it also include near response. So mention it also if time allows.

4.Errors of refraction:

The normal eye in which parallel rays are focused sharply on the retina is called emmetropic eye. A deviation from this is called ametropia.

- Myopia (near sightedness): Eye ball is long in relation to the refractive power of eye and hence parallel rays from a distant object focus in vitreous , in front of the retina and distant vision is impaired. But the divergent rays from near object, focus on the retina and near objects are seen without accommodation. Myopia can be caused because of this ciliary muscle atrophy also. Defect is corrected by concave lens of suitable power which causes divergence of rays. (diagram important)
- Hypermetropia (farsightedness): Eye ball is too short in relation to refractive power of the eye. Parallel rays of different objects are brought to the focus on the retina by accommodation and subject is able to see distant objects clearly. But even with maximum accommodation the divergent rays from near object do not focus on the retina. It is corrected by convex lens of suitable strength. They cause convergence of rays. Eye ball is smaller in young children and they some times manifest hypermetropia. As age advances it is corrected by it self due to appropriate growth of eye ball. But sometimes it may persist causing hypermetropia giving rise to headache, eye strains and complications can give rise to glaucoma.
- Astigmatism: A refractive error due to unequal curvature of cornea causing unequal refraction in different planes. Therefore light rays do not come to a common focus. The rays passing through the meridian of greater curvature encounter greater refraction and are focused in front of the rays passing through the lesser curvature. For astigmats the stars appear as radial lines. They can see only vertical or horizontal lines of a graph paper at a time. Astigmatism is present in mild degree in all eyes, but when it is marked give rise to astigmatism and need correction. Corrected by cylindrical lens, so that refractions at all meridians are equal.

Types of astigmatism

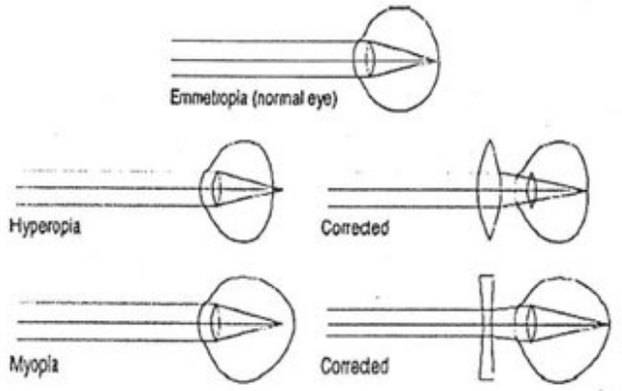
(1) Regular: In which different meridians have different curvatures, but the refractive index of each meridian is uniform. As seen in scars left over by the healing of corneal ulcers.

(2) Irregular: Here parts of different meridians have different foci. As seen in corneal ulcers or cataracts.

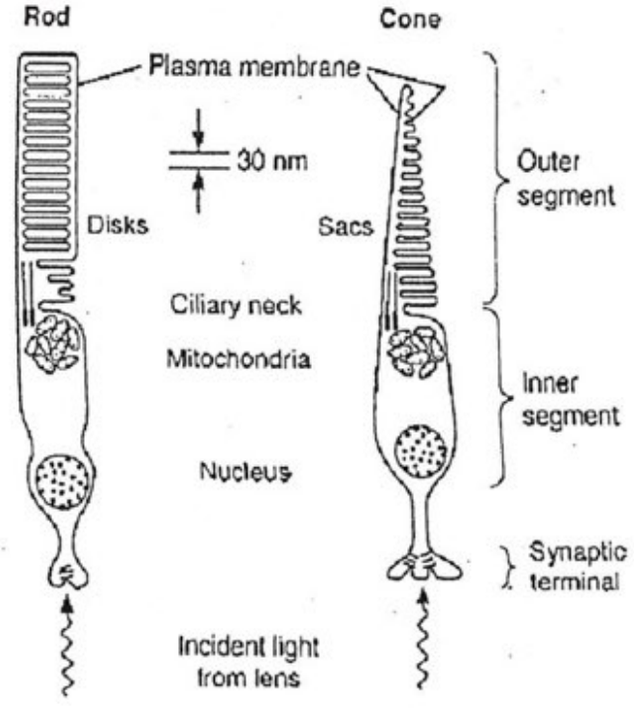
In all eye surgeries incisions are put at the limbus and not on the cornea, to prevent scar formation and hence to prevent astigmatism

- Aphakia: Crystalline lens has been removed due to cataract or trauma and eye becomes hypermetropic. And treated by spectacles with convex lens (10-11 diopters).

In such an eye there is no accommodation and image formed by a corrected aphakic eye is about 25-30% bigger. If the aphakia is uniocular,diplopia results due to changes in size of images formed by both eyes and visual field is also decreased.



5.Differences between rods and cones

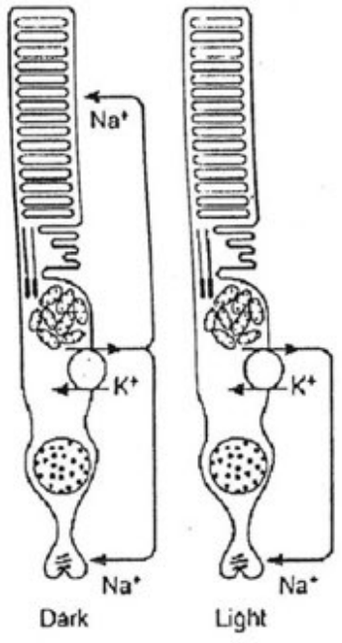


Rods	Cones
•120 million in number	•6 million in number
• More in the periphery	•found both in periphery and centre.
•Narrow and longer centre	•Long and slender cones in Broader ones in the periphery
•Outer segment thin and rod like	•Outer segment is conical
•Discs are separated from membrane	•Saccules are formed in the outer segments by membrane infolding
•Discs have photosensitive pigment rhodopsin	• Saccules have pigment iodopsin
•Renewal by formation of new disc in inner edge of of segment and phago cytosis by pigment cell	•Renewal is a more diffuse process and occur at multiple sites in outer segment
•Inner segment same size	•Inner segment thick, oval & larger
•Help in dim light vision or scotopic vision, peripheral vision	•Have greater thershold & acuity and responsible for photopic vision or color vision
•low visual acuity	•high visual acuity
•slow reaction to light	•faster reaction to light
•low threshold	•high threshold
•more sensitive	•less sensitive
•abnormalities causes night blindness	•abnormalities causes coloud blindness

6.Electrical events in photoreceptors

In the dark,

Na+-K+ pump is present in the inner segment, Na+ efflux and k+ influx occurs.cyclic AMP gated Na+ channels are present in the outer segment and synaptic junction. when Na+ enter in to the cell, it causes depolarisation of the cell and causes release of neurotransmitter from synaptic vesicles.

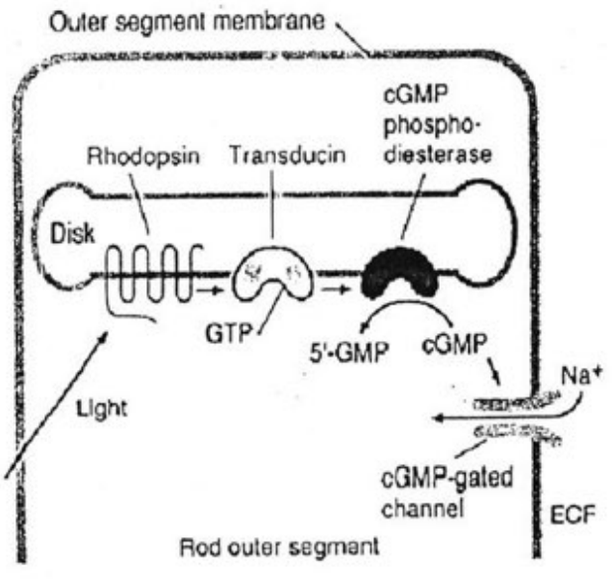


rodopsin, photopigment present in membrane of discof the outer segment of the rods,called as visual purple, In dark retinal rhodopsin is in 11 cis configruation. In presence of light , 11 cis retinal is converted in to all-trans retinal.it cannot fits in to opsin part, hence it begins to get separated.During this a series of short limp

intermediate components are formed and finally it leads to formation of scotopsin and all-trans retinal.this process is known as **bleaching,** since rhodopsin loses its purple colour.

Rhodopsin ⟶ Bathorhodopsin ⟶ Lumirhodopsin ⟶ Metarhodopsin I ⟶ Metarhodopsin II ⟶ All-trans retinal+ scotopsin

Changes in configruation of opsin stimulate the G-protein transducin,a G-protein contain alpha, beta, gamma subunits, when this activated GDP and alpha subunit together with GTP get separated from beta, gamma subunit.The alpha subunit inturn stimulates cyclic GMP phosphodiesterase, this phosphodiesterase will convert CGMP in to 5' GMP decreasing concentration of cyclic GMP will lead to the closure of CGMP gated Na+ channels. this prevent Na+ influx, finally leading to hyperpolarisation of photorecepters, results in reduced release of neurotransmitters, finally reducing response in bipolar cell and ganglionic cell.

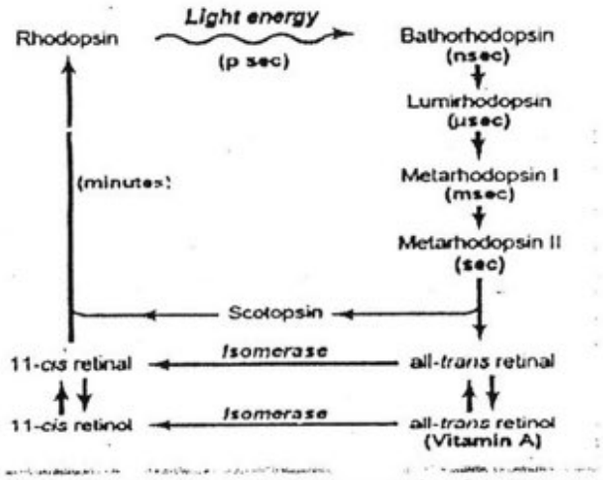


Importants of this cascade is that , there occurs enormous signal amplification. single light activated rhodopsin can activate 800 transducin molecule. each transducin can activate one phosphodiesterase, 800 phospho diesterase will be activated. each phosphodiesterase can convert 6 CGMP 6 *5'CGMP

This can result in prevention of movement of million of Na+ ion to photoreceptor.

Resynthesis of rhodopsin occurs through WALD'S VISUAL CYCLE.

Walds visual cycle



Rodes make use of 3 inhibitory mechanism to goes back to normal state,

1) becuase of the intrinsic GTPase activity of alpha subunit. GTP ⟶ GDP (hydrolysis)

2) rhodopsin will be phosphorylated by rhodopsin kinase, this permit beta subunit arrest on to get bounded to the phosphorylated rhodopsin, preventing further activation of transducin.

3)closure CGMP gated channel prevent Ca2+ in the cell. Guanilade cyclase decreases the levels of CGMP.

NIGHT BLINDNESS:; Also called Nyctalopia. Patient finds it difficult to read or dive a car in dim light. The active form of Vitamin A (11-cis retinal) is in a way needed for the regeneration of visual purple. So avitaminosis A produces visual disturbances of which the earliest to appear is Nyctalopia.

A (11-cis retinal) is in a way needed for the regeneration of visual purple. So avitaminosis A produces visual disturbances of which the earliest to appear is Nyctalopia. In this visual acuity is decreased and dark adaptation time is increased. Prolonged deficiencies are associated with anatomic changes in the rods and cones followed by degeneration of the neural layers of the retina. Long standing cases can lead to xeropthalmia. Treatment with Vitamin A can restore retinal function if given before the receptors are destroyed.

7. Color vision, theories and color blindness

COLOUR VISION: By the action of different types of cones.Explined by 3 different theories,

1)Trichromatic theory
2)Polychromatic theory
3) opponent process theory

1. Trichromatic theory:: there are 3 different types of cones, containing different photopigments,

a) Blue sensitive cones have blue sensitive pigment, S pigment, or cyanolap or maximally absorb at blue violet portion of spectrum (440nm)

b) Green sensitive cones have green sensitive pigments, or M pigments or chlorolab or maximally absorb at green portion (535nm)

c) Red sensitive cones have red sensitive pigment or Lpigment or erytrolab, maximally absorb at yellow portion (565nm), sensitivity to red is more for this cones.

Sensation of any other colour percieved on the basis of relative frequency of impulse from each of 3cone system.the cones detect the colours, P gnglionic cell processthe information send via different pahways to the visual cortex for analysis.

Red Green pathway:- signals difference between response L & M cones(L-M).

Luminance pathway:- signals the sum responses of L & M cones (L+M)

Blue Yellow pathway:- signals the difference between S cone and sum of response of L and M cone.(S-(L+M))

COLOUR BLINDNESS:

It is the inability to recognize the colors. Some individuals have inability to recognize colors while some have weakness. The suffix anomaly suggests weakness while anopia suggests blindness. Trichromats are individuals with normal color vision, in anomalous individuals protanomaly means color weakness associated with red color and deutero and tritoanomalies with green and blue respectively. Dichromats are those with only 2 cone systems. They have protanopia, deuteranopia or tritanopia. Monochramats suffer from the most common type of color blindness. Red Green CB :6% in males and 0.4% in females since it is x linked recessive. CB occurs due to an abnormal gene on the x chromosome and hence it is manifested in males. Females will manifest only when both the chromosomes are defective, otherwise they act as carriers and can pass the disease to the next generation.

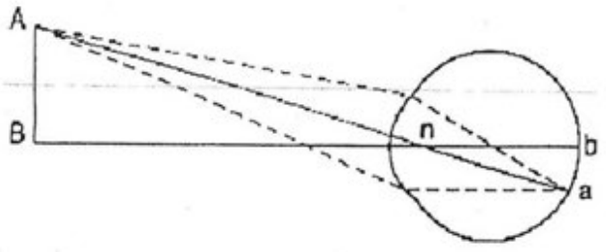
Tests for Color blindness·

Ishihara's chart : These charts are similar polychromatic plates with printed figures made of colored spots on a background of similar color spots. The figures are intentionally made up of colors that are likely to look the same as that of background for a color blind individual.

Yarn matching test/ Holmgreen's test: it is the oldest test. It depends on the matching between different shades of color wool. Subject is given one type of wool and is asked to pick from a large collection the one which matches it.

Edridge green lantern test : These are discs of colored lights of varied light or illumination. Various atmospheric conditions like fog, mist, rain etc are mimicked using suitable filters and perceptions of colored lights under such conditions are tested.

8.Visual Acuity and Tests



Reduced eye.n,nodal point.AnB and anb are similar triangles.In this reduced eye, the nodal point is 15 mm from the retina.All refraction is assumed to take place at the surface of the cornea,5mm from the nodal point,netween a medium of density 1.000 (air) and a medium of density 1.333 (water).The dotted lines represent rays of light diverging from A and refracted at the cornea so that they are focussed on the retina at a

The degree to which the details of countours of an object is perceived. It is a function of cones (day light vision) and is a complex property. But can be defined in terms of

- Minimum visible:The narrowest line that can be distinguished on a homogenous background. Minimum visible angle is the angle subtended on nodal point of eye by minimum visible.
- Minimum separable:The shortest distance by which 2 lines can be separated and still be visible as 2 separate lines (resolution threshold). This corresponds to a visual angle of 1min in normal man.

Visual angle:angle ANB

Visual acuity:reciprocal of visual angle.

Factors affecting visual acuity

- Stimulus factors:size, color and distance from eye of the object. Visibility is best when there is a contrast between brightness of object and back ground. Visual acuity increases with increase in illumination up to a limit; excess illumination decreases visual acuity and gives rise to glare.

Physiological Nystagmus:Determines visual acuity. When a subject stares at a stationary object the eye balls are not still but there is continuous jerky movement that is if the image fall readily on the same spot of retina the object disappears from view. So for continuous visualization of objects it requires that the retinal images be continuously and rapidly shifted from on receptor to another.

- Optic factors:Depend on state of image-forming mechanism eg. visual errors (refractive errors) decreases visual acuity. Adequate or optimum pupil size is needed

for greater visual acuity. Visual acuity is greatest at fovea because of densely packed cones and absence of rods. Here the cones are slender and one cone synapses with only single bipolar cell which in turn synapses with a single ganglion cell which continues as a direct pathway to brain. Also have no blood vessels and no overlying cells.

Clinical tests for visual acuity:

• **Distant vision: Snell en's chart.** It tests the ability of a subject to recognize text letters which are illuminated suitably. Used for detection and correction of refractive errors. Consist of thick block letters printed in black on a white background in horizontal rows. Each row has more letters with decreasing size and marked with distance 60, 36, 28, 12, 9, 6 and 5 (in meters). Thickness subtend an angle of 1' and height of 5' when viewed from these distances also each lines are separated by an arch of 1min.Subject is seated at 6 meters(because divergent rays are parallel and also because accommodation is eliminated). The individuals being tested reads aloud the smallest line distinguishable. The results are expressed as a fraction.

d/D = distance of subject from chart / distance from which the letters can be read by the normal eye.

6/6 or 6/5 is normal visual acuity

Illumination should not be less than 20 foot candles. If he cannot read even the top line, ask him to walk towards the chart. The farthest point at which he can read the top line is noted (if 3 m then VA= 3/60). If still not able to read then ask him to count your extended fingers at one meter. If still no success, take him to a dark room and ask him to give indication on direction of light.

For children pictures are constructed on snellen's chart.

• **Near vision chart:** Jaegers chart based on printers point system. Arranged in graded letter sizes from top to bottom. Top smallest (N6). The subject has to read it from a distance of 30 cm from eye.

9.Homonymous & Heteronymous Hemianopia

The fibers from the nasal half of each retina decussate in the optic chiasma, so that the fibers in the optic tract are those from the temporal half of one retina and the nasal half of the other. Therefore each optic tract sub serves half of the field of vision.

• **Homonymous hemianopia:** Lesion in one optic tract causes blindness in half of the visual field. Eg., lesion of right optic tract causes blindness in nasal field of right eye and temporal field of left eye. Lesion of left optic tract causes blindness in nasal field of left eye and temporal field of right eye. Since the blindness is in the same side of both visual field (left or right) it is called homonymous.

• **Heteronymous Hemianopia:** Lesions affecting the optic chaisma. is of 2 types. Example, such as pituitary tumors expanding out of sella turcica (lesion of central part of optic chaisma), cause destruction of the fibers from both nasal hemiretinas. This causes blindness in temporal fields of both eyes. Also called bitemporal hemianopia. Lesion of outer margins of optic chiasma causes blindness in nasal fields of both the eyes. Also called binasal hemianopia.

10.Binocular vision and Scotoma

The central part of visual field of 2 eyes coincides and anything in this part of the field is seen in both the eyes. Major area of visual field is binocular. Main role is for the appreciation of depth and to understand the proportions of an object. The impulse set up in 2 retinas by the light rays from an object is fused at the cortical level into a single image. The points on the retina on which the image should fall, if it is to be seen binocularly as a single object is called corresponding points. If one eye is pushed out of line while fixed on an object causes diplopia (double vision). This is because the image on the retina is displaced and does not fall on the corresponding points. This is usually seen in extra ocular muscle palsy.

Scotomata (singular= Scotoma) is an abnormality of field of vision in which abnormal blind spots appear. In Central Scotoma, there is a blind spot in the centre of the visual field. Seen in degeneration and damage to optic nerve.

When visual images chronically fall on non corresponding points in the 2 retinas in children younger than age 6, one is eventually suppressed (suppression Scotoma) and diplopia disappears. This suppression is a cortical phenomenon, and it usually doesn't develop in adults.

11.Strabismus (squint)

When visual images no longer fall on corresponding retinal point, it is called strabismus or squint. The main cause is extra ocular muscle paralysis or weakness. When squint is congenital it is called concomitant squint. Here there is no limitation of movements and no diplopia. In paralytic squint movements are limited, vertigo and diplopia are present, head is turned in the direction of the function of the paralyzed muscle and there is false orientation of field of vision. Successful treatment of some strabismus is possible with careful shortening of the eye muscles, by eye muscle training exercises, and by the use of glasses with prisms that bend light rays sufficiently to compensate for the abnormal position of eye ball. However congenital abnormalities my cause both strabismus and defective depth perception.

12.Near point and Far point

The nearest point to the eye at which an object can be brought into clear focus by accommodation is called near point of vision. The near point recedes throughout life, slowly at first and rapidly with increasing age. The recession is due to increasing hardness of the lens, with

a resulting loss of accommodation due to the steady decrease in the degree to which the curvature of lens can be increased. By the time a normal individual reaches age 40-45, the loss of accommodation is usually sufficient to make reading and close work difficult. This is called **Presbyopia.** It is corrected by wearing glasses with convex lenses. But if he has a refractive error also then the bifocal lens are used.Far point is the furthest point at which an object can be clearly seen. (theoreticanfinity but practically 6m)

13.Argyll Robertson pupil:

Causes are neurosyphillis or lesion between the points where fibers of light reflex leave the optic tract to pretectal nucleus. But Argyll Robertson pupil is also seen in other diseases producing selective lesion in the midbrain.Features:Both pupils are constricted with unequal size and irregular margin. Both direct and indirect light reflex absent. But accommodation reflex is present.

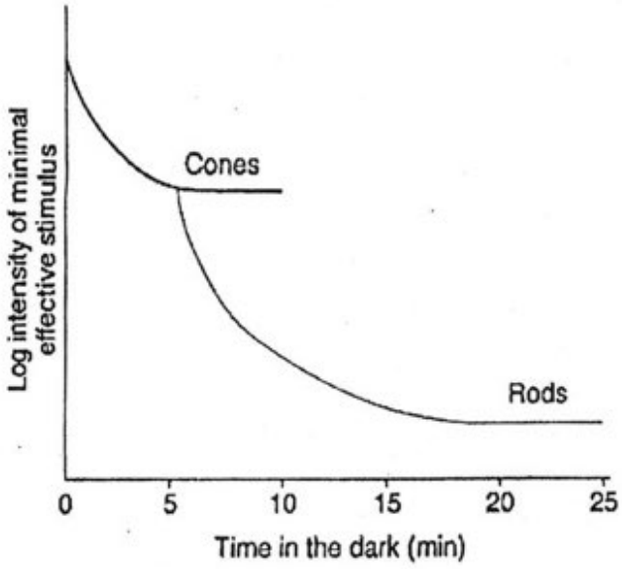
14.Scotopic and photopic vision:

Photoreceptors of retina include rodes and cones. Rodes have low threshold for detecting light and they operate best under conditions of reduced lighting. This is known as scotopic vision. The rods neither provide a well defined visual image nor contribute to Color vision. Photopic vision is associated with cones. They are not as sensitive to light as rodes. They operate best under day light conditions. Cones are responsible for high visual activity and color vision.

15.Dark adaptation

Ability by the eye to adapt itself to decreasing illumination .Person goes from bright environment to a dark environment , at first he is not able to see anything, gradually he able to see the objects, though the details and contour of the objects are not perceived. There is increse in retinal sensitivity and decrease in visual threshould, it become maximal in 20 min.

First reaction is rapid and shorter due to dark adaption of cones,second one is slower and prolonged due to the adaptation rodes.During dark adaptation there isa change of function from cones to rods.during scotpic vision there is resynthesis of rhodopsin bacuase bright light causes bleaching of rhodopsin. Its actually, time taken for resynthesis of rhodopsin.



(Dark adaptation. The curve shows the change in the intensity of a stimulus necessary to just excite the retina in dim light as a function of the time the observer has been in the dark).

Applied physiology:: Aircraft piolets and radiologist ...etc need maximal sensitivity in the dim light, if they wear red goggles, time taken for dark adaptation can be minimized. Because red goggles will allow only red light topass through it. It stimulates cones , which can function well while in bright light. Red light will not stimulate the rods, rhodopsin will not be bleached. Once enter the dark they won't have to wait for 20 minutes to get dark adapt.

Physiological basis:

1.Radiologist use red goggles in bright light.
Refer shortnote-15

2.pituitary tumors cause bitemporal hemianopia.
Refer effect of lesions of optic pathway;page no 141

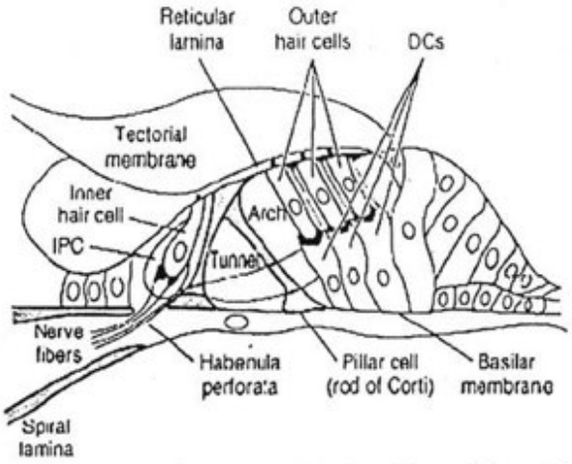
3.near point reduces rapidly with advancing age.
Refer shortnote-12

Hearing, Smell and Taste

Prepared by
DILEEP.C.U
SHABEER.P

SHORT NOTES

1. Organ of Corti:



Neural apparatus for the transduction of sound, it contain hair cells, which are auditory cells extend from apex to base, locatd on the basilar membrane.

Rods of Corti:it is 2 in number, epitheloid structures that are separate at the base where meet at apex at an angle together with the basilar membrane, they form the tunnel of corti.

SUPPORTING CELL: There are inner cells to support inner hair cells , outer phalangeal cell to support outer hair cell,also called Dieters cell. cells of hausen and cells of claudius are also supporting cells, they lies outer the outer hair cells.

Tectoreal membrane: Thin viscous elastic membrane that cover the hair cells, tip of outer hair cells are embeded in it.

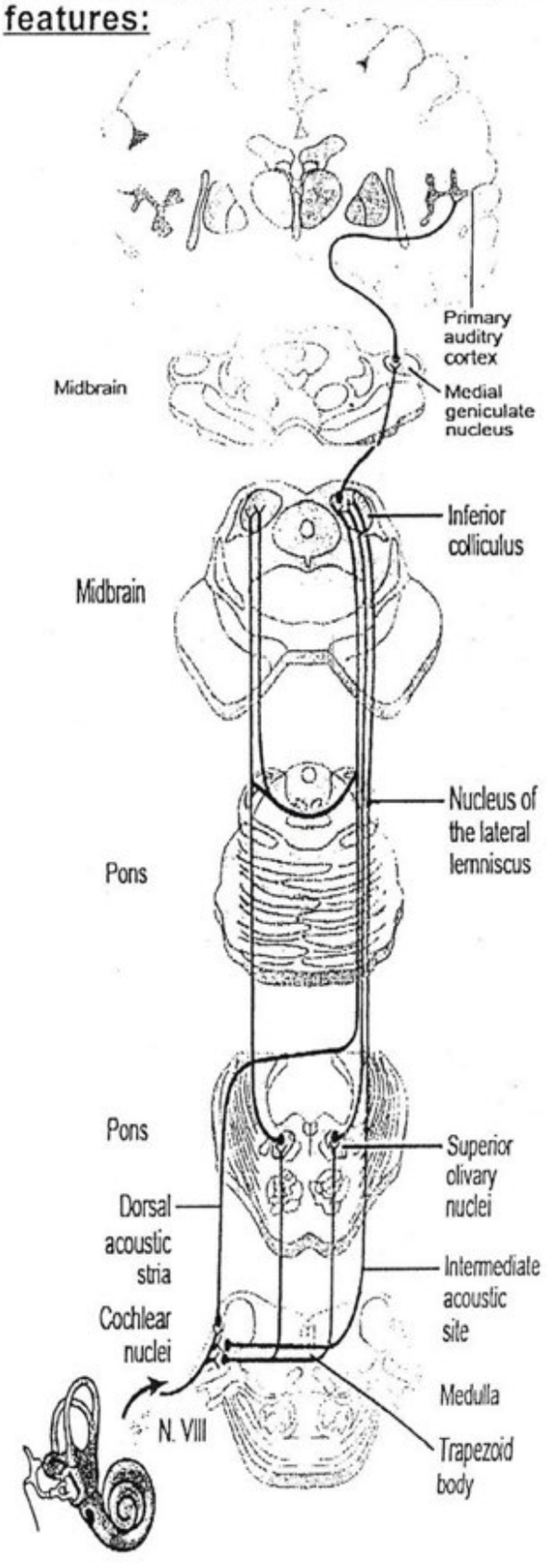
Reticular lamina;It is a huge membrane supported by rods of corti.

Hair cells; This are the receptor for hearing and equilibium. Outer hair cells 20000in number, arranged 3rows and lies medial to tunnel of corti, inner hair cells 3500, arranged single row and lies lateral lateral to the tunnel. Minute hair project from the apex of this cells, stereocilia.The base of hair cells are bathed in perilymph, tip of hair cells are bathed in endolymph.

Innervation of organ of corti:afferent:Peripheral process of this penetratethe organ of corti, terminate at the base of hair cell, 90-95% this fibers innervate the inner hair cells, 5-10% innervate the outer hair cells.

Efferent: Originate from superior olivary nucleus, most of this efferent fibres terminate on the outer hair cell, few on the inner hair cell.

2. Auditory pathway & its special features:



1st order neurons: Formed by the axons of the nerves in the spiral ganglion in the modiolus. They form the cochlear division of the VIII nerve and ends in the dorsal and ventral cochlear nuclei near the cochlea.

2nd order neuron: Arise from here and pass to opposite side of brainstem to terminate in the contralateral superior olivary nucleus. Some fibers remain uncrossed. Crossing fibers of a side form a conspicuous body called **trapezoid body**

3rd order neuron: Arises from SON and forms an important ascending tract called **lateral lemniscus.** Some cochlear N fibers that do not relay in SON join the lemniscus after relay in the nucleus of trapezoid body.Still other cochlear fibers relay in cells that lie within lemniscus itself. All these ascend to mid brain and terminate in the inferior colliculus. Fibers arising in the colliculus enternferior brachium to reach medial geniculate body. The fibers from there form the acoustic radiation which terminates in primary auditory centre on superior temporal gyrus
(area 41). Here low tones are represented anterolaterally and high tones, posteromedially.

Brodmann's area 22 is concerned with processing of auditory signals related to speech. This area is more active on left side and area on right is concerned with melody, pitch and sound intensity.

PLANUM TEMPORALE: Portion of posterior superior temporal gyrus. It is larger on left than on right cerebral hemisphere. This asymmetry is more for musicians.

Special features of auditory pathway:

1.High degree of spatial orientation is maintained in the fiber tract in the cochlea all the way to cortex. There are different tonotropic maps for different sound frequencies in cochlear nuclei, SON, ION, inferior colliculus, MGB and auditory cortex.

2.Each auditory cortex receives input from both ears.

3.Signals from both ears are transmitted through pathways of both side with

4.Crossing can occur in 3 regions:

i) Trapezoid body
ii) Commisure of probest
iii) Inferior Colliculus

5.Collateral fibers pass to reticular formation & cerebral vermis.

6.They project diffusely upwards to brain stem and downwards to spinal cord. So results inof entire nervous system,Applied physio;ogy: central lesion don't produce unilateral deafness b/c of large number of crossing over of fibers, but this lesion may interfere with sound localization and discrimination.

unilateral lesion of cochlear nucleus and peripheral structure produces unilateral deafness.

3. Functions of Middle Ear:

Middle ear is an air filled cavity in petrous part of temporal bone containing 3 ossicles (malleus, incus & stapes), 2 muscles (tensor tympani, stapedius) and openings of Eustachian tube and mastoid antrum. Its functions are:

i.Conduction of sound waves from external to internal ear:-

The vibration of tympanic membrane causes movement of the ear ossicles as a single unit which causes rocking movement of the oval window and is transmitted to the inner ear fluid.

ii.Impedance matching.

As sound passes from medium of middle ear to fluid in inner ear, there is loss of 99.9% of sound energy, because of the difference in acoustic properties of the two media. This is overcome by the middle ear property, impedance matching. This occurs by 2 mechanisms:

i) Difference in cross sectional area of tympanic membrane and oval window.

CSA of T.M.: 55 mm^2

CSA of oval window: 3.2 mm^2.

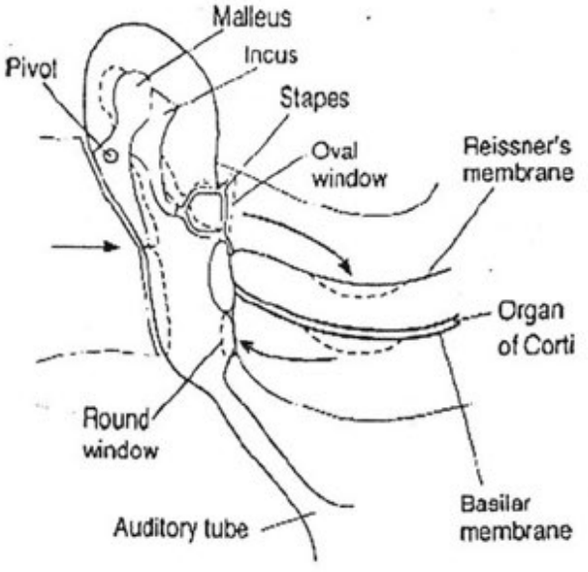
So there is 17 times magnificatlon of sound.

ii) Ossicular lever system.

Greater length of handle of malleus compared to long process of incus. The ossicular chain lever ratio is 1.3:1.

So net magnification is 17 x 1.3 =22.3 times.

Thus 60% of sound energy below 3000Hz is conducted to the round window.



iii.**Tympanic reflex:-**

Tympanic or attenuation reflex is a protective reflex that guards the inner ear from enduring loud sound. There is contraction of tensor tympani which pulls the handle of malleus inwards and makes tympanic membrane taut. The stapedius also contracts which pulls the foot plate of stapes outwards restricting the movement of ossicular chain. The threshold of activation of this reflex is 70dB and the force of contraction increases with intensity till 100dB. But the reflex does not provide protection against sudden unexpected sound like explosion or gunshot and provide protection against anticipating sound. Another feature of this is that it causes ipsilateral and contralateral contraction when sound is delivered to one ear. It has a latent period of 40-160 msec.

iv. **Middle ear helps in masking** environmental noises and permits conversation. It decreases sensitivity to one's own voice by sending collaterals to middle ear muscles. It is not a reflex response.

v. **Eustachian tube equalizes** the pressure in both middle ear and outside. So common cold and mucosal swelling of Eustachian tube can cause ear pain.

vi. Decreses sensitivity to once own voice: collateral signals are sent to middle ear musle.

4. Tests to differentiate between conductive and nerve deafness:

There are 3 tuning fork tests to differentiate conduction and nerve deafness. They are:

i)Rinne's test: The base of a vibrating tuning fork is placed on the mastoid process of subject until he no longer hears it. Then it is held in front of ear. If the subject can hear test is positive.

ii)Weber's test: The base of vibrating tuning fork is placed over the vertex of skull. In normal, hears equally on both sides. It is lateralized in abnormal condition.

iii)Schwabach's test: Base of vibrating tuning fork is placed on mastoid process of the subject and when he ceases to appreciate, tuning fork is placed on examiner's mastoid process.

5. Conduction & nerve deafness:

Conduction deafness:

It is due to impaired transmission in external ear or middle ear. Its reasons are:

a)Plugging external auditory canal with wax.
b)Perforation of tympanic membrane
c)Thickening of ear drum due to repeated infection
d)Destruction or fibrosis of ear ossicles
e)Abnormal attachment of stapes to oval window.
f)Temporary deafness can result from the difference in

Nerve deafness:

This is due to damage to hair cells or neural pathways. The causes are:

a)Drugs like aminoglycoside antibiotics e.g.: Streptomycin
b)Prolonged exposure to noise, rock music
c)Tumors of vestibulocochlear nerve or cerebellopontine angle.
d)Vascular damage to medulla
e)Presbyacusis: Gradual loss of hearing due to ageing, due to cumulative loss of hair cells and neurons
f)Deafness due to genetic mutations. This can be syndromic. e.g.: Barter's syndrome, Pendred syndrome

6.Vestibulo ocular reflex:

The reflex that maintains visual fixation on stationary points while the body rotates is vestibulocular reflex. It is not initiated by visual impulses and is present in blind individuals. When the rotation starts, the eyes move slowly in a direction opposite to the direction of rotation and maintains visual fixation. When the limit reaches, it quickly snaps, and starts moving in opposite direction. The slow component is initiated by impulses from labyrinth and quick component by center in brain stem. The condition in which this reflex is absent is called **nystagmus.**

7. Theories of hearing:

There are 3 proposed theories regarding hearing.

a)Endolymphatic potential.

There is a steady potential difference between endolymph in S.media and perilymph in S.tympani and S.vestibuli with endolymph positive by +85mV. This is called endocochlear potential. It is due to increased amount of K^+ Ions in endolymph which is because of the activity of stria vascularis due to high level of Na^+ - K^+ ATPase. The RMP of the hair cells is -60mV. Therefore total potential difference is +145mV. This sensitizes the cells thereby increasing its ability to respond to slightest sound.

b)Cochlear microphonics.

They represent the sum of resting potential of number of hair cells. They are indirectly responsible for nerve firing. It is graded potential and has no latency, refractory period and fatigue.

c)AP in auditory neuron

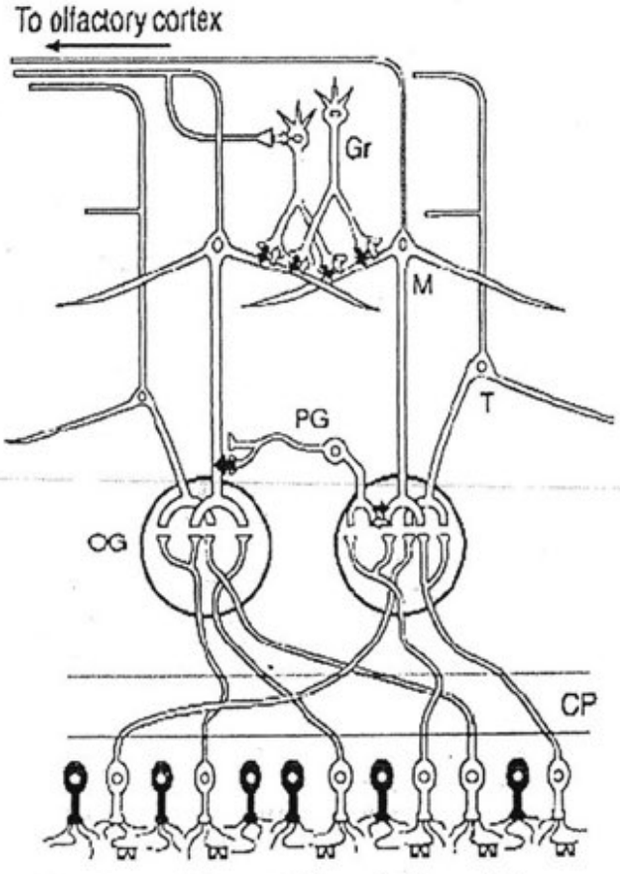
It is the spike potential and obeys all or none law. The AP has latent period, refractory period and is affected by ischemia, anoxia, cold and anaesthesia.

8. Cochlear apparatus:

Cochlear apparatus is a part of inner ear involved in hearing. It is a 35 mm long, coiled tube making 2 ¾ turns. It is divided into 3 compartments by 2 membranes. The Basilar and Ressiner's membrane divide the tube into

scala tympani, scala vestibuli and scala media.
S. tympani and S. vestibule contain perilymph and S. media contain endolymph. The S.tympani and S.vestibuli are connected by helicotrema at the apex. The S.tympani is connected to the oval window and S.vestibuli to the round window. The basilar membrane lodges the organ of Corti which is the apparatus transducing the vibrations to the electrical impulses. It contains 20000 to 30000 basilar fibers that project from bony centre of cochlea towards the outer wall. These fibers are still, elastic reed like structures that are fused at their basal ends in modiolus and distal ends are not fixed. The length of these fibers progressively increases from base to apex and it is important in pitch discrimination.

9. Olfactory pathway:



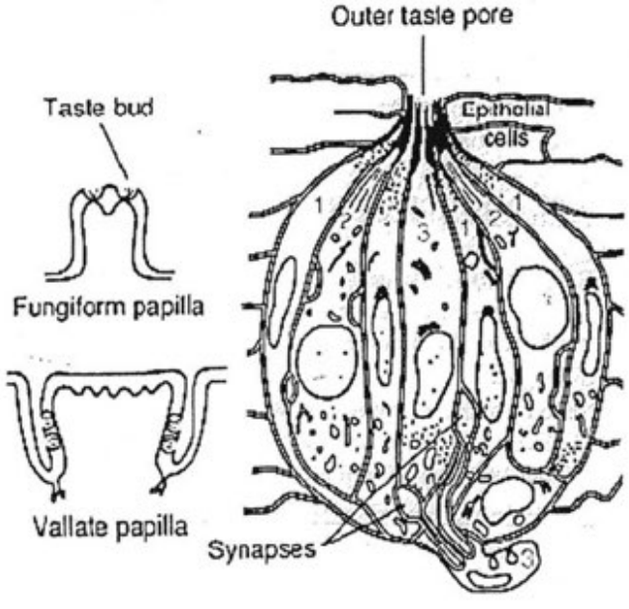
In the above diagram CP is cribriform plate, PG:periglomerular cell,M:mitralcell, OG:Olfactory Glomerulus,T: tufted cell, Gr:Granule cell

- Axons of receptors terminate on dendrites of ***tufted*** and ***mitral*** cells to form complex globular synapses called olfactory glomeruli.
- An average of 26,000 receptor cells axon converge on each glomerulus.
- ***Periglomerular*** cells connect one glomerulus with one another
- ***Granule*** cells synapse with dendrites of mitral and tufted cells.
- Tufted and mitral cells are excitatory neurons.
- Periglomerular cells are inhibitory neurons
- Granule cells inhise pass posteriorly through the lateral and intermediate olfactory striae to the olfactory cortex

Mechanism: There are many different odorant receptors on the membrane of cilia, this receptors are coupled to G protein . When a odorant molecule bind to it, G protien subunits are dissociated. The alpha subunit activate adenyl cyclase, which catalyse the production of cAMP, act as a second messenger to open cation channels, cuasing an inward directed Ca2+ current, produces graded receptor potential, leads to an action potential in the olfactory nerve.

10. Taste buds:

- Ovoid bodies about 50-70µm.
- Made up of 4 type of cells
  - ➢ Basal cell
  - ➢ Type 1 & 2 cells which are sustentacular cells
  - ➢ Type 3 cells which are gustatory receptor cells
- Each bud is innervated by about 50 nerve fibres. Each nerve fiber receives input from an average of 5 taste buds
- Replaced with a half time of 10 days
- Found in mucosa of epiglottis, palate, pharynx and in the walls of papillae of tongue
  - ➢ **Fungiform papillae**: near the tip of tongue (5 taste buds in each).
  - ➢ **Vallate papillae**: arranged in v on the back of tongue (100 taste buds in each).
  - ➢ **Filiform papillae**: on the dorsum of tongue (usually no taste bud).



11. Taste modalities:

There are 5 basic taste modalities: sweet, sour, salt, bitter and recently introduced umami

- Salt: NaCl via epithelial NaCl channels
- Umami: monosodium glutamate via truncated metabotropic glutamate receptor(mGluR4)
- Sweet: acts via Gs which activate adenylate cyclase increasing cAMP
- Sour: H^+ via HCN(hyperpolarized voltage gated cation channel)
- Bitter: via G protein coupled receptors and phospholipase C to increase calcium trigger. (e.g.: á gusducin).

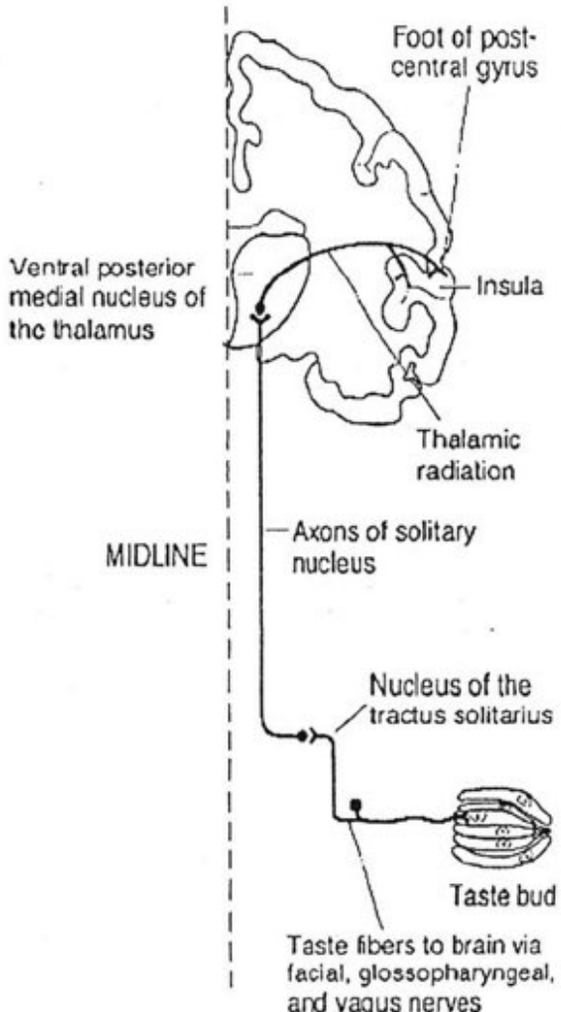
Physiological basis:

1.Removal of one auditory cortex does not result in hearing loss

Refer special features of auditory pathway page no.151(Because there is extensive crossing of fibres after the level of dorsal and ventral cochlear nuclei.Most of fibres reach contralateràl superior olivary nucleus but some reach ipsilateral also.Thereafter crossing of fibres takes place at the level of nucleus of lateral lemniscus and inferior colliculus.Thus the auditory impulses from one ear reaches both the auditory cortex).

12. Taste pathway:

- Anterior 2/3rd of tongue: chorda tympani branch of facial nerve.
- Posterior 1/3rd of tongue: glossopharyngeal nerve
- Areas other than tongue: vagus nerve



Unite at medulla to enter nucleus of Tractus Solitarius where they synapse

↓

2nd order neurons from here cross the midline to join the medial lemniscus

↓

Ends in specific sensory relay nucleus of thalamus

↓

Impulses from here are relayed to taste projection area in insula.

Endocrinology

Prepared by
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ESSAYS

1. Thyroid Hormone- synthesis, action, regulation & disorders:

Biosynthesis of thyroid hormones:(Short note)
It involves 5 steps:
1.Iodide trapping
2.Oxidation
3.Organification
4.Coupling
5.Secretion & release

1.Iodide trapping:

This is by a symporter or iodide pump called Na – I^- symporter or **NIS** which is present on thyroid cell membrane on the side facing the capillaries. The interior of the cell as well as colloid are negative in relation to the interstitium.

The NIS transports Na^+ & I^- into the cell **against** the electrochemical gradient for iodide by secondary active transport mechanism.The energy is provided by transport of Na^+ out of the cells by Na^+-K^+ **ATPase.**

Iodide then diffuses to the apical surface of epithelial cells & from there its transported to the lumen by a transporter named Pendrin (Na^+ independent I/Cl transporter).

Iodide pump is stimulated by TSH & also by decreased dietary intake of I, decrease circulatory I pool. It is inhibited by hypophysectomy & a number of anions like thiocyanate, perchlorate, pertechnitate, chlorate etc. They compete with iodide for transport into thyroid cells.

2.Oxidation.

In thyroid gland, the iodide is oxidized to iodine or nascent iodine (I_3).Then it is bound to carbon. C_3 position of tyrosine residues that are part of thyroglobin molecule in the colloid.

Thyroglobulin is synthesized by thyroid glands & secreted into the colloid by exocytosis of granules that also contain the enzyme **thyroid peroxidase.** There is exocytosis through the apical membrane into adjacent lumen.The thyroid peroxidase is situated on the apical membrane.The enzyme and the accompanying H_2O_2 catalyses oxidation as well as binding of I_2 to tyrosine. Blockage /absence of this enzyme cause a decreased rate of formation of thyroid hormones.

3.Organification

Binding of iodine with thyroglobulin molecule. The enzyme **iodinase** causes this reaction to occur within minutes.Therefore as the thyroglobulin molecule is released from the golgi apparatus or as it is secreted through the apical membrane into the follicle, iodine binds with one sixth of the tyrosine residues within thyroglobin molecule forming monoiodotyrosine, then diodotyrosine. Both MIT & DIT remain attached to thyroglobulin.

Organification is facilitated by **TSH** & inhibited by antithyroid drugs.

4.Coupling

2 DIT molecules join together by oxidative condensation to form T_4, with the elimination of alanine side chain. There are 2 theories as to how coupling occurs:

- **Intramolecular coupling:** holds that coupling occurs with both DIT molecules attached to thyroglobulin.

- **Intermolecular coupling:** holds that the DIT molecules that forms the outer ring is first removed from thyroglobulin, and then coupling occurs.

T3 is formed by condensation of MIT wit DIT.A small amount of RT3 is also formed by condenssationof DIT with MIT

In the normal human thyroid,the average distribution of iodinated compounds is 23% MIT,33% DIT,35% T4 and7% T3

Storage of thyroid hormones

The thyroid gland is unique among endocrine glands in its ability to store large amounts of thyroid hormone. Each thyroglobulin molecule contains 30 T_4 molecules and a few T_3 molecules.

The stored amount meets the need of the body for thyroid hormones for **2-3 months** even without hormone secretion.

5.Secretion and Release of T_3 and T_4 from thyroid gland.

When hormones are to be secreted, colloid is ingested by endocytosis. The chewing of the edge of the colloid gives rise to reabsorption lacunae in active gland. **Megalin**, an apical transport molecule is involved in the endocytosis of colloid. The colloid globules merge with the lysosomes.

The peptide bonds between the iodinated residues and thyroglobulin are broken by proteases in the lysosomes as a result T_3, T_4, DIT and MIT are liberated into the cytoplasm.

The iodinase enzymes are deiodinated by microsomal **iodotyrosine deiodinase.** The enzyme does

not alter the iodinated tyrosine. i.e. T_3 and T_4. They pass into circulation.

The iodine **liberated** from DIT and MIT **is reutilized** by the gland and provides 2 times the amount of iodides *compared to that taken in by the iodide pump for thyroid* hormone synthesis.

Absence of iodotyrosine deiodinase cause DIT and MIT to appear in urine.

During secretion, 90% is normally T_4 and 7% T_3. During next few days, half of T_4 is deiodinated to form additional T_3. Finally it is T_3 that is mainly used by tissues.

ACTIONS:

a)Metabolic Action:

i)Calorigenic Action:Thyroid hormone(TH) increases metabolic activities of almost all tissues iof body and causes increased heat production.

- TH increases meatabolic rate by increasing O_2 consumption of tissues.
- Increasing the number and activity of mitochondria.
- Increasing activity of Na-K ATP ase.

ii)Carbohydrate Metabolism:

- TH increases the rate of absorption of carbohydrates from GIT.
- TH also causes rapid uptake of glucose by cells.
- Enhance glycolysis,gluconeogenesis and increased insulin secretion.

iii)Fat Metabolism:

- Lipids are mobilised rapidly from tissues which decreases fat stores of body ⟶ Increases free fatty acids concentration in the plasma.
- Accelerates the oxidation of free fatty acids by THe cells.
- Decrease plasma cholesterol concentration due to increased formation of LDL receptors in liver ⟶ Increased hepatic removal of cholesterol from circulation.

iv)Protein Metabolism:

- Rate of protein synthesis is increased.
- Rate of catabolism is also increased.
- More catabolic activity.

b)Action on Growth:

TH is essential for normal growth and skeletal maturation. When TH is deficient,linear growth is decreased,tooth eruption is delayed.

In the absence of TH,GH is secretion is also depressed. TH promotes growth and development of brain foetal life and for the first few years of post natal life.

c)Action on CVS:

TH causes increased metabolism ⟶ release of increased amount of metabolic end products ⟶ vasodilation ⟶ increased blood flow ⟶ increased caridac output(CO)

+ve chronotropic effect

+ve ionotropic effect

System blood increases as CO increases

Vasodilation ⟶ decrease Pulse rate ⟶ decrease diastolic BP

Circulation time is shortened

a MHC level in heart is increased ⟶ Increases speed of cardiac contraction

d)Nervous System:

- Effects on brain development,cerebral cortex and basal ganglia.
- TH required for axonal and dendritic development and myelination.
- Increased activation of Reticular Activating System.
- enhance wakefulness,alertness,responsiveness,auditory sense,memory and learning capacity.
- Exerts effects on reflexes.The reaction time of stretch reflexes are shortened in hyperthyroidism and prolonged in hypothyroidism.

e)Skeletal Muscle:

Normal function of skeletal muscle requires optimal amount of thyroid hormone.Muscle weakness occur in both hypothyroidism and hyperthyroidism.

f)Respiratory System:

Increased rate of metabolism ⟶ increases utilisation of O_2 and formation of CO_2 ⟶ Increases rate and depth of respiration.

g)GIT:

Increases appetite and food intake.increases secretion and motility of GIT.

h)Sexual function:

TH are essential for normal menstrual cycles and fertility in females.

Needed for normal sexual function in males.

Deficiencies of thyroid hormone:

Cretinism

Cretins are children who are hypothyroid from birth or before.

Causes:

- Iodine deficiency in mother
- Congenital lack of thyroid gland
- Iodine deficiency in diet (endemic cretinism)
- Inborn errors of thyroid hormone synthesis

- Maternal antithyroid substances.
- Abnormalities of hypothalamohypophyseal pathway-thyroid axis.

Clinical features:

- Persistence of periodical jaundice in newborn.
- Hoarse cry, macroglossia, feeding problems and somnolence.
- Constipation, delayed milestones.
- Mental retardation, delayed dentition.
- Retarded physical, mental and sexual growth.
- Maternal TH can cross placenta and cause normal growth and development. If the mother is euthyroid, then features in fetus are manifested few weeks after birth.
- If mother is also hypothyroid, then features are more severe and mental retardation is less responsive to treatment.
- Use of soluble iodine salt reduces the incidence of iodine deficiency in mother.
- Rate of growth will be disproportionate, soft tissues are likely to enlarge excessively.
- Obese, short stature
- Macroglossia cause difficulty in breathing and swallowing.
- Pot Bellies.
- Deaf mutism and Rigidity.

Myxoedema - Adult hypothyroidism

Syndrome of adult hypothyroidism is referred to as myxoedema. This term is also used specifically to the skin changes in the syndrome.

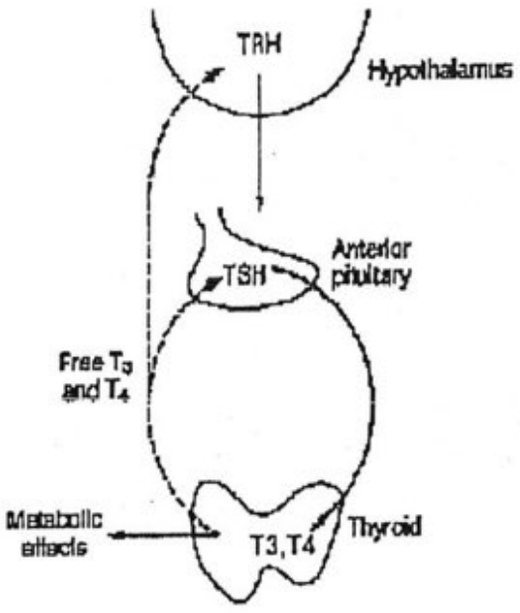
Causes:

- Diseases of thyroid gland secondary to pituitary or hypothalamic failure.
- Iodine deficiency causing goiter.
- Surgical removal of gland.
- Irradiation of the gland.
- Deficiency of enzymes involved in TH synthesis.
- Goitrogens.
- Autoimmune thyroiditis.

Symptoms:

- Hair will be coarse and sparse.
- Skin –dry and yellowish due to carotene accumulation
- Poor tolerance to cold.
- Voice husky.
- Mentation is slow and memory, poor.
- Severe mental symptoms called myxoedema madness
- Extreme muscular sluggishness.
- Decreased activities.
- Constipation.
- Slight slurred speech.
- Elevated plasma cholesterol.
- Increased atherosclerosis, arteriosclerosis and coronary artery diseases.
- Decreased heart rate.Decreased cardiac output, decreased blood volume, angina pectoris shortness of breath.
- When of reproductive age, menstrual abnormalities occur
- Myxoedema develop in patients with almost total absence of TH function, there is periorbital puffiness especially under eyes, swelling of face, increased quantities of hyaluronic acid, chondroitin sulphate bound with proteins.
- Form a tissue gel in the interstitial space. Edema- non pitting type. Also slow retardation of tendon reflexes.

Regulation of thyroid hormone secretions



Regulated by 2 major specific mechanisms:
1)Hypothalamic-Pituiutary-Thyroid Axis
2)Autoregulation:

i)Hypothalamic-Pituitary-Thyroid Axis:

Thyroid function is regulated primarily by variation in the circulating levels of TSH.

It causes:

Increased proteolysis of T4 wiTH release of TH into blood

Increased activity of iodide pump which Increases the rate of iodide trapping.

Increased iodination of tyrosine to form TH.

Increased size,number and secretory activity of Thyroid cells.

The effects of TSH results from activation of 2nd messenger cAMP.

TSH binds to cell membrane receptor to activate **adenyl cyclase** THrough **Gs** to increase cAMP.

cAMP activate protein kinases.

Protein kinases catalyse phosphorylation of proteins that alter cell function.

TSH secretion is regulated by TRH released from hypothalamus and by circulating free T3 and T4.

TSH secretion is increased by TRH.

Exposure to cold--->Increased TRH--->Increased TSH--->Increased TH

Exposure to heat--->Decreased TRH--->Decreased TSH--->Decreased TH

TSH secretion is inhibited in a negative feed back fashion by circulating free T3 and T4.
This negative feedback effect is mainly exerted on anterior pituitary and in posterior hypothalamus.TH inhibits synthesis and secretion of TSH.

ii) Autoregulation

It is an intrinsic control mechanism within the thyroid gland which modifies the responsiveness to TSH & maintains constancy of stored hormone inspite of variations in iodine intake.
Some iodide is necessary for normal thyroid functioning. Too little and too much iodine causes abnormal thyroid function. In food iodine deficiency, the iodide trapping mechanism becomes super efficient. So T_3 and T_4 synthesis occur normally unless there is severe food iodide deficiency.
Iodide by itself can inhibit the thyroid functioning under certain conditions. In normal individuals, large doses of iodine act directly on the thyroid to produce mild inhibition of organic binding of iodine & hence hormone synthesis. This inhibition is known as **Wolf- Chaikoff effect** (auto regulatory phenomenon).

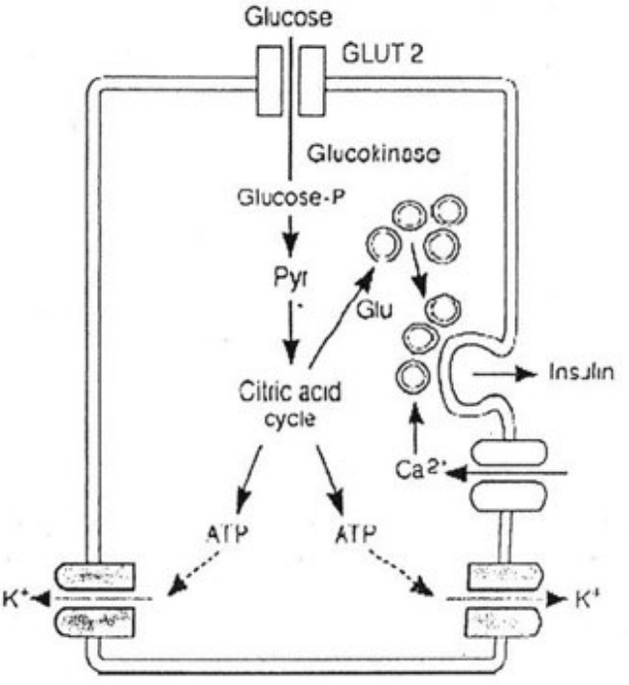
The effect is greater and prolonged when the iodide transport is increased and in patients with hyperthyroidism are more responsive to iodine than normal. Two more ways by which excess iodine inhibits thyroid function are:
i)Decrease the effect of TSH by decreasing cAMP response to TSH.
ii)Inhibits proteolysis of thyroglobulin.

Intake of iodine more than 2mg/day causes increased intraglandular iodine; it suppresses NADPH, NIS and TPO genes and decrease hormone synthesis.

2.Insulin-Secretions,actions& regulation:

Insulin Secretion:

Glucose enters B cells by GLUT-2 transporters.It is phosphorylated and metabolized to pyruvate in the cytoplasm.The pyruvate enters the mitochondria and is metabolized via the citric acid cycle. The ATP formed by oxidative phosphorylation inhibits ATP-sensitive K^+ channels,reducing K^+ efflux.
This depolarizes the B cell,and Ca^{2+} influx is increased. The Ca^{2+} stimulates release of insulin by exocytosis.Glutamate (Glu) is also formed,and this primes secretory granules,preparing them for exocytosis.



B Cell

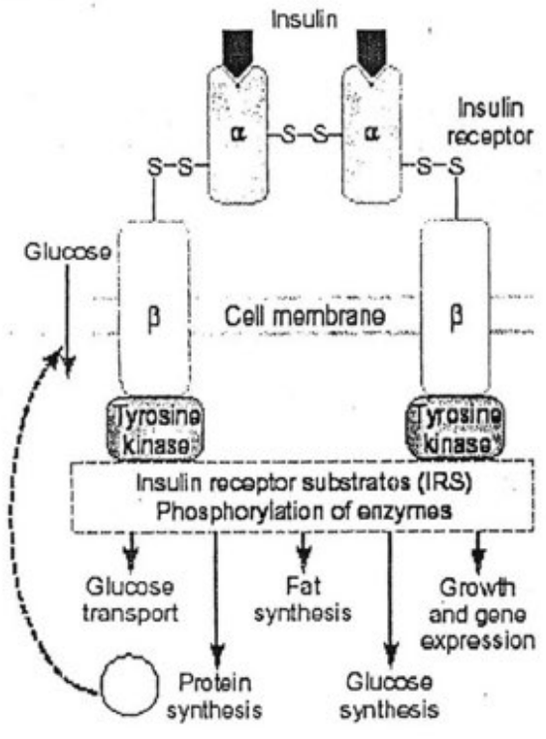
Mechanism of Action:

- Insulin binds to cell surface receptor
- Insulin receptor is a tetramer-
  - ➢Molecular weight: 3,40,000
  - ➢Has 4 subunits: 2 α,2β linked by sulphide bonds.
  - ➢Gene for receptor is located on **chromosome 19.**

•First step in action of Insulin is the binding of insulin to cell surface receptor. The α subunits bind insulin and are extracellular where as β subunits span the membrane. The intracellular portion of β subunits has tyrosine kinase activity. The binding of Insulin to the α subunit triggers the **tyrosine kinase activity** of the β subunit producing autophosphorylation of the β units. This is an example of enzyme linked receptor.
The autophosphorylation which is essential for insulin to exert its biological effects triggers phosphorylation of some cytoplasmic proteins including IRS and dephosphorylation

of others. In this way, Insulin produces desired effects on carbohydrate, fat, and protein metabolism. **Within seconds of insulin binding, glucose transport is increased except in brain, RBC.**

- Insulin promotes glucose entry to all cells except brain, liver, RBC, renal tubule , intestinal mucosa.
- Increased glucose transport occurs due to translocation of intracellular vesicles containing glucose transporters into cell membrane. Transporters separate from cell membrane and move back to cell interior to be used again.
- Cell membrane becomes permeable to amino acid, K^+, Phosphate
- Slower effects occur by changing activity of many enzymes in next 10-15 minutes.
- Much slower effects occur by changing rate translation of mRNA and also by changing rate of transcription of DNA in cell nucleus.



Factors affecting Insulin receptors:

Factors INCREASING:

- Low Insulin
- Fasting
- Deficiency of GH
- Oral antidiabetics

Factors DECREASING:

- Excess Insulin
- Obesity
- High carbohydrate diet
- Excess GH

There is an inverse relationship between insulin receptors and insulin.

- Excess insulin **decreases** number of insulin receptors (down regulation).
- Low insulin **increases** number of insulin receptors (up regulation).

Effects:

- Anabolic hormone – synthesis of proteins, fats etc..
- Hormones of abundance-storage of carbohydrates, proteins, fats etc..
- Its action may be Rapid ,Intermediate or Delayed

➢Rapid:

Increase transport of glucose, amino acids, K into insulin sensitive cells.

➢Intermediate :

- Increase stimulation of protein synthesis
- Inhibition of protein degradation
- Activation of glycolytic enzymes and glycogen synthase
- Inhibition of phosphorylase and gluconeogenic enzymes

➢Delayed:

Increase mRNA s for lipogenic and other enzymes.

Actions of Insulin:

1. Metabolic actions:

- Effect on Carbohydrate metabolism:

Insulin decreases blood glucose by increasing uptake into all cells of the body except liver, renal tubules, brain, intestinal mucosa, RBC

- Action on Muscles:
  - ➢Normally resting muscle membrane only slightly permeable to glucose in the absence of insulin
  - ➢Also in between meals insulin level is less
  - ➢Hence muscle depend on fatty acid

Conditions where muscle require large amounts of glucose:

- During moderate or heavy exercise, even without much insulin exercising muscle is permeable to glucose due to contraction process
- After meals there is increase blood glucose that leads to increased insulin secretion resulting in rapid transport of glucose into muscle cell.
- Insulin increase the rate of glucose transport into resting muscle by 15 times.
- Most important effect of insulin is to store glucose as glycogen in liver

- So in between, when food is not available, there is a decrease in blood glucose, which in turn decreases insulin secretion, and liver glycogen is split into glucose.

Effect on Lipid Metabolism:

- Insulin functions as a **fat sparer** by increasing utilization which decreases the fat utilization
- Insulin promotes fatty acid synthesis in liver
- When amount of glucose entering is more than that can be stored as glycogen, then insulin converts excess glucose to fatty acid.
- When excess amount of glucose is used for energy, an excess of citrate and isocitrate ions are formed. These ions activate first stage of fatty acid synthesis.
- Triglycerides(TGs) are usual forms of fat storage.
- Insulin activate **lipoprotein lipase** in the capillary wall of adipose tissue which splits TG to FA, requirement for them to be absorbed into adipose tissue where they are converted again to TG and stored.
- Insulin inhibit action of hormone sensitive lipase, enzyme causing hydrolysis of TG there by FFA release
- Insulin promotes glucose transport through cell membrane into fat cells.
- Glucose is converted into α glycerol phosphate which supplies glycerol.
- Glycerol + FA ⟶ triglycerides,storage form of fat in adipose tissue.

Effect on protein metabolism:

- Insulin increases protein synthesis and storage.
  1. Insulin stimulates transport of AA into cell: increases protein synthesis.
  2. Insulin increases translation of mRNA forming new proteins.
  3. Insulin increases transcription of DNA sequences: increasing the quantity of RNA: increasing protein synthesis.
- Insulin inhibit catabolism of proteins: decrease release of amino acids
- Insulin decreases the rate of gluconeogenesis.

In short insulin promotes protein formation and prevent its degradation.

Effect on Growth:

- GH and insulin act synergistically to promote growth
- Insulin is a growth promoting hormone
- GH is less effective in growth promotion in the absence of insulin.

Effect on ion Transport:

- Insulin causes K^+ to enter cells lowering the K^+ level
- Insulin and glucose given for hyperkalemia treatment in patients with RF
- Insulin increases the activity of Na^+-K^+ ATP ase, so more K^+ is pumped into cells.

Action on Adipose Tissue:

- Increased glucose entry.
- Increased fatty acid synthesis.
- Increased glycerol phosphate synthesis.
- Increased triglyceride deposition.
- Activates lipoprotein lipase.
- Inhibition of hormone sensitive lipase.
- Increased K^+ uptake.

Actions on Muscle:

- Increased glucose entry.
- Increased glycogen synthesis.
- Increased Amino acid uptake.
- Increased protein synthesis in ribosome.
- Decreased protein catabolism.
- Decreased release of gluconeogenic Amino acids.
- Increased K^+ uptake and ketone uptake.

Actions on liver:

- Decreased ketogenesis.
- Increased lipid synthesis.
- Decreased glucose output due to decreased gluconeogenesis, increased glycogen synthesis and increased glycolysis.

Regulation of Insulin Secretion:

1.Neural level: Sympathetic, Parasympathetic:

Insulin secretion controlled by blood glucose by a feed back system. Increase in glucose activates β cells that increases the secretion of Insulin.

Insulin secretion is biphasic:

- Rapid but short lived increase in Insulin secretion due to release of preformed Insulin from β cells of islets.
- Slowly developing prolonged response- due to additional release of preformed insulin and release of newly synthesized Insulin and from the activation of enzyme system.

At the normal fasting level of blood glucose (80-90 mg/dl),rate of insulin secretion is minimal.

As the concentration rises above 100 mg/dl rate of insulin secretion rises rapidly and reaching a peak at blood glucose between 400 and 600 mg/ dl.

2.Substrate level control:

a) Glucose:

Glucose enters the β cell of islet through GLUT-2 transporter and is phosphorylated by **glucokinase** and then metabolized to pyruvate in the cytoplasm.

The glucose enters the mitochondria and is metabolized to CO_2 and H_2O via citric acid cycle, with the formation of ATP by oxidative phosphorylation. This ATP inhibits ATP sensitive K^+ channels reducing K^+ efflux.

This depolarizes the β cell and there is opening of voltage gated Ca^{2+} channel. Calcium enters and causes exocytosis of readily releasable pool of insulin containing secretory granules producing the initial spike of insulin secretion.

Metabolism of pyruvate also causes increase in glutamate that appears to act on the second pool of secretory granules committing them to a releasable form.

The release of these granules produces prolonged second phase of insulin response to glucose.

b) Amino acids & Fat derivatives:

Amino acids especially arginine and leucine stimulate insulin secretion. They act by generating ATP and this closes ATP sensitive K^+ channels in β cells increasing the insulin secretion.

β ketoacids like acetoacetic acid increases insulin secretion.

3.Hormonal Control:

a)G.I hormones:

Gastrin,secritin,CCK,GIP cause moderate increase in insulin secrertion.These hormones are secreted after food intake.Recently a glucagon like polypeptide- Gut factor increases secretion.

b)Paracrine Hormones:

Control cell to cell contact.The hormone secreted by three different types of cells can affect the rate of hormone secretion by the other.Glucagon stimulates and somatostatin inhibits insulin secretion.Insulin inhibits glucagon secretion.Somatostatin also inhibits glucagon secretion.

c)Other Hormones:

Cortisol,GH,Thyroxine,Estrogen and progesterone causes increase insulin secretion.

Prolonged secretion of these causes exhaustion of beta cells which leads to Diabetes Melitus.

3.Glucocorticoids:Actions& Regulations:

Mechanism of Action:

a)Multiple actions of glucocorticoids are triggered by binding to glucocorticoid receptors. The steroid receptor complex act as transcription factor that promotes the transcription of certain segments of gene.This Increases the production oof appropriate mRNA which in turn increases synthesis of enzymes that alter cell function. In addition it seems slightly that glucocorticoids have non-genomic actions.

Action of Glucocorticoids:

a)Metabolic Actions:

(i)Carbohydrate Metabolism:

- Stimulation of gluconeogenesis(formation of glucose from proteins and some other substances) by:
  - ➢Cortisol increases the enzyme required to convert amino acid into glucose in the liver cells
  - ➢Cortisol causes the mobilization of amino acids from extra hepatic tissue, mainly from muscles so more amino acids become available in plasma to enter into gluconeogenesis.

- Increase blood sugar level:
  - ➢ Decrease in peripheral glucose utilisation-Anti insulin effect.But spares brain and heart so that these vital organs recieve enough glucose.
  - ➢ Increase in glycogen Synthesis.
  - ➢ Increase in protein catabolism more amino acids formed which in turn increases gluconeogensis.

Both the increased gluconeogenesis and moderate reduction in the rate of glucose utilization lead to increased blood glucose concentration. This condition is called **adrenal diabetes**.

(ii)Protein metabolism:

- Reduction in cellular proteins:
  - Theres decrease in protein storage in all cells except liver cells due to decreased protein synthesis and increased protein catabolism.
- Liver protein becomes enhanced:
  - Plasma proteins are increased because cortisol enhances amino acid transport into liver cells and enhance the liver enzyme for protein synthesis.

(iii) Fat metabolism:

- Mobilisation of fatty acids:

Cortisol promotes mobilization of fatty acids from adipose tissue→This increases the concentration of free fatty acids in plasma →enhance oxidation of fatty acids→increases utilisation of fatty acids for energy.

- People with excess cortisol secretion develop a particular type of obesity with excess deposit of fat in chest and

head regions giving rise to appearance of a **buffalo hump** and **rounded moon face**.

(iv) Water Metabolism:

- Adrenal insufficiency is characterised by the inability to excrete a water load leading to a danger of water intoxication. Only glucocorticoids can repair this defect. In patients with this disease who have not received glucocorticoids, glucose infusion cause high fever(glucose fever), followed by collapse and death.

Glucose is metabolized, water dilutes the plasma,and the resultant osmotic gradient between plasma and cells causes the cells of thermoregulatory centres in hypothalamus to swell to such an extent that their function is disrupted.

(v) Calcium Metabolism:

- Lowers serum Ca levelby decreasing intestinal Ca absorption and renal Ca reabsorption.

As serum Ca drops, secretion of PTH increases→ PTH mobilises Ca from bone.

Hence excessive use of Cortisol results in **Osteoporosis.**

(vi)Nucleic acid Metabolism:

- Inhibits nucleic acid synthesis in all tissues except liver.

In liver RNA synthesis is Increased

b)Permissive action of Glucocorticoids:

- Small amounts of glucocorticoids must be present for a number of metabolic reactions to occur, although glucocorticoids do not produce the reaction by themselves. This effect is called permissive action of glucocorticoids.

Eg:glucocorticoids are needed ;

- For glucagon and catecholamines to exert their calorigenic effects
- For catecholamines to exert their lipolytic effects
- For catecholamines to produce pressure response of bronchodilation.

c)Anti-inflammatory action:

There are 5 stages of inflammation:

1.Chemical substances that activate inflammation, like histamines, bradykinins, prostaglandin and leucotrienes are released from the damaged tissue.

2.There will be increased blood flow to the inflamed area due to the release of some products from the tissues and the effects are called erythema.

3.Tissue fluid leaks into the damaged area because of increased capillary permeability followed by clotting of tissue fluids causing a non-pitting type of oedema.

4.Infiltration of the area by leucocytes.

5.After days or weeks, ingrowth of fibrous tissue that often helps in the process of healing.

Effects of Cortisol:

It has the following effects in preventing inflammation:

1.Cortisol stabilizes the lysosomal membrane. So proteolytic enzymes that are released by damaged cells, causing inflammation, which are mainly stored in lysosomes, will be released in decreased quantities.

2.Cortisol decreases permeability of capillaries. This prevents loss of plasma into tissues.

3.It also decreases migration of WBC into the inflammed area and phagocytosis of damaged cells.

4.Cortisol suppresses the immune system causing lymphocyte production to decrease markedly.

5.Cortisol attenuates fever mainly because it reduces release of IL-I from WBC.

Cortisol causes reduction of inflammation. Even after inflammation has become well established, the administration of cortisol can often reduce inflammation within hours to few days. In addition, the rate of healing is enhanced.

Anti-inflammatory role of cortisol plays major role in certain types of diseases like rheumatoid arthritis, rheumatic fever and acute glomerulonephritis. All these diseases are characterized by several local inflammation and harmful effects on the body are mainly caused by the inflammatory effects and not by other aspects of the defects.

d)Anti-allergic effects:

Glucocorticoids do NOT influence the antigen-antibody combination or the effects of histamine once it is released.

But they reduce the number of mast cells, inhibit intracellular synthesis of histamine and its release from cells and possibly reduce responsiveness of tissues to histamine. Hence they are useful in allergic conditions, delayed hypersensitivity reactions and serum sickness.

e)Cardiovascular effect:

Glucocorticoids are required for maintenance of normal BP.

In the case of Cushing's Syndrome (increased cortisol secretion), there is hypertension. In Addison's disease, there is hypotension.

Glucocorticoids cause sodium retention and increased ECF volume leading to hypervolemia thereby hypertension.

Glucocorticoids sustains myocardial performance

Glucocorticoids are essential for vasoconstrictor effects of noradrenaline.In adrenal insufficiency, vascular smooth muscles become unresponsive to noradrenaline and adrenaline which leads to hypotension.

f)CNS effects:

In adrenal insufficiency, there are personality changes with irritability, apprehension and inability to concentrate.EEG waves are slow.

In excess conditions, EEG waves are fast and there is mental aberration, psychosis and insomnia.

Cortisol produces a sense of well-being.

g)GIT effects:

Increases gastric acid and pepsin secretion. Excess glucocorticoid may cause peptic ulcer. So steroids must be avoided in such patients.Hypercortisolism is frequently associated with weight gain because cortisol stimulates appetite.

h)Kidney:

Glucocorticoids have mild mineralocorticoid activity.It can cause Na retention and K excretion.

It also increases GFR.

It acts as ADH antagonist.In the absence of cortisol,ADH action is potentiated and theres increased chance of water intoxication

In adrenal insufficiency, there is impaired ability to excrete water load, mainly due to reduced GFR.

i)Bone:

Cortisol reduces osteoblastic activity, increases osteoclastic activity It increases bone resorption in a transient manner by increasing the osteoclastic activity and increasin the collagenase activity which destroys organic bone matrix.

Bone formation is decreased by effects of cortisol on Ca metabolism . Urinary Ca excretion is increased and Ca absorption in gut is decreased.

j)Muscular system:

Optimal amounts of glucocorticoids are essential for muscular efficiency. In deficiency, there is prolonged muscular weakness and easy fatiguability.

In hyperfunctioning also, there is muscular wasting and weakness.

k)Blood cells and lymphoid organs:

Glucocorticoids DECREASES the number of circulating Eosinophil by increasing their sequestration in the spleen and lungs. Glucocorticoids also lower the number of Basophils in circulation

INCREASE the number of Platelets, Neutrophils and RBC.

Glucocorticoids Decrease the circulating lymphocytes count and the size of lymph nodes and thymus by inhibiting lymphocyte mitotic activity.

They have the ability to reduce the secretion of cytokines. The reduced secretion of cytokines IL-2 leads to reduced proliferation of lymphocytes.

l)Anti Stress Effects:

The term stress is defined as any change in the environment, that changes, or threatens to change an existing optimal steady state.

Most stresses activate counteraction at the molecular, cellular or systemic level that tends to restore the previous state.

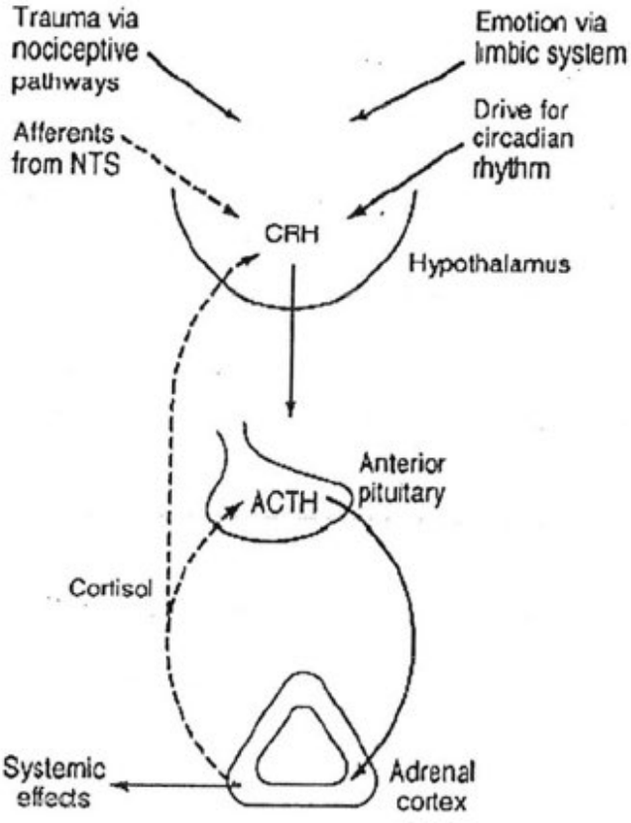
Some but not all stresses stimulate ACTH secretion. This increase in ACTH secretion is essential for survival when stress is severe.

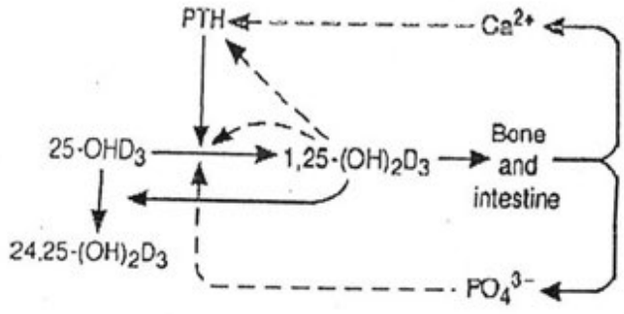
Most of the stressful stimuli that increase ACTH secretion also activate the sympathetic nervous system. Part of the functions of corticoids is maintenance of vascular reactivity to catecholamines.

Glucocorticoids are also necessary for the catecholamines to exert their full fatty acid mobilizing action and free fatty acids are an important emergency energy supply.

Glucocorticoids prevent other stress induced changes from becoming excessive. This stress causes increase in plasma glucocorticoids to high pharmacological level that in short run are life-saving.

Regulation of Glucocorticoids:





Action on bone:

Acts directly on the bone to increse bone resorption and metabolise Ca:

Action via 2 phases:

- Rapid phase of Ca & PO4 absorption (osteolysis).
- Slow phase of bone absorption (activation of osteoclast).

Action on kidney:

- Decrease calcium excretion.
- Increase calcium mainly in late distal tubule, collecting tubule, Collecting duct, ascending limb of henle.
- Diminishes PO4 reabsorption .

Action on intestine:

- Increase formation of 1, 25 DHCC.
- Enhance both Ca & PO4 absorption.

Calcitonin:

- Secreted by parafollicular cells of thyroid
- Generally antagonistic to PTH.
- Plasma Calcium Level is Decreased.

Actions:

- Inhibit bone resorption and osteoclast action leading to decrease in calcium level.
- Increase excretion of calcium through urine.
- Protection against post prandial hyper calcemia.
- Protect bones of mother in pregnancy.
- Deficiency symptoms not usually seen.
- Inhibits absorption of Ca & PO4 from intestine.

PTH- rP:

- 140 amino acids, gene on chromosome 12.
- PTH rP and PTH have same receptors.

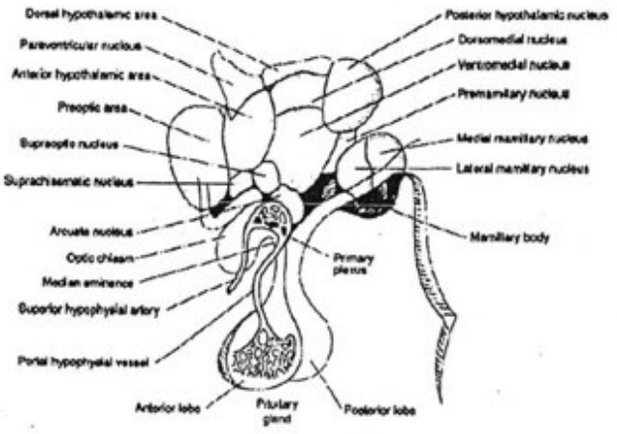
Actions:

- It is a tissue hormone and act locally.
- Has marked effect on growth and development of cartilage in-utero.
- Increase calcium transport across placenta.

Other factors:

1. Glucocorticoids-lower plasma calcium level.
2. Growth hormone – increase calcium excretion and increase absorption from intestine causing positive calcium balance.
3. Estrogen – prevent osteoporosis.
4. Insulin – increase bone formation.
5. Thyroid hormone- causes hypercalcemia,hypercalcuria and in some instance osteoporosis.

5.ADH- Biosynthesis, actions and regulations:



Biosynthesis:

ADH and Oxytocin are typical neural hormones secreted by neurons into circulation. These hormones are secreted by cell bodies of Magnocellular Neurons in the **Supraoptic** and **Paraventricular** Nuclei.

They are transported down the nerve fibers to the nerve endings in the posterior pituitary in combination with a polypeptide called Neurophysin.

ADH is formed primarily in the Supraoptic Nuclei even though small amounts are also secreted by the Paraventricular Nuclei.

Precursor molecules called prepropressophysin are secreted by ribosomes of cell bodies of neurons.

They are packaged into granules in the Golgi apparatus andtransported down the axons (hypothalamo hypophyseal axis) by axoplasmic flow to their endings in posterior pituitary.

The splitting of precursor molecules occurs as they are being transported down the axon.

The secretor granules are called **Herring bodies**. Storage granules contain free vasopressin in association with neurophysin II.

When osmolarity of ECF Increases

↓

Fluid pulled out of Osmoreceptor cell(shrinkage)

↓

Initiates nerve signals in Hypothalamus

↓

increased neuronal discharge of SupraOptic nuclei

↓

Additional ADH secretion

↓

Increased water resorption → Decreased Osmotic Pressure

And the reversal occurs when osmotic pressure decreases. Thus ADH secretion is controlled by delicate feed back mechanism.

2.Blood Volume:

Low ECF volume **decreases** osmotic pressure which in turn increases ADH secretion.

High ECF volume **Increases** osmotic pressure and thus decreases ADH secretion

There is an inverse relation between rate of stimuli from stretch receptors in low and high pressure areas of vascular system and rate of ADH secretion.

Low pressure receptors:

Located in low pressure areas like SVC,IVC,irght atrium left atrium and pulmonary vessels.

The low pressure receptors monitor the fullness of the vascular system or volume changes affecting vascular system.

Increase in blood volume stimulates stretch receptors in low pressure areas. These send impulses through vagus nerve to inhibit ADH secretion.

Even a moderate decrease in blood volume (hypovolemia), hypotension stimulates secretion of large amounts of ADH leading to water retention.

Water retention leads to decreased plasma osmolality and hyponatremia.

High pressure receptors: are seen in carotid sinus and aortic arch.

They respond to changes in BP---> Increase in ADH secretion.Normally pressure receptors tonically inhibit ADH secretion by modulating an inhibitiory flow of impulses from medulla to hypothalamus.

This inhibitory flow of impulses is reduced when BP decreases and hence an Increase in ADH secretion.

Other factors:

1) Pain, emotion, stress, exercise etc.. Increases secretion by direct action on supraoptic nucleus.
2) Nausea and vomiting Increases secretion.
3) Standing Up – there is **Decrease** in left atrial pressure causing **Increased** ADH secretion and antidiuresis
4) Alcohol Decreases ADH secretion.

7.Mineralocorticoids: Function, Regulation & abnormalities:

Actions:

1).Effects on Na+ and K+:

Aldosterone increases renal tubular resorption of Na & secretion of K. In the kidneys, they act primarily on the principal cells (P cells of collecting duct). Under the influence of aldosterone, increased amount of Na are in effect exchanged for K and H ions in the renal tubules producing a potassium diuresis & increase in urinary acidity.

2).Effects on ECF Volume & BP:

Excess aldosterone increases ECF volume and arterial pressure but has only a small effect on plasma Na concentration. The reason for this is that when Na is reabsorbed by the tubules, there is simultaneous osmotic absorption of almost equivalent amounts of water. Small increase in Na concentration stimulates thirst & increase water intake.

Therefore, ECF volume increases almost as much as the retained Na but without much change in sodium concentration.

Aldosterone mediated increased in ECF volume lasting for more than 1-2 days also leads to an increase in arterial pressure. This increase in arterial BP, then increases kidney excretion of both salt and water,this is called as **pressure natriuresis & pressure diuresis**. This return to normal of both salt & water excretion by the kidneys as a result of natriuresis and diuresis is called **aldosterone escape**.

3).Effect on K+:

- K+ secretion into tubules increases.
- Excess aldosterone also stimulates transport of
- K+ from ECF into most cells of the body, and this leads to hypokalemia.
- When the potassium concentration falls to a value less than half of the normal severe muscle weakness develops.
- Conversely when aldosterone is deficient,the ECF K+ concentration can rise to very high levels.
- When the levels increase to 60-100% above normal, serious cardiac toxicity occurs.

4.Effect on H+:

Excess aldosterone increases tubular H^+ secretion & causes mild alkalosis. The H^+ ions are secreted in exchange for sodium, in I cells.

5.Effect on Sweat glands,Salivary glands:

Aldosterone has almost the same effects on sweat glands & salivary glands as it has on renal tubules. It increases greatly the Reabsorption of NaCl & Secretion of K^+ by the ducts. The effect on sweat gland is important to conserve the body salt in hot environment & the effect on salivary gland is necessary to conserve the salt when an excessive quantity of saliva is lost.

6.Effect on Interstitial epithelium:

Aldosterone also greatly enhances Na^+ reabsorption by the intestine, especially in the colon, which prevents the loss of Na^+ in the stools.

Regulation:

1.ACTH from pituitary:

When 1st administered, ACTH increases output of aldosterone as well as glucocorticoids & sex hormones.

The amount of ACTH required to increase aldosterone output is somewhat greater than the amount that stimulate maximal glucocorticoid secretion.

The effect is transient and even if ACTH secretion remains elevated, aldosterone output declines in 1 or 2 days. After hypophysectomy, the basal rate of secretion of aldosterone is normal. The increase that is normally produced by surgical and other stresses is absent.

2.Effect of angiotensinogen and renin:

Ingestion of angiotensin II stimulates adrenocortical secretion & in small doses affects primarily the secretion of aldosterone.

Angiotensin II act on 2 places in the steroid biosynthetic pathway:

- On the conversion of corticosterone to aldosterone.
- On the conversion of cholesterol to pregnenelone.

Renin is secreted from **JG cells** that surround the renal afferent arterioles as they enter the glomerulus. Aldosterone secretion is regulated via the Renin-angiotensin system in a feedback manner. A drop in the ECF volume leads to a reflex increase in renal nerve discharge & decreased renal arterial pressure.

Both these changes increase the renin secretion & angiotensin II formed by the action of renin increases the secretion of aldosterone.

The aldosterone causes Na retention & secondarily water retention expanding the ECF volume & shutting off the stimulus that initiated increased renin secretion.

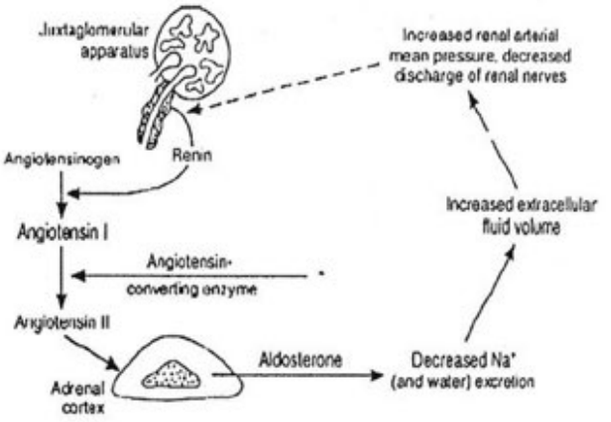
Factors that affect renin secretion:

Stimulatory

- Increased sympathetic activity via renal nerves
- Increased circulatory catecholaminesProtein Kinase .
- Prostaglandins.

Inhibitory

- Increased Na & Cl reabsorption.
- Increased afferent arteriolar pressure.
- Vasopressin.



3.Electrolytes:

A very small increase in plasma K^+ levels causes several fold increase in aldosterone secretion like angiotensin II.

K^+ stimulates the conversion of cholesterol to pregnenelone & the conversion of deoxycorticosterone to aldosterone.

It appears to act by depolarizing the cell , which opens voltage gated Ca^{2+} channels increasing intracellular Ca^{2+}.

An acute decline in plasma Na^+ conc. of about 20 meq/L stimulates aldosterone secretion.

Changes of this magnitude are rare & least important.

ANP inhibits rennin secretion & decreases the responsiveness of zona glomerulosa to angiotensin II.

Secretogogue	Intracellular Mediators
ACTH	cAMP, Protein Kinase A
Angiotensin II	Diacyl glycerol,Protein Kinase C
K^+	Ca^{2+}via voltage gated Ca^{2+} channel

Abnormalities:

Adrenal insufficiency:

1.Primary adrenal insufficiency:

Due to disease process that destroy adrenal cortex-Addison's disease.

Causes:
•Primary atrophy of adrenal cortex due to autoimmune disease.
•Destruction of adrenal cortex by TB/cancer.

2. Secondary adrenal insufficiency:
Due to pituitary disease that decreases ACTH secretion.

3. Tertiary adrenal insufficiency :
Due to hypothalamic disorders disrupting CRH secretion.

Secondary & tertiary adrenal insufficiencies are usually milder than primary adrenal insufficiency because electrolyte metabolism is affected to a lesser degree, in addition there is no pigmentation because in both of these conditions, plasma ACTH is low.

Primary adrenal insufficiency:

Features:

In Adddison's disease both the glucocorticoids & mineralocorticoids are deficient.

(a) Features due to Mineralocorticoid deficiency:

Lack of aldosterone → decreases renal tubular Na reabsorption → increased loss of Na , Cl & water through urine → decreased ECF volume → decrease cardiac output → hypotension → shock.
K+ is retained & plasma K+ rises.
If untreated death occurs within days of cessation of mineralocorticoid secretion.

(b) Features due to Glucocorticoid deficiency:

Poor maintenance of blood glucose conc. between meals because of inability to synthesize significant quantities of glucose,as a result hypoglycemia occurs during fasting and stress. Lack of cortisol also reduces the mobilization of proteins & fat from the tissue. There by depressing several metabolic functions of the body.
Muscle weakness occurs.
Anemia,decreased G.I motility and secretion,reduced appetite
Stress & even a mild respiratory infection can cause collapse and untimely death.

(c) Melanin pigmentation:

Circulating ACTH levels are elevated due to the normal negative feedback to hypothalamus from the anterior pituitary gland being depressed.
Due to MSH activity of ACTH there is diffuse pigmentation of skin and mucous membrane..

(d) Addisonian crisis:

Normally greater quantities of glucocorticoids are secreted in response to different types of physical or mental stress. In persons with Addison's disease the output of glucocorticoids doesn't increase during stress. The critical need for extra glucocorticoids & the associated severe debility in times of stress is called addisonian crisis.

SHORT NOTES

1.Mechanisms of hormone action:

Hormone acts on the target tissue by binding to a specific receptor.
Receptors are large proteins and target tissues are those that contain the receptors for the particular hormone.
The binding results in the formation of hormone receptor complex.
This binding alters the function of the receptor.
The receptor is activated and activated receptor initiates physiological effects.

Location of receptors:
- In or on surface of cell membrane .
- Eg: protein hormones, catecholamines have receptors on cell membrane
- In cell cytoplasm Eg: steroids
- In cell nucleus Eg: thyroid hormones, estrogen

Receptor proteins are not static components of the cell. Their number increases or decreases in response to stimuli.

Down regulation: When there is increase in concentration of hormones, number of receptors **decrease.** It occurs by internalization or desensitization of receptors.

Up regulation: Stimulating hormone induces greater than normal formation of receptors. As a result target tissues become more sensitive to hormones.

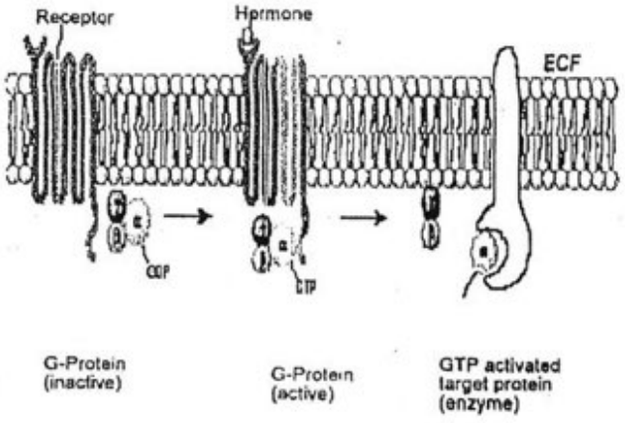
Intracellular signaling after hormone receptor activation:
Cell surface receptors (peptide hormones)
a) Ion channel receptor
b) G-protein linked receptor
c) Enzyme linked receptor
Intracellular receptors (steroid and thyroid hormones)

Ion channel linked receptors

Many neurotransmitter substances and some hormones combine with receptors in post synaptic membrane. They either open or close ion channels. Eg: Na^+, Ca^{2+} ion channels.

Actions:
•Direct action to open channels
•Indirect action through G proteins
•Altered movement of ions through the channels in turn brings changes in cell function.

G-protein linked hormone receptor



Hormones bind to surface receptors which are coupled to cell membrane proteins called **G-proteins**. They are serpentine receptors having seven trans membrane domains. The part of the receptor that protrudes into the cell cytoplasm is coupled to a G-protein. These G proteins are heteromeric nucleotide regulatory or binding proteins. It has 3 subunits: α, β,γ,α.

α subunit is bound to GDP. When a hormone binds to the receptor, the GDP in a subunit is exchanged for GTP.This causes the separation of the á-sub unit from the β and the γ sub units. It is the α-GTP mainly that brings about various biological effects inside the cell.

Effects:

1.Alter the permeability of ion channels.

2.Brings about various effects through production of second messenger.

á sub unit has intrinsic GTPase activity. It converts GTP to GDP. α-GDP can again bind to β and γ sub units i.e, association of α with β and γ sub units terminates activity.

G protein can be stimulatory (G_s) or inhibitory (G_i)

Eg: Hormones:

- TRH
- TSH,FSH,LH
- Vasopressin,oxytocin
- PTH
- AT-II
- hCG

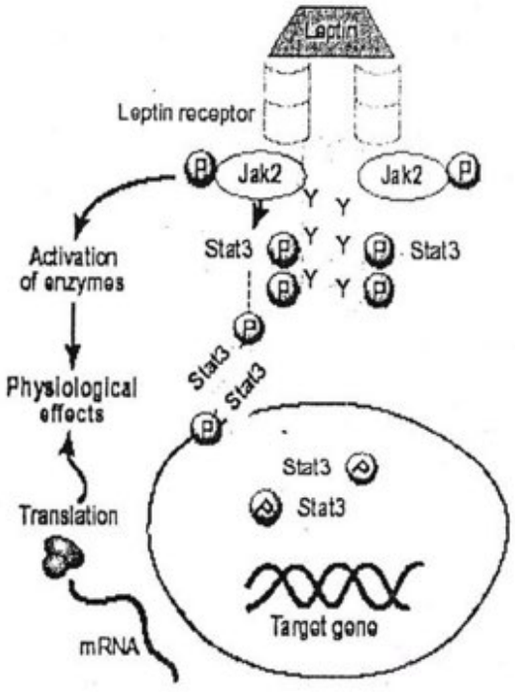
Enzyme linked receptors:

These are proteins that pass through membrane only once. They have a hormone binding site outside the cell membrane and a catalytic/enzyme binding site inside. They can be of two types:

1)Some enzyme linked receptors have intrinsic enzyme activity.e.g.: insulin receptors.

Binding of hormone to extra cellular part of receptor activates tyrosine kinase activity of intracellular part. This causes auto phosphorylation and alteration of gene expression

2)Some enzyme linked receptors have no tyrosine kinase domain in intracellular part.



They initiate tyrosine kinase activity in cytoplasm through associated enzymes. e.g.: GH, prolactin.

In particular they activate **Janus tyrosine kinases** (JAK) in cytoplasm.

This causes phosphorylation of STAT proteins. STAT will dimerise, move to nucleus and cause altered gene expression

Second messenger system:

Many hormones exert intracellular action by formation of 2nd messengers inside the cell.

e.g.: cAMP, cGMP, IP3, DAG, Ca^{2+}-calmodulin etc.

2nd messengers activate **protein kinases.**

I. Adenylyl cyclase cAMP second messenger system:

CRH, ACTH, FSH, LH, TSH, PTH, calcitonin, glucagon, secretin, somatostatin

Mechanism:

When a hormone bind to a membrane receptor coupled to a G protein, G protein stimulate adenylyl cyclase enzyme which is a transmembrane protein with 12 transmembrane segments. Adenylyl cyclase is activated by a-GTP which in turn promotes conversion of

ATP→cAMP.

cAMP activates cAMP dependent protein kinases causing phosphorylation of some proteins, altering function and bringing about desired physiological effects.

II. cGMP:

GTP —(Guanylyl cyclase)→ cGMP

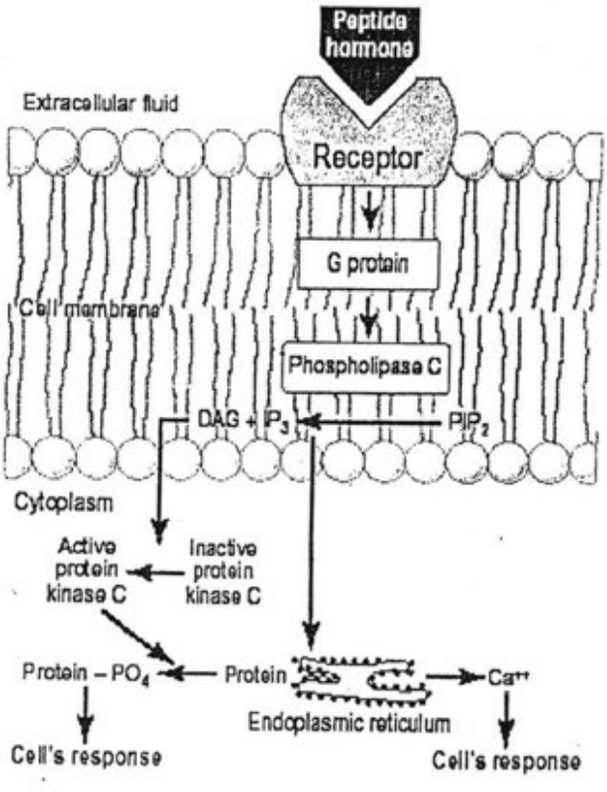
cGMP is important in vision in rods and cones.
cGMP activates cGMP dependent protein kinases to bring about desired effects.

III. IP_3 – DAG:

When hormone binds to transmembrane receptor, this receptor is activated. This through G protein activates Phospholipase C on the inner surface of the cell membrane. PLC catalyses breakdown of phosphatidyl inositol diphosphate into diacyl glycerol (DAG) and inositol triphosphate (IP3).

IP3 diffuses through the cell membrane into the endoplasmic reticulum where it causes release of Ca^{2+} from ER into cytoplasm. Ca^{2+} brings about 2nd messenger effects.

DAG stays in cell membrane and activates protein kinase C. PKC in turn phosphorylates proteins which lead to cell's response.
e.g.: TRH, GHRH, GnRH, Vasopressin (via V1 receptor), Angiotensin II, NE via a receptor.



The cell membrane phospholipid second messenger system by which some hormones exert their control of cell function. DAG, diacylglycerol; IP_3, inositol triphosphate; PIP_2, phosphatidylinositol biphosphate.

Ca²⁺ - calmodulin 2nd messenger:

It operates in response to entry of Ca^{2+} into the cells. Normally intracellular Ca^{2+} is low. Ca^{2+} enters cell in many ways.
1) Changes in membrane potential causing opening of voltage-gated Ca^{2+} channels.
2) Hormone binding to membrane receptor can open Ca^{2+} channels directly or indirectly.
3) Ca^{2+} released from intracellular stores e.g.: ER

In the cells Ca^{2+} binds with Ca^{2+} binding proteins – troponin, calmodulin, calbindin. This activates calmodulin dependent protein kinases which phosphorylates other proteins and activates proteins in the cell.

Intracellular receptors:

e.g.: Steroid hormones- cortisol, corticosterone, estrogen, progesterone, Vit. D, thyroid hormones.
These are lipid soluble hormones that readily cross cell membrane. They interact with intracellular receptors.

In case of thyroid & estrogen, receptors are intranuclear.
The hormone-receptor complex binds to specific DNA binding sites. This binding increases transcription of mRNA which moves to the cytoplasm and binds to ribosome causing translation of proteins. (Mention heat shock proteins)

2. Somatomedins:

Most of the actions of GH are brought about by acting through intermediate substances called somatomedins. They are polypeptide growth factors ssecreted by liver an dother tissues. The effect on growth is as same as the effect of insulin and hence called as insulin like growth factors(IGF)
2 types of IGF:
i) IGF-I or Somatomedin C
ii)IGF-II or Somatomedin A

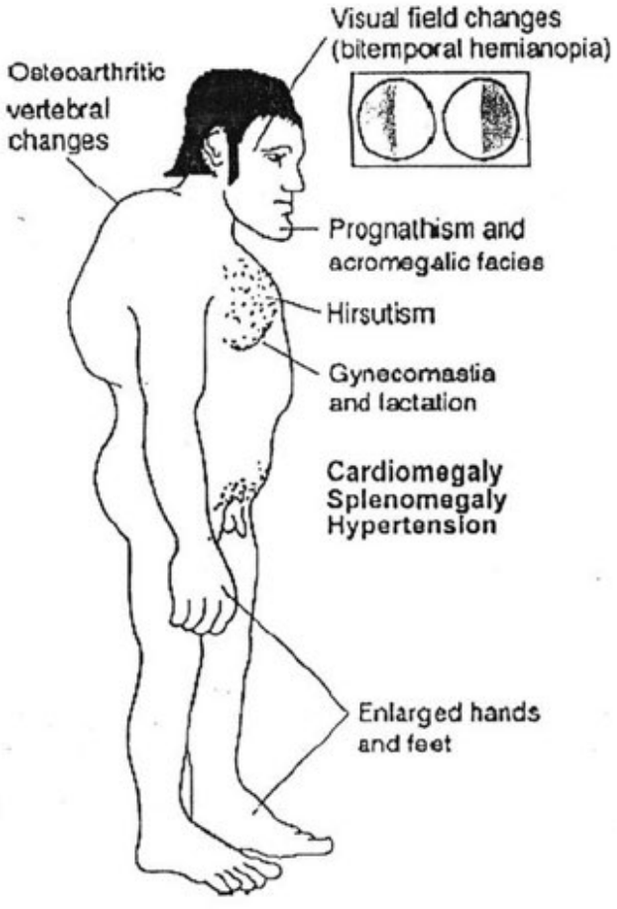
IGF-I:

It is primarily involved in skeletal and cartilage growth and is the principal secreting somatomedin. The half life of Somatomedin C is 10 hours. IGF-I receptor is similar to insulin receptor. Insulin can bind to it. Secretion of IGF-I before birth is independent of GH. After birth, secretion is stimulated by GH and IGF-I has growth promoting activity, because it is stimulated by GH. Its concentration in plasma depends on GH concentration. So its concentration increases during childhood and peaks at the time of puberty and declines as age advances.
It can bind to insulin receptors

IGF-II:

It has a mannose and phosphate receptor to which insulin **Cannot** Bind. It plays an important role in the growth of fetus before birth and the Excessive secretion in fetus causes disproportionate growth of organs.

3. Acromegaly,Gigantism,Dwarfism:



Typical findings in acromegaly.

Acromegaly:

It is due to excessive secretion of GH, after adolescence ie; after the closure of epiphysis. Bones cannot grow in length, or person cannot grow in height BUT bones can become thicker.

Causes:

1. Acidophilic tumor of ant. Pituitary.
2. Rarely hypothalamic tumors which secrete excess quantity of GRH which stimulate GH.

Features:

1. Broadening and thickening of hands and feet.
2. Fingers are extremely thickened and hands are twice the normal size.
3. Membranous bones like cranium, bosses on forehead, supraorbital ridges, lower jaws, portions of vertebra are enlarged markedly.
4. Prognathism-enlargement of lower jaw.
5. Forehead slants forward.
6. Nose increases twice the normal size.
7. Person has acromegalic facies that gives appearance of a gorilla.
8. Skeletal changes – that predisposes to osteoarthritic changes in vertebra that leads to kyphosis.
9. Soft tissues continue to grow and size of most of viscera is enlarged.
10. In 25% patients there is hyperglycemia and glycosuria.
11. Gynaecomastia and lactation.In 20-40% there is increased production of prolactin because tumor affects somatomammatropes.
12. Hirsuitism-increased body hair.
13. Bitemporal Hemianopia – as tumor presses on optic chiasma.

Gigantism:

It results from increased secretion of GH before adolescence i.e. before the epiphysis has fused with the shaft.

Causes:

1.Excessive activity of acidophilic cells of ant. Pituitary.
2.Tumors of somatotropes of Anterior Pituitary.

Features:

- The person becomes a giant as tall as 8 ft and the limbs grow disproportionately.
- Hyperglycemia due to anti insulin action of GH. This results in excessive stimulation of β cells and leading to its subsequent degeneration. This will result in diabetes mellitus.
- Pituitary tumor enlarges and will result in destruction of the gland itself causing panhypopituitarism.

Treatment:

- Microsurgical removal of tumor.
- Irradiation of pituitary gland.

Dwarfism:

It is short stature most often due to generalized deficiency of anterior pituitary secretion (panhypopituitarism) during childhood.

It can also be due to GH, GRH, IGF-I deficiency and abnormalities of GH receptors.

Panhypopituitary Dwarf:

- All physical parts grow proportionately but rate of development is reduced.(proportionate dwarf)
- The child never attains puberty, because the gonadotropic hormonal secretion is not sufficient to develop adult sexual functions. However in1/3rd of dwarfs, only GH is deficient. They mature sexually and may even reproduce.
- Mental development is normal.

Treatment

- Persons having deficiency of GH alone if detected early in life can be cured.
- hGH synthesized by rDNA technology is available.

Laron Dwarfism:- GH Insensitivity Syndrome:

- Here the GH level is normal or elevated but the receptors are insensitive to GH because of mutation of gene for receptors. Plasma IGF- I is also markedly reduced.

In African pigmies or Levi Lorain dwarfs, GH level is normal or elevated. But levels of GH intermediates called somatomedins decreased. They have hereditary inability to form IGF-I.Plasma IGF-I fails to increase at time of puberty.

Other Causes of Short Stature:

- Cretinism.
- Precocious puberty.
- Turners syndrome.
- Bone and metabolic disease.
- Constitutional delayed growth.
- Psychosocial dwarfism (Kaiper-hauser syndrome).
- Achondroplasia (here limbs are short with normal trunk).

4. Synthesis of Thyroid Hormone:

refer Essay 1.

5. Action of GH and Regulation:

Actions:

Metabolic Actions:

1.Protein Metabolism:

- GH is an anabolic hormone.
- Enhances the transport of amino acid into the cell through cell membrane.
- Increases the amino acid concentration in the cell in turn increase the protein synthesis.
- It also increases the translation of RNA which in turn increases the protein synthesis by ribosome in cytoplasm.
- Over prolonged period, GH also increases the transcription of DNA in the nucleus, which leads to increased quantity of RNA and protein synthesis.

In addition to increased protein synthesis, there is decrease of break down of cell protein.GH acts as a **protein Sparer.**

GH enhances all facets of amino acid uptake and protein synthesis by cells while reducing the break down of protein.

2.Fat Metabolism:

- GH causes the release of free fatty acids from adipose tissue; this increases the concentration of circulating FFA. It provides ready source of energy in hypoglycemia, fasting and stress.
- Enhances the conversion of FA to Acetyl CoA and utilizes this for energy. So it increases the use of fat for energy in preference to use of carbohydrates and proteins. Fat utilization and protein anabolism leads to an increase in lean body mass.
- Fat mobilization takes several hours to begin where as protein synthesis begins in minutes.

Ketogenic Effect of GH:

In the presence of excess GH large quantities of fat is mobilized from adipose tissue. It results in production of ketone bodies like acetoacetic acid by liver. This result in condition called ketosis.GH said to have a ketogenic effect.

3.Carbohydrate Metabolism:

GH is said to be diabetogenic because it exerts anti-insulin effects like:

- It decreases uptake of glucose by cells like adipose tissue and skeletal muscles.
- It increases hepatic glucose output.

Excess GH can produce metabolic disturbances similar to Type II diabetes mellitus. It also increases insulin secretion but this is not by a direct effect on pancreatic β cells. It does not increses the ability of pancreatic cells directly but increases ability of pancreatic cells to respond to insulogenic stimuli like arginine and glucose.

4.Electrolyte Metabolism:

- GH increases Ca^{2+} absorption from GIT.
- It reduces Na^+ and K^+ excretion probably because these electrolytes are derived from kidneys to growing tissues. There by these are conserved.
- It produces positive nitrogen and phosphorus balance.
- It decreases plasma amino acid and urea.

Actions on Growth:

Most obvious effect of GH is to increase the growth of skeletal frame of the body.

Action on growth of **cartilage and bone:**

- GH accelerates the production of cartilage cells.
- It enhances chondrogenesis.
- Enhances widening of cartilaginous epiphyseal plate
- It also enhances the conversion of chondrocytes into osteogenic cells thus causing deposition of new bone.
- GH increases the deposition of protein by chondrocytic and osteogenic cells.
- It accelerates all facets of cartilage and bone growth. This results in elongation of shaft and lengthening of bone.
- Osteoblasts are bone forming cells and are strongly stimulated by GH. Osteoblasts can deposit new bones on the surface of older ones.

So under the influence of GH, bone can continue to become thicker through out life especially membranous bones like skull bones.

GH has direct and indirect actions.GH was originally thought to produce its effects directly, but later it was known that GH exerts much of its effects through intermediates called **Somatomedins.**

Somatomedins (Insulin like Growth factor):

- It has been found that GH enhances liver and to much less extend some other tissues to form several small proteins called Somatomedins that has potent effect on increasing all aspects of bone growth.
- Since many of the effects of somatomedins on growth are similar to that of insulin, they are called insulin like growth factors (IGFs).
- At least 4 somatomedins have been isolated, but the most important of this is Somatomedin-C (IGF-1).The molecular weight of Somatomedin-C is 7500, and its concentration in plasma closely follows rate of GH secretion.
- Most of the GH results from the IGF-I and other Somatomedins rather that it's direct effects. GH can cause formation of enough Somatomedin-C in local tissues to cause local growth.
- GH has a short duration of action but Somatomedin-C has prolonged action.

Most of the growth effects of GH results from IGF and other Somatomedins rather than its direct effects.GH can cause the formation of enough Somatomedin C in local tissues to cause local growth.

GH has a short duration of action but somatomedin C has prolonged action.

GH is regulated in a feedback manner by-

1.GHRH:

Secreted by arcuate nucleus of hypothalamus.

Stimulates GH secretion by binding to cell membrane receptors of GH secreting cellsin ant. pituitary.

It activates adenyl cyclase → Increases cAMP

It has got both short term as well as long term effects.

Short Term:

Increase transport of Ca into cell→Increases intracellular Ca→Causes movement of vesicles conatining GH to cellmembrane.→fusion of vesicles with cell membrane→hormone released by exocytosis

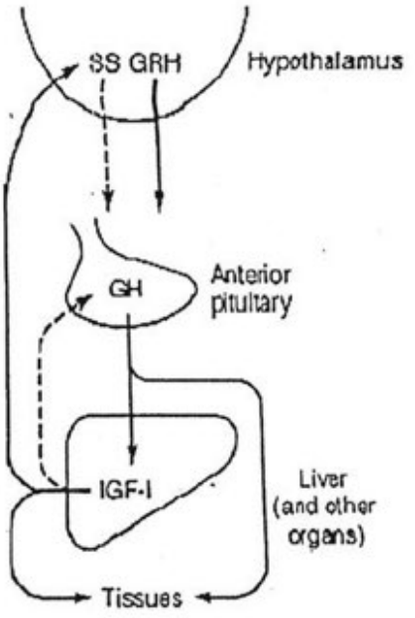
Long Term:

Increases transcription which stimulates synthesis of GH.

2.GHIH (somatostatin): It is inhibitory to secretion of GH.

3.Ghrelin:

It has marked stimulatory action of anterior pituitary. It is secreted by stomach and also by hypothalamus.GHRH secretion is episodic.GH secretion undergoes marked fluctuations,Increase in GHRH coincides with surges of GH secretion. Somatostatin secretion is more tonic.



Other Factors:

That Increases:

1. Decrease in substrate for energy production in cells as in hypoglycemia, fasting, decrease in free fatty acid level, starvation.
2. Trauma and stress.
3. Exercise.
4. Estrogen and androgen.
5. Increased during first two hours of sleep.
6. Glucagon.

That Inhibits:

1. Increase in blood glucose.
2. Increase in FFA level in blood.
3. Cortisol.
4. Medroxyprogesterone.
5. REM sleep.
6. GH administered exogenously.

6.Hyperthyroidism:

This is a condition resulting from Increased circulating levels of free T3 and T4.

Causes:

Can be due to thyroidal over-activity or due to extra-thyroidal causes.

1.Thyroid overactivity:

a. Graves' disease
b. Solitary toxic adenoma
c. Toxic multi-nodular goiter
d. Hashimuto's Thyroiditis
e. TSH secreting pituitary tumor.

f. Mutations causing constitutive activation of TSH receptor.

g.Other rare causes.

2.Extrathyroidal:

a.Administration of T_3 or T_4 (factitious or iatrogenic hyperthyroidism)

b.Ectopic thyroid tissue.

Features:

- Increased BMR 60-100% above normal.
- Skin is warm soft and moist withIncreased sweating.
- Heat intolerance/.
- Nervousness,anxiety extreme worrying.
- Reaction time of stretch reflexes is shortened.Fine tremor of outstretched fingers of frequency of 10-15 times per second.
- Increased Heart rate,Cardiac output and Decreased Pressure and Wide pulse pressure.
- Exophthalmos.
- Muscle weakness due to increased protein catabolism.
- Constant tiredness due to exhausting effects of TH on muscles and CNS.
- Weight loss due to increased metabolic rate.
- Hyperphagia.Diarrhea.
- Impotence in men.
- Oligomenorrhea and amenorrhea in women.

Graves' Disease:

It is an auto-immune disease.

Most common cause of hyperthyroidism. Accounts for 60 to 80% of the cases.

The condition is much more common in women. .

Circulating antibodies are found against TSH receptors. Through cyclic AMP, they cause the activation of these receptors. There will be prolonged action for around 12 hours.

Gland is Hyperactive. T3 and T4 levels are HIGH. However due to feedback effect, TSH is LOW. The increased hormone level is associated with Increased Antibody Secretion.

Graves Disease

Exophthalmos:

Considered as a hallmark of Graves' disease. It is the occurrence of swelling of tissues of orbit producing protrusion of eyeballs. This occurs in 50% of the patients and often precedes the development of obvious hyperthyroidism.

A subpopulation of fibroblasts in the orbit ultimately develop into adipocytes and these pre-adipocyte fibroblasts often contain TSH receptor protein.

The current theory of exophthalmos is that this is stimulated by the TSH receptor stimulating antibodies in the circulation, these cells release cytokines, that promote inflammation and edema.

There is auto-immune attack on extra-ocular muscles and orbital connective tissue.

Diagnostic Test:

T3 and T4 is high.

TSH level is lowered.

Radioactive I2 intake is high.

TSH receptor antibodies are increased.

Treatment:

•Antithyroid drugs.

•Surgery: Administration of radioactive iodide for preparing the patient for surgery. High conc. of iodide given 1–2 weeks before surgery decreases the size of the gland and vascularity. Propyl thiouracil for several weeks helps to decrease total BMR to normal.

7. Myxoedema : Refer Essay 1

8.Antithyroid Drugs:

They are drugs that inhibit thyroid function.

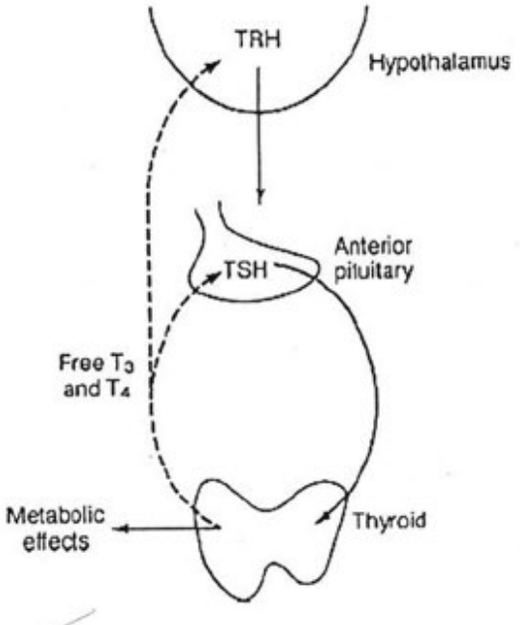
They act in 3 ways.

1.By interfering with iodide trapping:

Many monovalent ions like;
Chlorate,Perchlorate,Periodate,Thiocyanate,Nitrate Inhibit iodide trapping.
These anions compete with iodide for transport in thyroid *via Na+ I- symporter.*
Thyroglobulin synthesis occurs normally. But iodination of it is inhibited. T_3,T_4 decreases and TSH increases leading to Goiter.

2.By blocking organic binding of iodide:
Thiourylenes are group of compounds related to thiourea. Compounds like Propyl Thiouracil, Carbemazole, Methymazole prevent the hormone formation by inhibiting the iodination of tyrosine and blocking the coupling reaction.
The drugs compete with tyrosine residues to bind with iodides and also by partly blocking peroxidase enzyme system. Propylthiouracil also inhibits D_2 iodinase. There is decreased conversion of T_4 to T in many extrathyroidal tissues. In hyperthyroidism they suppress immune system and depresses the formation of stimulating antibodies , decreases TSH receptor stimulating antibodies

3.Auto regulation of iodides:
Refer essay 1



9. Diabetes Mellitus:

Diabetes mellitus is a syndrome of impaired carbohydrate, fat and protein metabolism.
Caused by
Lack of insulin secretion (Type 1)
Or Decreased sensitivity of tissues to insulin and impaired secretion (Type 2).

Diabetes mellitus can be:
– Primary:
- ➢Type 1
- ➢Type 2

- Secondary:
Due to chronic pancreatitis, Cushing's syndrome, acromegaly, and total pancreatectomy.

Type 1:
- Insulin dependent.
- Onset less than 40 years (juvenile diabetes)
- Autoimmune with selective destruction of β cell, anti β cell is present. Recently thought to be a T lymphocyte mediated disease.
- Genetic susceptibility is present. 33% concordance in identical twins.
- Insulin sensitivity is normal.
- Plasma insulin level is absent or low. Glucagon level is high.
- Associated with ketosis.
- Complication at the time of diagnosis absent.
- Treatment- insulin and adequate diet.

Type 2:
- Non insulin dependent.
- Occurs after 40 years (patients are obese).
- Caused by decreased sensitivity of target tissues to the metabolic effects of insulin called insulin resistance.
- Genetic susceptibility present. (100 % concordance in identical twins).
- Insulin sensitivity is decreased.
- Plasma insulin level is normal or high. Glucagon level is high.
- Rarely associated with ketosis.
- Complications are present.
- Treatment: diet and oral hypoglycemic drug.

10.Glucagon:

Glucagon is a linear polypeptide with 29 amino acids.
- Produced by A cells of pancreatic islets and upper GIT
- Synthesized from a pre – pro glucagon (precursor protein found in pancreatic A cells , α cells in lower GIT and in brain.)
- A cells – glucagon , major proglucagon fragment.
- L cells – Glicentin (a polypeptide that consists of glucagon extended by additional aminoacid residues at either end plus GLP polypeptide) , glucagon like polypeptides GLP-1,GLP-2 .
- GLP 1 and 2 have no definite biological activity by themselves where as Glicentin has some glucagon activity.

Actions:
1). Glycogenolysis in liver.

2). Gluconeogenesis in liver.
(Biological effects are opposite to that of insulin).
3). Lipolytic effect.
4). Ketogenic effects also.

On Carbohydrate Metabolism:

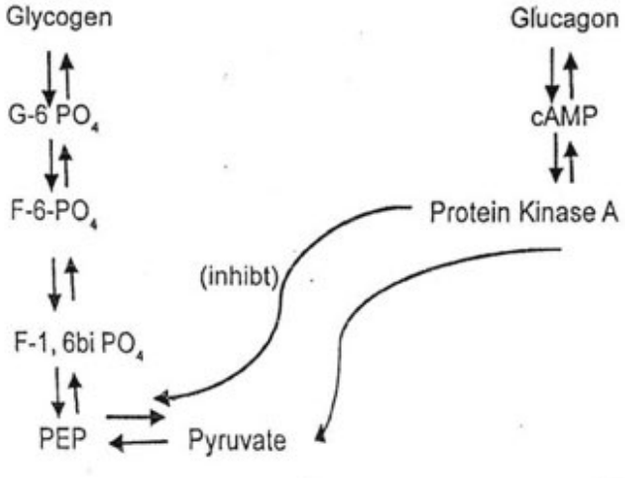
It causes both Glycogenolysis and gluconeogenesis in liver.

Acts via **G protein coupled receptor** (serpentine receptors in liver).

Activate adenyl cyclase
↓
Increases cAMP
↓
Activation of protein kinase A
↓
Activation of phosphorylase
↓
Increase breakdown of glycogen
↓
Increase glucose

Glucagon acts on glucagon receptors located on hepatic cells to activate PLC and the resultant Increase in cytoplasmic Ca^{2+} also stimulate glycogenolysis. Protein kinase A also decrease the metabolism of glucose phosphate by inhibiting the conversion of PEP →pyruvate

It also decreases the concentration of Fructose-2,6 bi phosphate and this inturn inhibits the conversion of fructose 6 phosphate to fructose 1,6 bi-phosphate. The resultant increase in glucose 6 phosphate leads to increased release of glucose.



Glucagon increases amino acids uptake by α liver cells and the conversion of amino acids to glucose by gluconeogenesis . This is achieved by activating multiple enzymes that are required for amino acid transport and gluconeogenesis.

Effect on Lipid Metabolism:

Glucagon activates adipose cell lipase there by decreasing D-malonyl coA in liver .

Glucagon in high concentration causes:
- Increased strength of heart due to increased myocardial cAMP.
- Increased bile secretion.
- Inhibition of gastric acid secretion.
- Increased blood flow in some tissues, especially Kidneys.

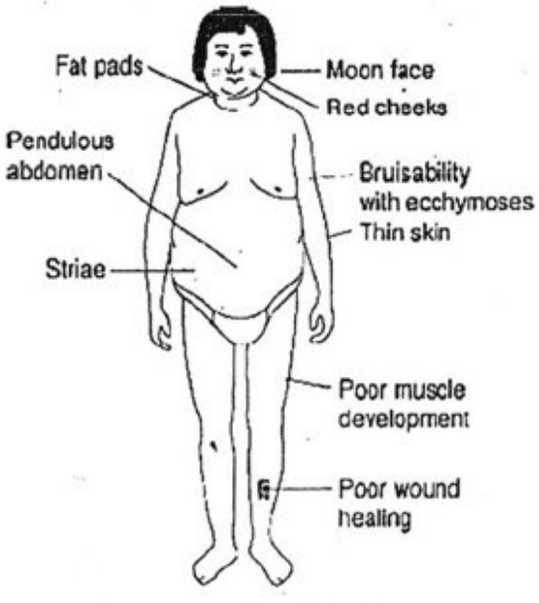
11. Cushings Syndrome:

It is caused by excess glucocorticoid secretion. The clinical picture produced by prolonged increase in plasma glucocorticoid was described by Harvey Cushing & hence called Cushing's syndrome.

2 types:

a). ACTH Independent: caused by:
- Glucocorticoid secreting tumors.
- Adrenal hyperplasia.
- Prolonged administration of exogenous glucocorticoids.

b). ACTH Dependent: caused by
- ACTH secreting tumors of anterior pituitary.
- Tumors of other organs like lungs.



CUSHING'S SYNDROME

When Cushing's syndrome is secondary to excess secretion of ACTH by anterior pituitary gland, this is called Cushing's disease.

Signs and Symptoms:

1. Patients with Cushing's syndrome are protein depleted as a result of **protein catabolism**. So skin and subcutaneous tissues are thin and muscles are poorly developed.

2. Poor Healing of Wounds. Minor injuries cause ecchymoses and bruises.

3. Hair is thin. Some have an increase in facial hair which is caused by INCREASED secretion of adrenal androgens that often accompanies the increased glucocorticoid secretion.

4. Cortisol promotes mobilization of fatty acid from adipose tissue. This increases the concentration of free acids in the plasma. Body fat is redistributed in a characteristic way. Extermities are thin but fat collects in abdominal wall, face, upper back where it produces a **Buffalo Hump**. As the thin skin of the abdomen is stretched by the increased subcutaneous fat, the subdermal tissue ruptures to form prominent reddish **purple striae**.

5. Many of the amino acids liberated from the catabolised protein are converted into glucose in liver resulting in **hyperglycemia**. There is also decreased peripheral utilization of glucose. This precipitates insulin-resistant diabetes mellitus. Hyperlipidemia and ketosis are associated with the diabetes but acidosis is usually not severe.

6. Glucocorticoids are present in large amounts in Cushing's syndrome. So they exert a significant mineralocorticoid activity. This leads to salt and water retention and facial obesity giving characteristic **rounded moon faced appearance.** There may be significant K^+ ion depletion and weakness.

7. About 85% of the patients with Cushing's syndrome are **hypertensive** which is due to Increased deoxycorticoids which inturn increases angiotensinogen secretion or a Direct glucocorticoids effect on blood vessels.

8. There is bone dissolution by Decreased bone formation and Increasing bone resorption. This leads to **osteoporosis.**

9. Glucocorticoids in excess accelerate the basic EEG rhythm produce mental aberration ranging from Increased appetite, insomnia and euphoria to frank toxic cytosis.

Treatment:

- Removal of adrenal tumour if it is the cause.
- Pituitary tumours can be surgically removed or destroyed by radiation.
- Drugs that block steroidogenesis. They are metyropone, ketoconazole, aminoglutethimide.
- Drugs that inhibit ACTH secretion – serotonin antagonist, GABA transaminase inhibitors.
- Adrenalectomy, if ACTH secretion can't be easily decreased. Bilateral, partial or even total adrenalectomy is done. This is followed by administration of adrenal steroids to make up for any insufficiency that develops.

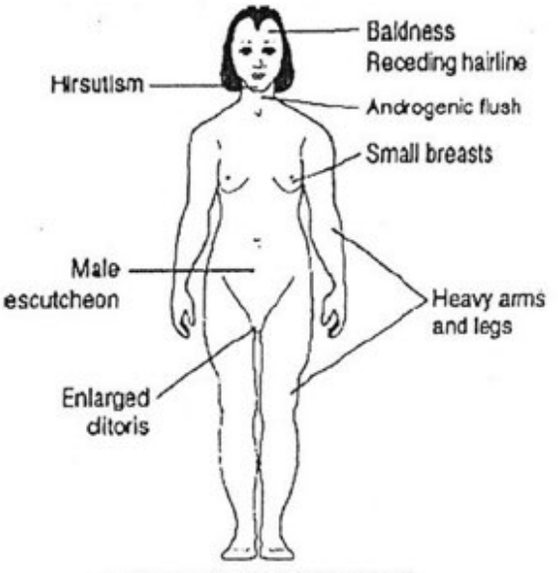
12. Adrenogenital Syndrome:

It is the characteristic pattern that develops in females due to excessive secretion of adrenal androgens that cause intense masculinising effects throughout the body.

Causes:

1. **Mutations** at different sites of **21 β hydroxylase gene**, causing the deficiency of the enzyme. Production of cortisone and aldosterone are generally reduced, so ACTH secretion and consequently production of precursor steroids increased. These steroids are converted to androgens producing virilisation.

2. Deficiency of the enzyme **11β hydroxylase**. In this condition there will be virilisation as well as excess secretion of 11-deoxycortisol and 11-deoxy corticosterone. Since the former is an active mineralocorticoid, patients with this condition also have salt and water retention and in 2/3 of the cases hypertension (hypertensive form of congenital adrenal hyperplasia).



ADRENOGENITAL SYNDROME

Features:

Development of male secondary sexual characters.
Growth of beard.Deep voice.Balding.
Masculine distribution of hair on body and pubis.
Hirsuitism,Receding hair line.
Small breasts,Androgenic flush.
Heavy legs and arms.
Enlargement of clitoris.

Treatment:

Administration of glucocorticoids, since it repairs the glucocorticoid deficit and INHIBITS ACTH secretion reducing the abnormal secretion of androgens and other steroids.

13. Regulation of mineralocorticoid secretion:

(Refer Essay 7)

14. Addison's disease:

(Refer Essay 7)

15. Permissive action of Glucocorticoids:

(Refer Essay 3)

16. Circadian Rhythm:

(Refer Essay 3)

17. Actions of Thyroid Hormone:

(Refer Essay 1)

18. Vitamin D Actions:

- 1, 25 DHCC increases the no. of Ca^{2+}-H^+ ATPase molecules in the intestinal cells which are needed to pump Ca into the interstitium.
- It increases ALP formation in epithelial cells
- It increases absorption of PO_4^{3-} & Mg^{2+}.
- In the kidney, increases Ca^{2+} & PO_4^{3-} absorption from the renal tubules & their excretion in urine.
- In the bone, it has a role in both bone absorption & deposition. It increases the synthetic activity of osteoblast & is necessary for normal calcification of matrix. The stimulation of osteoblast causes a secondary increase in the activity of osteoclast.
- In large quantities, vitamin D causes absorption of bone. The decrease or absence causes PTH action decreased bone resorption.

In smaller quantities it promotes bone calcification, bone mineralization. This effect may be due to action on calcium transport or on the osteoclast & osteoblast.

- In other tissues, 1, 25 DHCC appears to be involved in the regulation of growth & production of growth factors.
- 1, 25 DHCC stimulates differentiation of immune cells & keratinocytes in skin.

Mechanism of Action:

1,25 DHCC is a steroid hormone.Receptors may be cytoplasmic or nuclear.Steroid receptor exposes a RNA binding site.

Increased transcription of some mRNA leads to production of Ca binding protein Calbindin.

Calbindin proteins are found in kidney, brain and intestine.

2 calbindins are induced:- Calbindin D9k & D28k.

Calbindins Increase absorption of Ca^{2+} & PO_4^{3-} from intestine.

19. Parathyroid Hormone: Actions & regulations:

Actions:

1.On Bone:

Acts directly on the bone to increase bone resorption and mobilizes Ca^{2+}.

This Occurs by 2 phases:

- Rapid phse of Ca^{2+} & PO_4^{3-} absorption-Osteolysis
- Slow phase of bone absorption-Activation of Osteoblasts

Rapid Phase of Ca^{2+} & PO_4^{3-} Absorption:

Seen within few minutes of PTH Administration.

PTH causes removal of bone salts from 2 areas in bone:

a)From bone matrix in the vicinity of osteocytes.

b)In the vicinity of osteoblasts along bone surface.

The cell membrane of both the osteoblasts and osteocytes have receptor proteins for binding PTH.

PTH can activate the Ca^{2+} pump,Increasing the Ca^{2+} permeability of osteocytic membrane allowing Ca^{2+} to diffuse into the membrane cells from bone fluid.

Then Ca^{2+} pump on the other side of cell membrane transfers Ca into ECF.

Slow Phase of Bone Resorption:

- Activation of osteoclasts.

Constant exposure to PTH causes activation and formation of new osteoblasts→causes resorption of mineralised mature bones

On Kidneys:

3.It increases reabsorption of Ca^{2+} in the distal tubules.
4.It increases the formation of 1, 25 DHCC.

On Intestine:

Enhances both Ca & PO4 absorption from intestine.

Regulation:

Circulating ionized Ca^{2+} acts directly on the parathyroid gland in a negative feedback fashion to regulate the secretion of PTH.

The key to this regulation is a cell membrane Ca^{2+} receptor. This serpentine receptor is coupled via a G protein to phosphoinositide turnover & is formed in many tissues.

In the parathyroid, its activation inhibits PTH secretion. In this way when plasma Ca^{2+} is high, PTH secretion is inhibited & the Ca^{2+} is deposited in the bones.

When its low, secretion is increased & Ca^{2+} is mobilized from the bones.

- 1, 25 DHCC acts directly on the gland to decrease preproPTH mRNA.
- increased plasma PO_4 stimulated PTH secretion by lowering plasma Ca^{2+} & inhibiting the formation of 1, 25 DHCC.

20. Hypocalcemic tetany:

It is due to the decrease in the extra cellular Ca that which exerts a net excitatory effect on nerve & muscle cells.

The disease characterized by extensive spasm of skeletal muscles,especially the muscles of the extremities. Laryngospasm becomes very severe that the airway is obstructed & fatal asphyxia is produced.

Ca^{2+} plays a very important role in clotting, in vivo, however the level of plasma Ca^{2+} at which fatal tetany occurs is still above the level at which clotting defects occur.

In humans, the signs of tetany include;

Chovstek's sign,a quick contraction of the ipsilateral facial muscles elicited by tapping over the facial nerve at angle of the jaw.

Trousseau's sign,a spasm of the muscles of the upper extremities that cause flexion of wrist & thumb with extension of the fingers.

Treatment:

I.V admininstration of Ca.
PTH administration,Vit D administration.

21. Calcitonin- Actions:

- Calcitonin decreases circulating Ca^{2+} & PO_4^{3-}levels. Actions are seen mainly in the bone & kidney & also to some extent in the intestine.

Mechanism of Action is via cAMP. It is the 2nd messenger. It increases **exocytosis** of calcitonin.

Actions in the Bone:

It has a Ca^{2+} lowering effect.

Calcitonin inhibits bone resorption , It has a direct action. It inhibits the activity of osteoclasts.

Calcitonin binds with membrane receptors on osteoclasts & finally causes its deactivation & hence decreases bone resorption. Effect is more in young animals.It occurs in two ways.

➢ An immediate effect:It is to decrease the absorptive activity of osteoclasts & decrease the osteolytic effect of osteolytic membrane system & thus favours Ca^{2+} deposition into the exchangeable Ca^{2+} salt pool.

It is more important in young animals because of rapid interchange of absorption & deposition of calcium.

➢ A more prolonged effect :Calcium decreases the formation of new osteoclasts & that in turn decrease activity of osteoclasts.So on a long term basis both osteoclastic & osteblastic activity is decreased. There is only a transient effect on plasma calcium which lasts for a few hours to few days.

- It decreases plasma PO_4 level due to inhibition of bone resorption & promotes phosphate entry into bone. There is a small increase in urinary PO_4 excretion.
- Calcitonin inhibits renal tubular Ca^{2+} reabsorption & there by increases Ca^{2+} excretion in urine.
- Calcitonin is a physiological antagonist to PTH with respect to Ca^{2+} and has agonist action to PTH w.r.t. phosphate.
- Exact physiological role of calcitonin is uncertain. The calcitonin content in thyroid is low. After thyroidectomy, the bone density & plasma Ca^{2+} levels are normal as long as parathyroid gland is intact. No deficiency syndrome has been described.
- In young individuals, it has a role in skeletal development.
- It may protect against post prandial hypercalcemia.
- It protects the bones of mother from excess Ca^{2+} loss during pregnancy as bone formation & lactation in infants are major factors that drain the maternal Ca^{2+} reserves.

22. Aldosterone Escape:

(Refer essay 7)

23. Thyroid Function Tests:

Classified into 2, Direct and Indirect:

1.Direct tests:

a)Radio immune assay:

Measurement of plasma total free T3,T4 & TSH

Normal levels of serum T_4 is 4-12 microgram/100ml and T_3 is 80-180ng/100ml.

There is a negative feedback of TH on hypothalamus & pituitary.So in hyperthyroidism,when plasma concentration of T3 & T4 are raised,TSH secretion is suppressed.

In hypothyroidism T3 & T4 associated with high TSH.

b)Response to TRH:

TSH is increased means function of anterior pituitary is normal. Radioactive iodine I^{123},traces are administered and the uptake is determined by placing a gamma ray counter in neck. Rapid uptake/incorporation or accelerated rate of release of iodine is seen in hyperthyroidism and low in hypothyroidism.

c)Radioactive I_2 uptake(RAIU):

I_2 uptake is an index of thyroid function.It can be easily measured by using trace doses of radioactive isotopes of I_2 that have no known deleterious effects on thyroid.

Isotope used is determined by placing a G ray counter over neck.

In Hyperthyroidism RAIU is High and in Hypothyroidsim RAIU is Low.

d)Thyroid imaging:

Using radioactive iodine or sodium pertechnitate,This is taken up by the gland and.by scanning on the area of thyroid function, both defects can be made out.

e)Ultrasonography: To differentiate cystic and nodular lesions

f) Measuring circulating antibodies to detect autoimmune thyroid disease.

g) Fine Needle Aspiration biopsy.

1.Indirect Test:

a.BMR increases up to +40 in hyperthyroidism and decreases up to -20 in hypothyroidism.

b.**Serum cholesterol** increases in hypothyroidism and decreases in hyperthyroidism

c.**Protein bound iodine**; normal value is 4-8 microgram/100ml.It increases in hyperthyroidism and decreases in hypothyroidism.

d.**Sleeping pulse rate** increases in hyperthyroidism.

24.Diabetes Insipidus-types:

(Refer Essay 2)

25. Role and regulation of Oxytocin:

(Also neuroendocrine essay)

It is a typical neural hormone secreted by **paraventricular nuclei** primarily and some from supraoptic nuclei. It is carried by hypothalamohypophyseal tract to posterior pituitary and stored there.

It is also synthesized in gonads, adrenal cortex and thymus.

Role of oxytocin (S.N.):

1). Importance in Lactation:

It causes contraction of myoepithelial cells that line the ducts of breast. This squeezes milk out of alveoli into the sinuses and then out of nipple. This process is known as milk ejection.

Milk ejection reflex (Neuroendocrine reflex –S.N.):

It is a typical neuroendocrine reflex.

Receptors:– Touch receptors on nipple and surrounding areola of breast.

Afferent:-

Signals carried through sensory nerve

↓

Somatic touch pathways

↓

Supraoptic and paraventricular nuclei.

It causes secretion of ADH from posterior pituitary.

Efferent:-

Hormones carried by blood to breast which causes contraction of myoepithelial cells. This causes ejection of milk into sinuses and through nipple into baby's mouth. It is called neuroendocrine as afferents are neuronal and efferent is circulatory system.

Other stimuli which cause milk ejection are emotional stimuli like cry of baby,which inhibit;

i) Psychogenic factors-fear

ii) generalized sympathetic stimulation like E and NE

2) Importance in parturition:

It causes **contraction of myometrium** of pregnant uterus, thus helping in parturition.

Oxytocin secretion from hypothalamus is Increased during labour. In late pregnancy, uterus becomes very sensitive to oxytocin. There is an increase in number of

oxytocin receptor mRNA and a 100 fold increase in number of oxytocin receptors.

It reaches its peak during early labour.

This Increase is by:

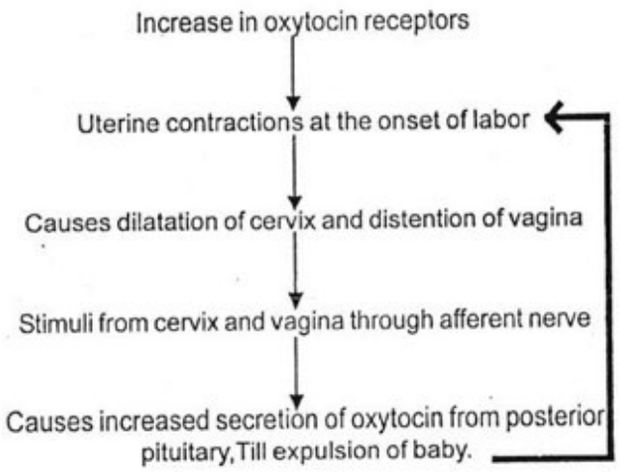
i) Estrogen increases number of oxytocin receptors.

ii) Uterine distention increases their formation.

With increase in number of oxytocin receptors, the uterus responds to even normal plasma concentration of oxytocin at the onset of labor.

The amount of oxytocin in uterus also increases during labour. Some amount of oxytocin may be produced locally also.

The reflex is initiated as follows:



This is an example of positive feedback.

In addition there is secretion of prostaglandin(PG) which is helpful in uterine contractions.

Oxytocin increases contraction of uterus in two ways:

i) Acts directly on uterine smooth muscles.

ii) Stimulates formation of prostaglandins in decidua. PGs enhance oxytocin induced contraction.

3).Oxytocin may act on non-pregnant Uterus:

It facilitates the sperm transport up the genital tract up to uterine tubes where fertilization occurs.

Action in Males:

Contraction of smooth muscles in vas deferens and propels sperm towards urethra.

26.Features of excess mineralo-corticoid secretion:

(Refer Essay 7)

27. Renin Angiotensin System:

(Refer Essay 5)

28. Regulation of Glucocorticoid secretion:

(Refer Essay 3)

29. Regulation of ADH secretion:

(Refer essay 5)

30. Insulin regulation, receptors and functions:

(Refer Essay 2)

31.Addisonian Crisis:

(Refer Essay 7)

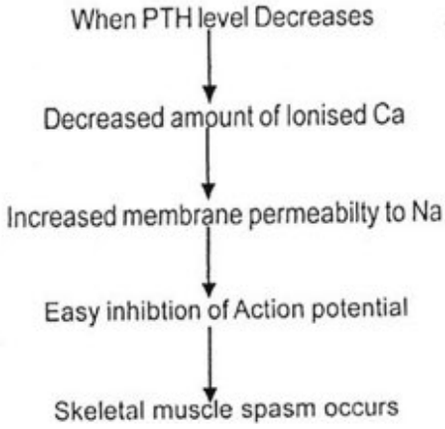
32. Exopthalmos is seen in Hyperthyroidsism.Why?

(Refer SN6)

33.Oedema is manifested in Hypothyroidism.Why?

Skin normally contains a variety of proteins combined with polysaccharides hyaluronic acid and chondroitin sulfuric acid.In hypothyroidism,these complexes accumulate promoting water retention and characteristic puffiness of skin causing myxoedema.

34.Hyperexcitibality is seen in Tetany.Why?



35.Osteoporosis in Cushings Syndrome.Give Reason

Refer action of Cortisol on Bone(Essay 3)

36.Milk ejection Reflex/Neuroendocrine Reflex: (Sn25)

primary spermatocyte.Spermatogonia are small

Reproduction

Prepared by
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ESSAYS

1.Menstrual cycle:

The rhythmical changes occurring in the rate of secretion of female hormones and corresponding physical changes in ovaries and other sexual organs during the reproductive period of a female is known as Menstrual Cycle.Its duration is of 28 days.It can vary from 20-40 days even in a normal female.Menarche is the onset of menstruation. Menopause occurs around an age of 40-50 years.

During menstrual cycle cyclical changes occurs in ovary, Uterus vagina and breast. So it is divided to ovarian cycle, uterine cycle, cervical, vaginal cycle and changes in breast.

Ovarian Cycle:

It is ivided into 3 phases:

a) Follicular phase:

About 3-4 lakhs of primordial follicles are present in the ovarian cortex at the time of birth and each contain an immature ovum. Through out childhood, the cells surrounding the oocyte provide nourishment and also secrete Ovarian Maturation Inhibiting Factor which keeps the ovum suspended in the primordial state.

At the start of each cycle, several of these follicles enlarge. On about 6th day, one of the follicle starts to grow rapidly and becomes the dominant follicle.The process of atresia of other follicles involves apoptosis. The proposed hypothesis is that it is related to the ability of the follicle to secrete estrogen that is needed for its final maturation.

The flattened follicular cells become columnar and a homogenous membrane called zona pellucida appears between follicular cells and oocyte. The follicular cells proliferate to form several layers of cells called membrana granulosa.

The mass of granulosa cells secrete follicular fluid with high concentration of estrogen and the accumulation of these follicular fluid results in formation of fluid filled cavity,the antrum. The size of the cavity rapidly increases. As a result wall of the follicle formed by the granulosa cells becomes relatively thin. The oocyte now lies eccentrically in the follicle surrounded by some granulosa cells called as cumulus oophorus.The cells attached to the wall of the follicle forms discus proligerus.

The stromal cells from the ovarian interstitium collect in several layers outside the granulose cells giving rise to a second mass of cells called theca.They are arranged in 2 layers

➢Theca interna - are cells with epitheloid lining. They form primary source of circulating estrogen.

➢Theca externa – develops to highly vascular connective tissue capsule that becomes capsule of developing follicle.

graafian follicle:

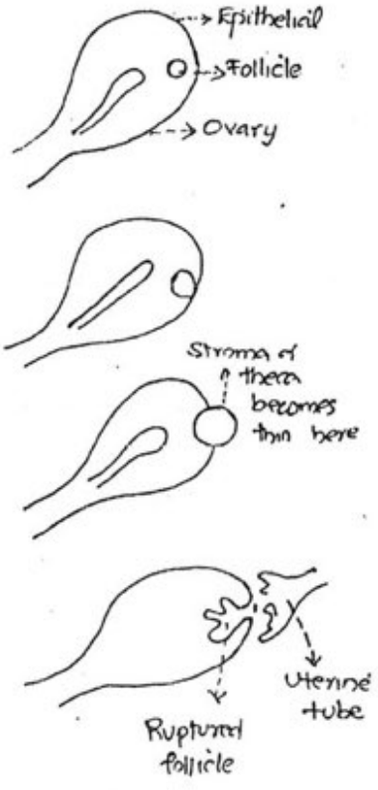
During the follicular phase primordial follicle is converted in to primary follicle and then into the matured,graafian follicle.Graafian follicle has got a diameter of 1-1.5cm .As the follicle matures approximately 1000 fold increase in size occurs due to accumulation of follicular fluid. This fluid contains – estradiol, progesterone, androgens, LH, FSH, prolactin, oocyte maturation inhibiting factor,and prolactin aromatase inhibiting protein.

b)Ovulatory Phase:

Shedding of ovum from ovary by the rupture of a mature graafian follicle into the abdominal cavity .Occurs on 14th day of a 28 day cycle. For ovulation, LH surge is needed. Ovulation occur 9 hours after LH surge.

LH surge:

Two days before ovulation LH secretion from pituitary is increased 6-10 times due to possitive feedback mechanism of estrogen produced by graafian follicle



b)Secretory phase/Luteal phase:

From 15th to 28th day. It represents preparation of uterus for implantation of the fertilized ovum. This phase is influenced by both estrogen and progesterone from corpus luteum. Progesterone causes marked enlargement of endometrial glands. The glands become coiled and tortuous. They begin to secrete a clear fluid. Estrogen caused the further proliferation of endometrial stroma. Lipids and glycogen deposit increases in the stromal cells .Stromal cells become edematous and their vascularity increases .At the peak of secretory phase (1 week after ovulation) the endometrium has a thickness of 5-6mm.Endometium is thick, soft and richly supplied with blood. The purpose of secretory endometrium with large amount of stored nutrients is to provide an appropriate environment for implantation of fertilized ovum.

c) Menstruation:

If the fertilization doesn't occur , corpus luteum regresses and hormonal support for endometrium is withdraw and reversal occurs .Endometrium becomes thinner. There is vasospasm of spiral arteries , due to locally released prostaglandin. Vasospasm along with necrosis of the walls of the spiral arteries leading to spotty hemorrhages that becomes confluent and produce the menstrual flow.

Menstrual blood – predominantly arterial , 25% of venous origin. It contain tissue debris , prostaglandins and fibrinolysin from endometrial tissue . Fibrinolysin lyses the clot. Therefore menstrual blood doesn't colt normally. It may contain clot when flow is excessive. Duration is 3-5 days. Range 1-8 days. Amount of blood may vary from slight spotting to 80ml.Avg is 30ml.

Cervical Cycle

During proliferative phase cervical mucous is thinner and more alkaline .This promote survival and transport of sperm. The mucous will be thinnest at time of ovulation and its elasticity increases. This is called **spinnbarkeit**. Such that a drop of mucous can be drawn into a long thin thread of 8-12cms length.When a thin layer of cervical mucous is spread on a slide,it dries up forming a **fern pattern.** During Luteal phase the mucous is thick tenacious and cellular to prevent the entry of sperm.

Vaginal cycle

Under influence of estrogen vaginal epithelium become cornified (columnar to stratified squamous).Progesterone cause proliferation of epithelium and they become infiltrated with leucocytes.

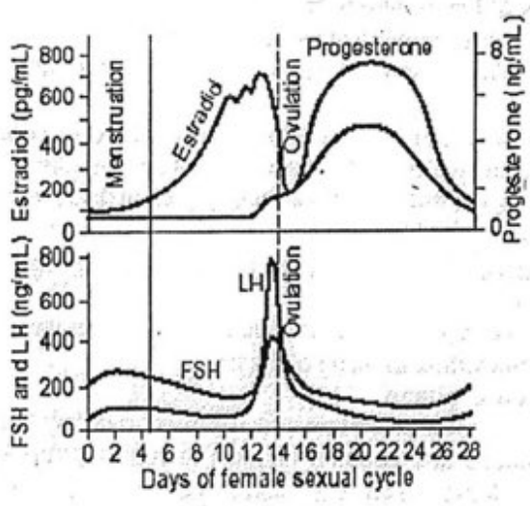
Changes in the breast

Estrogen causes proliferation of mammary ducts. Progesterone causes growth of lobule and alveoli. Many females experience pain swelling and tenderness on the breast during 10 days preceding menstruation due to distention of mammary duct, hyperemia and edema of interstitial tissue. These symptoms regress with menstruation.

2.Hormonal regulation of menstrual cycle

It is controlled by hypothalamo – pituitary ovarian axis. Hypothalamus secretes GnRH which regulate secretion of both FSH and LH from anterior pituitary. In females hypothalamic influence is easily demonstrated by fact that various type of mental stress commonly disturbs the menstrual cycles. Secretion of GnRH occurs mainly from the preoptic area of hypothalamus .The secretion is pulsatile.Release of GnRH causes intermittent output of LH secretion. Constant infusion of GnRH causes down regulation of GnRH receptors in anterior pituitary .So that LH secretion declines to zero.FSH and LH are glycoprotein hormones. FSH is responsible for initial maturation of follicle. LH responsible for final maturation of follicle, secretion of estrogen, formation of corpus luteum and secretion of progesterone.

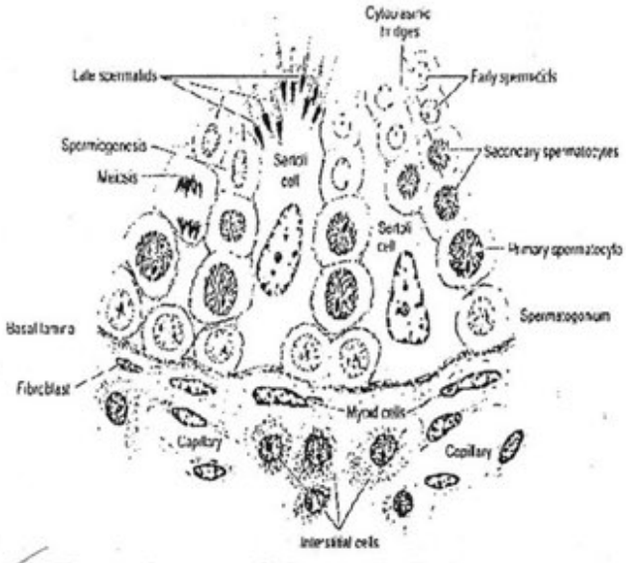
Ovaries secrete – estrogen , progesterone , and inhibin .Plasma LH,FSH,estrogen ,progesterone and inhibin have feedback regulation .A moderate level of estrogen causes a negative feedback on LH secretion .Inhibin acts directly on anterior pituitary cells and inhibit FSH secretion. The frequency of GnRH burst is increased by estrogen. In late follicular phase when estrogen secretion increases frequency of GnRH pulses increases.



During early follicular phase Inhibin B is low and FSH is moderately increased .It favors follicular growth .Moderately increasing levels of serum estrogen have negative feedback effet,holds LH secretion in check .During late follicular phase or 26-48 hours before ovulation when estrogen secretion increases leading to increase in frequency of GnRH pulses which leads to maximum secretion of LH.That is called LH surge and it is responsible for ovulation.

•Steroids penetrate the barrier with ease and evidence suggests that some proteins pass from sertoli cells to leydig cells and vice versa in a paracrine fashion.

3.Draw & label vertical section of testis and functions of each cell:



4. Functions of Sertoli Cells:

• Role of sertoli cells in spermatogenesis

1.Provides support, maturation and suitable environment for development of germinal cells to spermatozoa and conversion of spermatid to sperm.

2. Also helps in release of mature sperms to seminiferous tubules (spermiation)

3.It has got phagocytic function. They phagocytose defective sperm and residual bodies formed during spermatogenesis.

4.Formation of blood-testis barrier.

• Endocrine functions of sertoli cells

1.Fetal sertoli cells secrete MIS (Mullerian Inhibiting Substance) or MRF (Mullerian Regressing Factor), in adults secrete Inhibin which inhibit FSH secretion and also secrete Activin which stimulate FSH secretion.

2.Secrete ABP (androgen binding protein) which maintains high stable supply of androgen in tubular fluid.FSH and androgen maintain gametogenic function of testis, so sertoli cells are regulators of spermatogenesis. Also circulating FSH and interstitial androgen stimulate sertoli cell function leading to optimal spermatogenesis.

3.It also helps in the formation of estrogens, by secreting enzyme required to convert androgen to estrogens (aromatase).

5.Klinefelter's Syndrome:

Klinefelter's Syndrome/Seminiferous Tubule Dysgenesis/44XXY:

- It is most common
- Genetic pattern-47 chromosomes-44XXY
- They have normal male internal and external genetalia.
- Poorly developed testes with highly degenerated seminiferous tubule causing sterility.
- Patient will be tall and under weight.
- High chance for mental retardation.
- Gynaecomastia
- Penis is small or of normal size
- Testis is small
- Secondary sexual characteristics poorly developed.
- Positive chromatin test
- Low or normal plasma testosterone level
- High plasma LH,FSH and estradiol

6.Turners Syndrome

Gonadal Dysgenesis/Ovarian Agenesis/Turners Syndrome:

- Karyotype 44-XO
- Since Y chromosome is absent the patient is phenotypically female.
- Gonads are rudimentary or absent and may consist of undifferentiated stroma with absence of sex cells and only fibrous tissue. These type of gonads is called Streak gonads.
- Short stature
- Delayed puberty
- Scanty menstruation, usually amenorrhea and there is primary infertility
- Low hair line, webbed short neck. Low set ears.
- Ptosis, exaggerated epicanthic folds.
- Dwarfism
- Pubic and axillary hair scanty or absent
- Vagina and uterus underdeveloped
- Broad chest with widely placed nipples, amastia
- Digital deformity present
- Coarctation of aorta
- Renal anomalies like horse shoe shaped kidney

7.Factors Influencing Spermatogenesis:

They are divided into:

1.Hormonal factors:

- Testosterone: It is secreted by leydig cell and it is essential for growth and division of testicular germ cells in forming sperm. High level concentration of testosterone is necessary for spermatogenesis. Spermeogenesis is the only androgen dependent step in spermatogenesis. Androgen binding protein (ABP) concentrates testosterone in seminiferous tubule.
- FSH: It acts to facilitate last stages of spermatid maturation. Also promotes production of ABP and stimulates sertoli cells to produce estrogen.
- GnRH: It acts on AP causing production of FSH & LH.
- LH/ICSH: It stimulate leydig cell to secrete testosterone.
- GH: It is necessary for metabolic function of testis and promotes early division of spermatogonia.
- Inhibin: It inhibits FSH secretion from anterior pituitary.

• Estrogens: It is formed from testosterone by sertoli cells. It is stimulated by FSH and essential for spermeogenesis.

2.Non hormonal factors:

• Temperature: Testis is, maintained at optimum temperature of 32 degree by:

➢Air circulating around scrotum. Scrotum has got thin skin, less subcutaneous fat, scanty hair .All these enable air to circulate around scrotum and keep it cool.

➢Heat exchange in counter current action between spermatic arteries and veins.

➢Contraction of dartos helps to keep temperature at optimum level when atmospheric temperature varies.

• Seasonal effect- Sperm count is higher in winter.

• Descend of testis - Impaired spermatogenesis is found in cryptorchidism because testis is exposed to higher body temperature.

• Varicocele: Dilatation of veins of pampiniform plexus results in impaired sperm production.

• Mumps virus infection- Mumps virus can attack seminiferous tubule and damage it. Bilateral orchitis due to mumps after puberty causes sterility.

• Chronic dilatation, stress medication, chronic renal failure etc also cause impaired sperm production.

8.Graph of Menstrual Cycle:

refer essay 1

9.LH surge: refer essay 1

10.Graffian Follicle: refer essay 1

11.Actions of Oestrogen :

Estrogens promote growth and development of uterus,fallopian tube,ovary,vagina,and external genitalia at puberty.Subsequently the maintenance of these organs in functional state is also estrogen dependent.

1.Effects on Uterus:

➢ Non pregnant uterus:causes proliferative changes of endometrium,increases length of uterine glands,increases blood flow.

➢ Pregnant uterus:uterine muscle fibres enlarge and become more excitable.It increases the content of contractile protein,uterine muscles become more active.Estrogen dominant uterus is more sensitive to oxytocin.

3.Effects on cervix:

➢Causes thin and watery secretion.Facilitates the movement of sperm into uterine cavity.

4.Effect on Fallopian tube:

➢ Increases the motility of fallopian tube.

5.Effect on ovary:

➢ Facilitates growth of ovarian follicles.

6.Effect on vagina:

➢ Cornification of superficial vaginal epithelial cells.So cells become more resistant to trauma and infection.

7.Effect on breast:

➢ Proliferation of duct
➢ Development of stromal tissue
➢ Development of fat in breast
➢ Pigmentation of areola.

8.Effect on endocrine organs:

➢ Decreases FSH secretion
➢ Both +ve and -ve feedback effect on LH secretion
➢ Increases secretion of angiotensinogen
➢ Increases Thyroid Binding Globulin (TBG)

9.Effect on female secondary sexual characteristics:

➢ Feminising hormone
➢ Narrow shoulder
➢ Hips become broader and thighs converge and arms diverge
➢ Distribution of fat in breast
➢ Not much enlargement of larynx and voice is high pitched
➢ Less body hair and more scalp hair
➢ Pubic hair with a flat top pattern known as female escuteneon.

10.Effect on bone:

➢ Cause increased osteoblastic activity leading to increased rate of growth of bone at puberty
➢ Causes early closure of epiphyseal cartilage so that girls stop growing in height several years before boys of same age.
➢ Important in maintaining bone mass primarily by retarding bone resorption
➢ Promote +ve Calcium balance by indicing renal hydrolase enzyme which generates active form of vitamin D3

11.Effects on Skin:

➢ Makes skin soft and smooth,increases vascularity

12.Other minor actions:

➢ Before menstruation, there is a minimal gain in weight due to salt and water retention,estrogen and increased aldosterone in the luteal phase is responsible for this.
➢ Estrogen makes sebaceous gland secretion more fluid
➢ Estrogen lowers plasma cholesterol level by increasing number of LDL receptors in liver and increases HDL level in plasma.
➢ Estrogen produces vasodilation by producing local NO.Vasodilation by NO and decreasing cholesterol reduces myocardial infarction in females.

12.Actions of progesterone:

1.Effect on uterus:

➢On non pregnant uterus:

Its responsible for the secretory function of uterus which is needed for implantation and maintenance of pregnancy.

➢On pregnant Uterus:

Exerts anti estrogen effect on myometrial cells decreasing their excitability and sensitivity to oxytocin by decreasing the number of estrogen receptors on endometrium and increasing the rate of conversion of 17β estradiol to less active estrogens.

2.Effect on Cervix:

Cervical mucous become thick.

3.Effect on breast:

➢Stimulates development of lobules and alveoli

➢Supports secretory function of breast during lactation.

4.Thermogenic effects:

Responsible for the raise in basal body temperature during ovulation.

5.Effect on respiration:

Stimulates respiration and alveolar pCO_2 during the luteal phase of menstrual cycle, is lower than that in men.

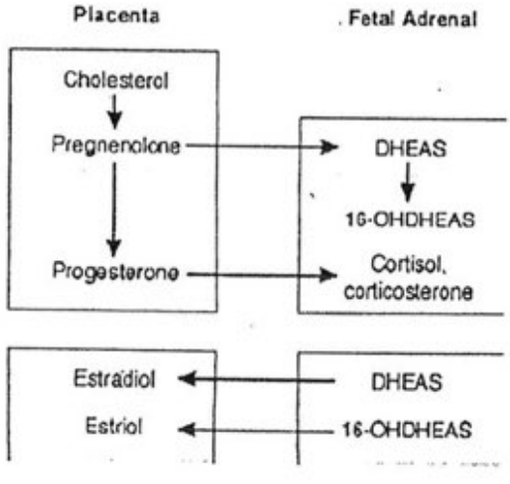
6.Natriuretic action:

Large dozes of progesterone produces natriuresis by blocking action of aldosterone.

7.Large dozes of progesterone decreases LH secretion and potentiates inhibitory effects of estrogen thus preventing ovulation.

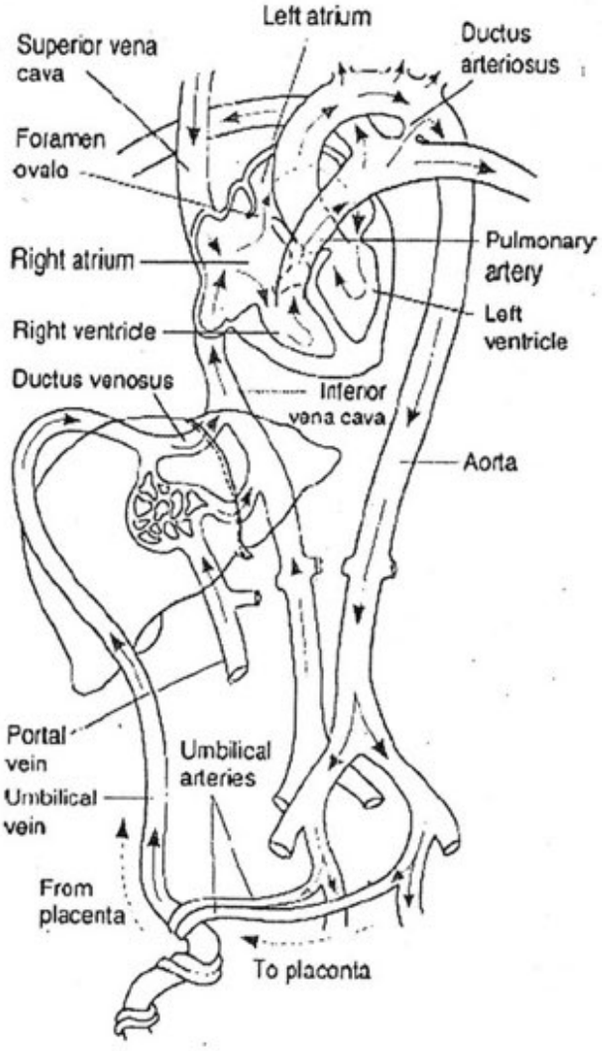
13. Feto placental unit

Placenta is an incomplete endocrine gland as it has no capabilities of independent steroidogenesis. Fetus and placenta interact each other for steroidogenesis. Placenta depends on precursors derived from fetus as well as maternal sources. It synthesizes pregnenolone and progesterone from cholesterol in maternal blood.Some progesterone enters the fetal circulation and provide substrate for cortisol and corticosterone in foetal adrenal gland. Placenta lacks the hormone which converts pregnenolone to estrogen (17 á hydoxylase).



Pregnenolone entering to the fetus forms the substrate for formation of DHEAS and 16 OH DHEA Sulphate along with pregnenolone synthesized in the fetal liver. Thus formed DHEAS and 16 OH DHEAS transported back to placenta where it forms estradiol and estriol respectively. Principal estrogen formed is estriol since 16 OH DHEAS is the principal substrate. Urinary excretion of estriol can be monitored and used as and index of state of fetus.

14. Fetal circulation



It operates with considerable differences from adult's circulation. Fetal heart pumps 55% blood to placenta and 45% to body parts. Fetal lungs are not functional. So that the pulmonary arterial pressure remains high so that blood shunted to left side through foramen ovale and ductus arteriosus. Foramen ovale is a valveless opening between right atrium and left atrium.Functional closure of Foramen ovale occurs within hours after birth. Ductus arteriosus connects pulmonary trunk with arch of aorta. Functional closure occurs within hours after birth. Anatomical closure occurs due to extensive intimal thickening and presence of cycloxygenase. Two ventricles of fetal heart pumps in parallel unlike in adults where they pump in series. Right atrium receives blood from SVC, IVC, and coronary sinus.

IVC carry oxygenated blood from placenta and deoxygenated blood from portal vein and lower parts of the body. Blood from placenta reaches the IVC through umbilical veins bypassing the liver. Most of blood entering the right atrium though IVC is diverted directly to left atrium. Thus well oxygenated blood from placenta reaches left ventricles from where it pumps to head and forelimbs. Most of blood from SVC entering to RA directed to Right ventricle. It passes through Ductus arteriosus to aorta and then via umbilical arteries to placenta for oxygenation. Reason for blood to flow through ductus arteriosus is that the resistance through collapsed lungs is high .So pulmonary pressure is much more than aortic pressure.

15.Hormones of Pregnancy:

hCG :

- Molecular wt - 39000
- Has alpha and beta subunits .It appears in blood a week after consumption .And found in urine in two weeks.It reaches peak in 10 -12 weeks and return back to a lower value by 16-26 weeks.

Functions:

a)Cause persistence of corpus luteum and continues production of progesterone and estrogen so that menstruation dont occur and decidual nature of uterine endometrium is maintained.

b)HCG exerts a stimulating effect on testes of male fetus to produce testosterone until birth.This can cause the growth of male sex organ and descend into scrotum.

Human Chorionic Somatomammotropin

- Human placental lactogen
- From fifth week of pregnancy
- Mol wt - 38000
- Secretion increases with pregnancy in proportion to weight of placenta.

Function:

- Lactogenic and stimulate growth of breasts.
- Decreases insulin sensitivity and decreases the glucose utilisation in mother so that more glucose is available to fetus.
- More lipolysis which can make more fatty acids which act as additional source of energy in mother.
- Retention of nitrogen , pottasium and calcium.
- It is a maternal growth hormone of pregnancy.
- Low HCS level indicate placental insufficiency.

Other placental hormones

- Proprio melano cortin
- GnRH which causes increases hCG.
- Inhibin - decreases hCG
- Leptin(satiety hormone)
- Prorenin

16. Milk ejection reflex/milk let down reflex: (refer short note 25 in endocrinology,page 178)

It is a neuro endocrine reflex.

Receptors – touch receptors on nipple and surrounding areola.

Afferent – sensory nerves via touch pathway.

Center – Paraventricular and supraoptic nuclei of hypothalamus that cause release of oxytocin.

Efferent – Oxytocin reaches to breast through blood that lead to the contraction of myoepithelial cells surrounding alveoli.

17.Hormonal Regulation of Lactation: refer short note 20

18.Contraception and oral contraceptive pills.

Contraception is defined as the protective measures which helps to avoid unwanted pregnancy. Methods for contraception are classified as two

1. Temporary

- Natural contraception
- Barrier method
- IUCD
- Hormonal – oral , injectible implants

2. Permanent

- Male sterilization
- Female sterilization

Natural contraception

It is based on identification of fertile period. To find out the safe period and appropriate time of ovulation we have:

- Calendar method

  Record the previous menstrual cycle.

  1st unsafe day = shortest cycle – 18

  Last unsafe day = longest cycle – 10

Eg: If the menstrual cycle varies 26-31 days the fertile period is 8-21days.

- Body temperature.

  Rise in temperature at time of ovulation due to thermogenic effect of progesterone.

- Cervical mucous method

  At the time of ovulation mucous is watery clear, thinnest and profuse. Elasticity(spin barkeit) increases by mid cycle. After ovulation mucous becomes thickened and quantity reduced.

- Symptothermic method

  Using the above three methods.

- Coitus interruptus: Withdrawal of penis before ejaculation
- Breast feeding(lactational amenorrhea)

Barrier method

By preventing the entry of sperms into vagina or uterus.

Physical methods

Males: Condoms:

- Most widely practiced .
- Absence of side effects.
- It provides protection against sexually transmitted diseases.
- Its cheaper, easy to carry, simple to use.
- Failure rate 20 per 100 woman year.

Females: Diaphragm/cervical cap:

Intravaginal device with plexible rings at margins.

Chemical methods:

Spermicides: local active agents that kill or immobilize the sperms. Physical methods can be combined with chemical methods .Eg: vaginal sponge.

IUCD

Conception is prevented by introducing a foreign substance into uterus.

- Ist generation IUCD – inert eg: Lippes loop
- 2nd generation – copper releasing eg: CuT200, CuT380A
- 3rd generation – Hormone releasing eg:progestrasert

Time of introduction: 2-3 days after menstruation

IUCD produces local inflammatory reaction in endometruim to prevent implantation. It causes thickening of cervical mucous. It increases motility of the fallopian tube. So that ovum reaches the uterus without fertilization or it reaches before the endometruim is ready for implantation.

advantages: – inexpensive , prolonged effect , no systemic side effects , reversible to fertility soon after removal.

Adverse effects: – pelvic pain, spontaneous expulsion , perforation of uterus , ectopic pregnancy.

Hormonal contraception

Oral:

Naturallyoccuring hormones if given orally, will be metabolized in liver.So, synthetic forms are used

- Progesterone only pill (mini pill)

It contains very less amount of progesterone. It makes cervical mucosa thick and prevents implantation. It delays sperm and ovum motility in the fallopian tube.

- Estrogen only pill(morning after pill)

Used for emergency contraception/post fetal contraception. Estrogen is taken in the morning after the sexual act. To avoid adverse effect combined preparation are preferred. Method of action is by preventing implantation.

- Combined preparations
  - Most effective method
  - Combination of estrogen and progesterone to reduce Estrogen dose and its side effects.
  - It ensures withdrawal bleeding.

Method of action – it suppresses ovulation. It makes cervical mucosa thick .Interferes with implantation.

Side effects of oral contraceptive pills:

Nausea, vomiting, headache , break through bleeding , thromboembolism , hypertension , depression etc.

Advantages of OCP:

Regular periods, reduced blood loss , relief from premenstrual tension , dysmenorrhoea , menorrhagia.

Injectible oral implants

These slowly release hormones with in the body e.g.: Depot injection, sialistic capsules.

Permanent methods

Male sterilization (vasectomy):

Segments of vas deferens on both sides are removed and cut ends are ligated. The ejaculate doesn't contain sperms. Additional contraceptives for 2-3 months as sperms may be released from stored spaces in rostral part of vas deferens. Failure rate is 0.15%

Female sterilization (tubectomy):

Bilateral decestion of fallopian tubes .Cut ends are ligated. Failure rate is 0.7%.

19. Prolactin

It is secreted by anterior pituitary and deciduas. Has 199 amino acid residues and 3 S-S bridges.

Mechanism of action – dimerises and activates JAK-STAT and other intracellular enzyme cascades.

Concentration increases 10-20 times in pregnancy .Its action is supported by hcG.

Suppressive effect of estrogen and progesterone prevent milk secretion during pregnancy so only a few ml of fluid is secreted by breast during pregnancy. After expulsion of placenta there is a sudden decrease in circulating estrogen and progesterone and this favors the lactogenic effect of PRL to assume its milk promoting role and breast progressively begins to secrete copious amount of milk. Prolactin peaks at parturition more than 100ng/ml (Normal value is 8ng/ml).

Suckling produces a prompt increases in the secretion about 10-20 fold surge which last for about one hour. But the magnitude of rise gradually declines after a woman has been nursing for more than 3 months. After prolonged lactation milk secretion occurs with normal prolactin level.

Actions of PRL:

- Initiation of lactation.
- Maintanance of lactation.
- Prevent ovulation by inhibiting LH secretion in mother.

- Reduce the responsiveness of ovaries to FSH.
- Acts in different areas of the brain of mother to stimulate maternal behaviour
- Increase apetite in mother so that the calories and nutrients for the breast feeding are met with.
- Helps in the concentration of lactose,protien,calcium,phosphorous etc.,in the vesicles of mammary gland.
- Prolactin along with placental growth hormone(hCS) helps in linear growth of foetus
- In male cause's impotence and the function of PRL in normal male is unsettled.

Regulation of secretion

Regulated by two hypothalamic hormones (PRH) and PRL inhibiting hormone (PIH).PIH has more dominant role than PRH. So a section of pituitary stalk leads to increase in PRL.

Factors affecting PRL secretion:

- Exercise.
- Stress.
- Stimulation of nipple.
- Sleep.
- Pregnancy.
- Estrogen – it produces a slowly developing increase in PRL secretion by a direct action on lactotroph.
- TRH and TSH.
- Chlorpromazine and related drugs block dopamine receptor.

Mechanical

- Stretch of uterine musculature.
- Stretch or irritation of cervix.

Lactation

Normal development of female breast begins at puberty (thelarche) and progresses with cyclical changes during each menstrual cycle.

Development is brought by coordinated activity of no of hormones

1-estrogen
2-progesterone
3-prolactin
4-oxytocin
5-GH, glucocorticoids, insulin, PTH and TH.

20.Cryptorchidism:

Incomplete descend of testis on one or both side in newborne is called cryptorchidism

Incidence:

- 10% in newborne
- 2% at one year of age
- 0.3% after puberty

Normally spontaneous descend is the rule.

Effects

1)High abdominal temperature cause damage to spermatogenic epithelium and affects spermatogenic function.

2) Higher incidence of malignant tumours in undescended testis.

Treatment:

1) Medical :Drugs like gonadotropins , hCG & testosterone.

2) Surgical correction

21. Functions of Testosterone:

1.During fetal Life:

- Causes development of internal genetalia i.e. during fetal life the hCG from placenta stimulates testis to produce testosterone throughout fetal life
- Causes the descend of testis during the last 2-3 months of gestation.

2.After puberty:

- Responsible for the development and maintenance of male secondary sexual characteristics at puberty
  - Enlargent of male external genitalia, internal genitalia
  - Seminal vesicle secrete fructose
  - Voice becomes deeper (as larynx enlarges and vocal cords increase in length and thickness)
  - Beard appears hairline receeds anterolaterally in scalp.
  - Development of male pattern of pubic hair and body hair
  - More aggressive and active interest in opposite sex develops.
  - Sebaceous gland secretions increases causing acne
  - Body conformation- shoulders broaden and muscle enlarge.
- Maintains spermatogenesis:
- Exert inhibitory feed back effect on pituitary LH secretion

3.Anabolic Actions:

- Androgen increases the synthesis and decreases the break down of protein. So there is a positive nitrogen balance and favors growth.
- It increases the quantity of bone matrix and causes Ca^{2+} retention
- It causes male pelvis development
- It increases the size and strength of bones
- Increases bone growth rate and muscle growth causing muscle growth spurt

- It causes retention of Na^+, K^+, Ca^{2+}, SO_4^{2-}, PO_4^{3-} and water
- It increases the size of kidneys
- Increases the basal metabolic rate by 5-10%
- Stimulates erythropoeisis
- Increases the thickness of skin over entire body

22. Tests of pregnancy

Based on detection of hcG in urine or serum.

hcG appears in serum 7days after consumption and in urine 14 days after consumption.

Tests are of two types

1. Biological (outdated)
2. Immunological (preferred)

Agglutination inhibition test

Suspected urine is mixed with hcG antiserum. Then hcG coated sheep RBC or latex particles are added. If there is no agglutination, test is positive for pregnancy.

Direct latex agglutination test

Latex particles coated with hcG ab mixed with urine. If agglutination occurs test is +ve for pregnancy.

ELISA test

In this test two antibodies are used. 1st one binds with hcG. Second one linked with alkaline phosphatase. It sandwiches the hcG which is detected by the color change after binding. It is more specific and sensitive.

Membrane ELISA (cart test)

Using this test pregnancy can be detected on the 1st day of missed period.

It can detect up to 30-50IU of hcG/ml of urine. Urine sample (3 drops) is put in a well provided in a cart, look for appearance of colored bands. If it appeared in control and test regions test is positive for pregnancy. If the colored band appeared only in control region test is –ve.

Flouroimmuno assay

Antibody tagged with fluorescent substance is used.

Radio Immuno Assay

Antibody tagged with radioactive substance is used.eg:I^{125}

Immuno radiometric assay

Ultra sonography – by 29-35 days. Gestation sac is detectable in 5th week. Cardiac activity of fetus can be detected in 6th week.

23. Physiological changes during pregnancy

Changes occur to all systems of the body during pregnancy. There are several maternal adaptation to met the increased demands of growing fetus.

a. Changes in genital organs

➢ Ovary – corpus luteum persists. Maximum size reaches in 8th week and regresses after 12th week. It secretes progesterone, estrogen, and relaxin. Continuous secretion of these hormones inhibits LH and FSH. No ripening of new follicles and no ovulation occurs.

➢ *Vulva – It becomes edematous hyperemic*

➢ Vagina – hypertrophied and pH become acidic. Important in preventing bacterial infection.

➢ Cervix – softened mucous plug occludes the cervical canal.

➢ Uterus – Enlarged considerably (15g to 1kg).

There is hypertrophy and hyperplasia. Elongated fibres arranged in a criss cross manner. They are called living ligators. Height of fundus reaches the level of umbilicus in 24 weeks. It reaches the level of xiphisternum in 36 weeks. In between these two thereafter. Growth of uterus us is due to estrogen.

➢ Breast – Enlarges with ducts due to action of estrogen and enlarges with glands due to action of progesterone. Nipple and areola become pigmented.

b. Changes in skin(Cutaneous changes)

➢ Striae gravidarum – abdominal wall distends and leads to rupture of subcutaneous elastic tissue producing irregular lines.

➢ Linea nigra – Brownish black pigmented line in the midline i.e. xiphisternum to symphysis pubis.

➢ Melasma – acne, hyperpigmentation on cheek and forehead.

c. Haemodynamic changes

➢ Blood volume – increases around one litre due to increased level of aldosterone and estrogen. Increased fluid retention by kidneys. Extra RBCs are produced due to increased erythropoietin level. Plasma volume increased more than that of RBC. Haemodilution occurs, hematocrit decreases, ESR increases. These changes are called **physiological anemia of pregnancy.**

➢ Cardiac output – Increases by 40 -50 %

➢ Blood pressure – BP remains in normal limits. Peripheral resistance decreases due to smooth muscle relaxing effect of progesterone.

➢ Blood flow – Increases all over the body especially to uterus, kidneys and lungs. Systolic murmers can be heard at apical and pulmonary areas. Pulse rate increases slightly.

➢ Physiological edema of pregnancy – due to gravid uterus lying on external iliac veins femoral pressure increases. This causes edema in the legs.

➢ Neutrophilic leukocytosis – due to increase in estrogen and cortisol

➢ Plasma proteins – total amount increases. A/G ratio changes from 1.7:1 to 1:1.

➢ Clotting factors – 2,7,8,9 and 10 are increased.

d. Changes in GI system

Nausea, vomiting in the morning (morning sickness) due to increased hCG level. Excessive vomiting which affect the health - hyperemesis gravidarum.

e. Changes in urinary system

- Renal plasma flow increases by 30%
- GFR increases by 40%
- Reabsorption capacity of Na^+, Cl^-, water increase by 50%
- Glycosuria, aminoaciduria may occur.

f. Respiratory changes

- Metabolic rate increases.
- Increase in O_2 consumption and CO_2 output
- Tidal volume increases without increase in respiration rate
- RV, ERV, FRC are decreased.

g. Changes in endocrine system

- Placenta secrete hCG , progesterone , estrogen.
- Pituitary, thyroid, parathyroid, adrenal cortex, pancreas– activity increases.
- LH,FSH amount decreased due to –ve feedback.
- Insulin level increases due to number of contra insulin factors like cortisol , prolactin , estrogen.
- Sensitivity of insulin receptors decreased – gestational diabetes mellitus.

h. Changes in nervous system

- Mood changes.
- Craving for unusual particles like food.

i. Nutritional requirement for Ca^{2+},PO_4^{3-},Fe and vitamins are increased.

j. Weight gain:

- Occurs at an average of 10-20kg.It is due to wt of fetus, placenta, uterus, water retention and fat storage.

24. Indicators of Ovulation:

In clinical practice it is important to know the exact time of ovulation in the treatment of infertility cases and conversely in family planning.

1) First indicator is basal body temperature – The woman is advised to record the body temperature each morning before getting out of bed .Body temperature is increased by 0.5degree Celsius during the Luteal as compared to that of follicular phase. Cause of change is probably increase in progesterone which is thermogenic.

2) Changes in cervical mucosa – it is thinnest at time of ovulation and spinnbarkeit increases so that a drop of mucous can be drawn to 8-12 cm long thread. When you spread a thin layer of mucous and examine under microscope a characteristic fern like pattern is obtained during the follicular phase and is absent in the secretory phase, Ovulation is indicated by absence of ferning.

3) Vaginal cytology – shows effect of progesterone

4) Endometrial biopsy – during second half of menstrual cycle take histological evidence of secretory endometrium. If it is secretory means ovulatory but if proliferative changes shown then anovulatory phase.

5) Serial ultra sonography of ovaries,Shows development of follicles and day of rupture of graffian follicle .More accurate and useful often employed in management of fertility.

6) Hormone estimation – serum progesterone is estimated on 8th and 21st day .Definitive increase during midluteal phase suggest ovulation. Daily serum LH estimation detect LH surge.

7)Urinary pregnanediol – rises during second half of an ovulatory cycle.

8)Laparoscopy