CHAPTER (8)
THE GASTROINTESTINAL TRACT

INTRODUCTION

- Also known as the digestive tract, alimentary tract, or gut.

Functions of the Gastro-intestinal tract (GIT):

- Breaks down complex food particles into simpler ones (Digestion).
- Transports products of digestion to the blood stream (Absorption).
- Expels the remaining waste to outside of the body (Excretion).

Structure of the GIT:

- Organs:
  - Upper GIT (mouth, pharynx, esophagus and stomach)
  - Lower GIT (small intestine, large intestine and anus)

- Associated glands:
  1- Salivary glands  2- Pancreas  3- Liver

Fig 8.1: Structure of the GIT
**Histology of the GIT:**
- The wall of the GIT consists of the following layers:
  1. Mucosa (epithelium, lamina propria & muscularis mucosae)
  2. Submucosa
  3. Muscular layer: (inner circular & outer longitudinal)
  4. Serosa (mesothelium)

**Fig 8.2: Histology of the GIT**

**Control of the GIT:**
- **Neural control by:**
  - Extrinsic nerves (Autonomic nervous system)
  - Intrinsic nerves (Enteric nervous system)
- **Hormonal control by:**
  - Peptide hormones released by endocrine cells scattered throughout the GIT.
  - These hormones include gastrin, secretin, cholecystokinin-pancreozymin “CCK-PZ”, vasoactive intestinal polypeptide “VIP”, somatostatin and other hormones.
The autonomic nervous system: “Sympathetic and parasympathetic”

- **The sympathetic:**
  - Inhibits GIT motility by relaxing walls & contracting sphincters.
  - Inhibits GIT secretion.

- **The parasympathetic:**
  - Stimulates GIT motility by contracting walls & relaxing sphincters.
  - Stimulates GIT secretion.

The enteric nervous system

- It is a part of the nervous system consisting of large number of neurons that form networks within the wall of the GIT.
- The neurons are distributed into two plexuses (see fig 8.2):
  - **The submucus plexus:** Also known as Meissner’s plexus. It is found in the submucus layer to control GIT secretion.
  - **The myenteric plexus:** Also known as Auerbach’s plexus. It is found between the 2 muscular layers to control GIT motility.

Remember that: The enteric nervous system (ENS) is connected with the autonomic nervous system. Through this connection, the parasympathetic increases motility & secretion whereas the sympathetic decreases motility & secretion.
- This connection is not essential for the function of the enteric nervous system because it can act independently after cutting the sympathetic and the parasympathetic innervations.
- That is why the enteric nervous system may be regarded as a second brain.
- The neurotransmitters released by the neurons of the ENS include vasoactive intestinal polypeptide “VIP”, substance P, nitric oxide “NO” and others.
THE MOUTH

- Also known as the buccal cavity or the oral cavity.

Functions of the mouth:

1- Orifice for food and water intake.
2- Mastication "or chewing" (the process by which food is crushed by teeth into smaller parts to increase its surface area for the action of the digestive enzymes).
3- Mixes food with saliva.
4- Initiates swallowing.

Mastication

- It is started and stopped voluntarily; however, it proceeds as an involuntary reflex.
- The involuntary reflex is initiated by presence of food in the mouth; this causes reflex inhibition of muscles of mastication, the lower jaw drops causing a stretch reflex that contracts muscles of mastication and closes the jaw. The compressed food within the mouth again causes reflex inhibition of the same muscles followed by dropping of the jaw and then reflex contraction of the muscles & so on the cycle repeats itself.
- The muscles of mastication are the temporalis, the masseter and the pterygoid muscles. They are supplied by the fifth cranial nerve.

SALIVA

- Fluid in the mouth produced by the following salivary glands:
  1- The parotid gland: The largest gland. Secretes 20-25% of saliva
  2- The submandibular gland: The main gland. Secretes 70% of saliva
  3- The sublingual gland: The smallest gland. Secretes 5% of saliva
  4- Minute glands in the mouth and pharynx: Secrete 5% of saliva
Fig 8.3: Major salivary glands

- Each salivary gland is an exocrine gland consisting of acini and ducts
- The acini have one or two types of cells: Serous cells (secrete water, electrolytes & enzymes) & mucus cells (secrete mucus)
- Each acinus may be purely serous, purely mucus or mixed, for example:
  - Acini of the parotid glands are purely serous
  - Acini of the submandibular glands are mixed
  - Acini of the sublingual glands are mixed but mainly mucus
  - Acini of the minute glands in the mouth & pharynx are purely mucus except Ebner’s glands in the circumvallate papillae of the tongue, which secrete serous fluid.
- The ducts are intercalated ducts that join to form striated ducts and then a main secretory duct that opens in the mouth.

Fig 8.4: Acini and ducts of an exocrine gland
Characteristics of saliva:
- Volume: 0.5 - 1.5 L/day.
- Osmolarity: hypotonic (due to aldosterone action, see below).
- pH: ranges between 6 & 7. It becomes alkaline (rises up to 8) in high rates of secretion.

Contents:
- Water
- Inorganic substances
- Organic substances

- The inorganic substances are electrolytes (Na⁺, K⁺, Cl⁻, HCO₃⁻ …)
- The organic substances include the following:
  - Mucus (glycoprotein, lubricates food & protects the oral mucosa)
  - Immunoglobulins (IgA)
  - Proline rich proteins (protect tooth enamel)
  - Lactoferrin (bacteriostatic substance, binds iron)
  - Lysozyme (bactericidal substance)
  - Carbonic anhydrase enzyme
  - Digestive enzymes:
    - α amylase (ptyaline): for digestion of starch
    - Lingual lipase: from Ebner’s glands of the tongue; for digestion of lipids
  - ABO blood group antigens (antigen H +/- A &/or B)

Remember that: The ABO blood group antigens are present in saliva of about 80% of individuals who are known as “secretors”; whereas those who do not secrete these antigens in saliva are known as “non-secretors.”
- It is worth noting that the non-secretors have higher incidence of oral disease, peptic ulcer & diabetes than the secretors.
Changes in ionic composition of saliva:
- Saliva is secreted by acinar cells as isotonic fluid. In the ducts, Na\(^+\) and Cl\(^-\) are absorbed whereas K\(^+\) and HCO\(_3^-\) are secreted.
- Aldosterone stimulates Na\(^+\) absorption and K\(^+\) secretion; however, Na\(^+\) is not followed by water that is why saliva becomes hypotonic.
- When the rate of salivary flow through the ducts is very high, there is less time for this exchange to occur, that’s why concentrations of Na\(^+\) & Cl\(^-\) are increased (Na\(^+\) & Cl\(^-\) concentrations in saliva are flow dependent).
- The concentrations of potassium and bicarbonate vary greatly in different species.
- The pH of saliva is also flow dependent (like sodium & chloride). It is high in rapid rates of secretion and low in slow rates of secretion (it is thought that as the rate of saliva production increases, more bicarbonate ion is produced as a by-product of cell metabolism).

Functions of saliva:
1- Protection against microorganisms by mucus, lysozyme, lactoferrin and IgA antibodies
2- Digestion of carbohydrates by α amylase and lipids by lingual lipase
3- Lubrication to facilitate swallowing, speech and taste
4- Buffer to neutralize gastric acid during vomiting and to relieve heartburn
5- Excretion of certain substances like mercury, iodide and lead

Control of saliva
- Exclusively neural (i.e. there is no hormonal control), by two reflexes:
  - Conditioned reflex
  - Non-conditioned reflexes

- The conditioned reflex “or response”:
  - Here, sight, smell or even thoughts about appetizing food stimulate salivary secretion.
The term "conditioned response" indicates a reaction that has been acquired by learning. It was first described by Pavlov in the 1890s.

In his famous experiment, Pavlov used a bell to call a dog to his meal and, after a few repetitions; the dog learned that the bell sound is followed by food; so it started to salivate in response to the bell sound.

The excitatory impulses that travel from the salivary nuclei in the medulla to supply the salivary glands are carried through:

- The chorda tympani branch of the facial nerve (VII): The preganglionic neurons relay in the submandibular ganglion, then postganglionic supply the submandibular & sublingual glands
- The glossopharyngeal nerve (IX): The preganglionic neurons relay in the otic ganglion, then postganglionic supply the parotid gland

**The non-conditioned reflex:**
- Presence of food in the mouth stimulates salivary secretion.
- Components of this neural reflex include:
  - Afferents: from taste receptors in the mouth
  - Center: salivary nuclei in the medulla (superior & inferior)
  - Efferents: the glossopharyngeal & the facial nerves to the salivary glands

**Other factors affecting salivary secretion:**
1. Sympathetic stimulation: Increases secretion (small amount, mainly mucus) and causes vasoconstriction
2. Parasympathetic stimulation: Increases secretion (large amount, watery) and causes vasodilatation. The vasodilatation is mediated by VIP not acetylcholine; that is why it is not blocked by atropine
3. Muscarinic blockers like “atropine”: Decreases secretion (results in dry mouth) by blocking acetylcholine. Atropine injection is used before
anaesthesia to inhibit salivary secretion and keep the mouth dry. This allows insertion of the endotracheal tube through the mouth with minimal risk of saliva aspiration into the respiratory system.

4- Dehydration: Decreases secretion
5- Sleep: Decreases secretion to a very low level

**Abnormal salivary secretion:**

**Xerostomia:**
= Dry mouth, due to lack of saliva. It results in difficulty in speech and swallowing, halitosis (unpleasant odor exhaled in breathing), dental caries and increased susceptibility to oral infections.
- It is caused by:
  o Dehydration (as in uncontrolled diabetes)
  o Sjogren’s syndrome (caused by auto-antibodies directed against the lacrimal and salivary glands resulting in absent tears and dry mouth (primary Sjogren’s). It may be associated with a connective tissue disease like rheumatoid arthritis (secondary Sjogren’s). It is more common in females.
  o Radiation (also destroys the salivary glands)
  o Drugs (anticholinergics, antidepressants …)

**Ptyalism:**
= Drooling of saliva to outside the mouth; due to either increased production or decreased swallowing.
- Although it may occur normally (e.g. in children due to teething), it may indicate acute poisoning, tonsillitis retropharyngeal abscess or a neurological problem like Parkinsonism.
THE PHARYNX & THE ESOPHAGUS

THE PHARYNX

- Lies immediately posterior to the mouth and the nasal cavity
- Common route for both air & food
- Involved in vocalization and in the swallowing reflex
- Divided into three parts: Nasopharynx (posterior to the nasal cavity), Oropharynx (posterior to the oral cavity) and Laryngopharynx (extends down to the larynx and the esophagus).

Fig 8.5: The pharynx

Swallowing Reflex

- Swallowing (or deglutition) is the process by which solids or liquids in the mouth reach the stomach through the pharynx & the esophagus.
- It occurs in three stages: Buccal (voluntary), pharyngeal (involuntary) and esophageal (involuntary).

- **The Buccal stage:**
  - The tongue moves upwards & backwards to propel the bolus into the pharynx while the soft palate rises to close the nasopharynx.
  - The larynx starts to rise. The lips & jaw should be closed (swallowing is difficult when they are open).
• **The Pharyngeal stage:**
  - The bolus is pushed backwards by the tongue against the epiglottis.
  - The epiglottis bends over the larynx to cover its opening; however, this bending is not essential to close the larynx since it is closed by other factors like contraction of the glottis (its upper part) and approximation of the vocal cords (adduction of vocal cords).
  - The swallowing reflex is initiated. The reflex components include:
    - Receptors: in the wall of the pharynx
    - Afferents: cranial nerves (5, 9 & 10)
    - Center: swallowing center in the medulla
    - Efferents: cranial nerves (5, 7 & 12)
    - Effectors: muscles of the pharynx, larynx & tongue
    - Response: coordinated contractions to propel the bolus towards the esophagus, avoiding the larynx, with inhibition of respiration.
  - The upper esophageal sphincter opens for only one second to allow entry of the bolus into the esophagus.

• **The esophageal stage:**
  - Contraction of the upper esophageal sphincter proceeds down as primary peristalsis. If the bolus is sticky or too large, secondary peristalsis occurs to move the remnants towards the lower esophageal sphincter.
  - Vagal impulses during swallowing relax the lower esophageal sphincter to allow entry of the bolus into the stomach whereas vagal impulses between meals close the lower esophageal sphincter.

**Peristalsis:**
- Occurs in all parts of the GIT starting from the pharynx.
- In peristalsis, stretch of the wall of the esophagus results in contraction behind the bolus (by release of acetylcholine and substance P) and relaxation in front of it (by release of NO, VIP or ATP).
- This pushes the bolus downwards & then the process repeats itself.
- It is integrated in the myenteric plexus, increased by parasympathetic stimulation, and decreased by sympathetic stimulation.
- Rate of peristalsis in the esophagus = 4 cm/s.

**THE ESOPHAGUS**
- Connects the pharynx to the cardiac part of the stomach.
- Ranges from 25 to 35 cm in adults.
- Guarded by two sphincters: The upper esophageal sphincter (UES) and the lower esophageal sphincter (LES)

**Fig 8.6: The esophagus**

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**The upper esophageal sphincter (UES):**
- The upper 3cm of the esophagus form the UES. Unlike the lower sphincter, it is an “anatomical sphincter” (formed by the cricopharyngeal muscle; and it is known as “the cricopharyngeal sphincter”. It is closed at rest at a high pressure (40-100 mmHg). It opens for one second during swallowing.

**The lower esophageal sphincter (LES):**
- The lowest 3 cm of the esophagus form the LES. It is not formed by a definite muscle (= Physiological sphincter). It is an area of high pressure.
(15-35mmHg) when compared to the rest of the esophagus, which is sub atmospheric (except at the UES). It is closed at rest and opens for few seconds with swallowing.

- Factors, which close the lower esophageal sphincter:
  - Gastrin, the vagus (between meals) & acetylcholine

- Factors, which open the lower esophageal sphincter:
  - Hormonal or humoral factors: Secretin, CCK, VIP & NO
  - Neural factors: the vagus (during swallowing)
  - Other factors: Coffee, alcohol, smoking, excess amounts of vitamin C, chocolate, milk & fat

**Competence of the lower esophageal sphincter (LES):**
- Although there is no definite muscle to form the LES, it is competent in preventing reflux of gastric contents into the esophagus.
- This competence is due to the following factors:
  - Its high resting pressure (15-35 mmHg).
  - The intra-abdominal location which is compressed from outside by high pressure (this is unlike the intra-thoracic part of the esophagus which is surrounded by the negative intrapleural pressure).
  - The crural fibers of the diaphragm, which act as an external sphincter & cause narrowing of the esophagus.
  - The mucosal folds of the stomach (act as valves that close the opening of the esophagus).
  - The oblique entry of the esophagus into the stomach (results in narrowing of its opening).

**Abnormalities of the lower esophageal sphincter**
- **Achalasia:**
  - Massive dilatation of the esophagus proximal to the LES resulting from failure of the LES to relax during swallowing.
- This occurs due to loss of the neurons which release the relaxing factors NO & VIP in the myenteric plexus at the LES whereas acetylcholine and substance P are released causing contraction of the LES.

**Medical treatment:** Botulinum toxin to inhibit release of acetylcholine.

**Surgical treatment:** Dilatation of the constricted area (Heller myotomy).

- **Gastro-esophageal reflux disease (GERD):**
  - Incompetence of the LES due to a defect in the factors that normally close it or due to protrusion of upper part of the stomach into the thorax through a defect in the diaphragm (Hiatus hernia). Theses result in regurgitation of gastric acid into the esophagus causing mucosal damage.
  - Patients complain of heartburn when they lie down after heavy meals.

**Medical treatment:** Lifestyle modifications e.g. weight loss, elevating foot of the bed and avoidance of heavy meals before going to sleep. In addition, some patients may need anti-acid treatment (see peptic ulcer).

**Surgical treatment:** Nissen fundoplication (if medical treatment failed as in cases of hiatus hernia)

**Fig 8.7: GERD and Achalasia of the esophagus**
THE STOMACH

INTRODUCTION
- The stomach is a “J”-shaped hollow muscular organ of the GIT, acting as a reservoir for food and involved in its digestion.
- It is divided into 4 parts:
  o Cardia: the region where esophageal contents empty into the stomach
  o Fundus: the upper curvature
  o Body: the main central region
  o Pylorus or pyloric antrum: the lower part that facilitates gastric emptying
- As in other parts of the GIT, the wall of the stomach consists of mucosa, submucosa, muscular layer, and serosa.
- The muscular layer is divided into three layers: Outer longitudinal, middle circular and inner oblique.

**Fig 8.8: Structure of the stomach**

- The mucosa of the stomach contains many deep exocrine glands (*gastric glands*). Many of the glands open through a common opening (*gastric pit*).
Types of cells in a gastric gland:
1- Mucus cells: At the neck of the glands (in the cardiac & pyloric regions of the stomach)
   - Secrete mucus.
2- Parietal cells (oxyntic cells): At the isthmus & body of the gastric gland (in the body & fundus of the stomach)
   - Secrete hydrochloric acid “HCL” & intrinsic factor.
3- Chief cells (peptic, zymogen): At the isthmus & body of the gastric gland (in the body & fundus of the stomach)
   - Secrete Pepsinogens
   - In addition, there are endocrine cells near the gastric glands:
     - G cells: Secrete Gastrin
     - ECL cells (Enterochromaffin like cells): Secrete histamine

Fig 8.9: The gastric gland

Functions of the stomach
1- Storage of food: up to about 4 hours, and controls its release into the duodenum.
2- Digestion of proteins & lipids: by pepsin and gastric lipase enzymes. However, these enzymes are less important than the enzymes of the exocrine pancreas.
3- Protection: by HCL which kills bacteria & vomiting which removes harmful substances.
4- Synthesis of the intrinsic factor (IF): this glycoprotein binds vitamin B$_{12}$ in the stomach and then facilitates its absorption in the terminal ileum.
5- Facilitates absorption of iron in the intestine: by maintaining iron in the ferrous state.
6- Absorption: the stomach absorbs small amount of water, ions, alcohol and some drugs.
7- Endocrine function: produces many hormones like gastrin, glucagon, somatostatin, ghrelin and VIP.

Remember that: Ghrelin is the growth hormone releasing hormone secreted by the hypothalamus. It is also released from fundus of the stomach to give sensation of hunger (opposite to leptin from adipose tissue, which gives sensation of satiety).

**GASTRIC SECRETION**

**Features of gastric secretion:**
- Volume: 2-3 L/day
- pH: Highly acidic (about 0.9). May increase up to 4 depending on the type of diet, its time and other factors
- Osmolarity: Isotonic
- Contents:
  - Water and electrolytes (H$^+$ / Cl$^-$ / K$^+$ / HCO$^-$ / Na$^+$)
  - Intrinsic factor
  - Digestive enzymes (pepsin & gastric lipase)
  - Mucus
**Hydrochloric acid (HCL)**
- Secreted by parietal cells (which also secrete the intrinsic factor).
- Each parietal cell is characterized by the following: It is pyramidal in shape, apical membrane of the active cell contains canaliculi for secretion of HCL (the canaliculi in an inactive cell are found within the cytoplasm) and its cytoplasm contains large number of mitochondria (to provide energy for the active pumps that secrete hydrogen ions).

  - **Synthesis of HCL**
    - HCL is synthesized from hydrogen ions (H⁺) and chloride ions (Cl⁻).
    - Sources of hydrogen ions (H⁺):
      1. From dissociation of H₂O into H⁺ & OH⁻: (H₂O = H⁺ + OH⁻)
      2. From the reaction of CO₂ with water at the presence of carbonic anhydrase enzyme: (CO₂ + H₂O = H₂CO₃ = H⁺ + HCO₃⁻).
    - H⁺ is secreted into the canaliculi against a very high concentration gradient by the H⁺-K⁺ ATPase pump (The proton pump).
    - HCO₃⁻ enters the blood in exchange to Cl⁻, which enters the parietal cell.
    - Cl⁻ enters the canaliculi with K⁺.
    - K⁺ returns back to inside the cell by the H⁺-K⁺ ATPase pump (i.e. K⁺ recycles between the cytoplasm and the canaliculi).
    - In the canaliculi, HCL is formed as follows: (H⁺ + Cl⁻ = HCL).
    - HCL escapes from the canaliculi to the lumen (through the gastric pits).

**Remember that:** For each H⁺ ion secreted to the lumen, HCO₃⁺ enters the blood.
- If secretion of HCL is increased e.g. following a meal or due to repeated vomiting, large amount of bicarbonate enters the blood.
- This changes pH of the blood to become more alkaline (= a condition known as post-prandial alkaline tide).
**Fig 8.10: HCL synthesis in a parietal cell**

- **Receptors on parietal cells for HCL secretion**
  - HCL secretion is stimulated through activation of the following receptors, which are found on the basolateral membrane of parietal cells:
  1. Muscarinic receptors (M$_3$): stimulated by acetylcholine to increase intracellular Ca$^{++}$, protein kinases and then the proton pump.
  2. G receptors: stimulated by gastrin to increase intracellular Ca$^{++}$.
     (Note: gastrin acts mainly on enterochromaffin like cells (ECL) to release histamine).
  3. H$_2$ receptors: stimulated by histamine (which is released by the ECL cells) to increase intracellular cAMP, protein kinases and then the proton pump.

**Remember that:**
- In absence of cAMP, activity of the proton pump becomes very low
- Unlike acetylcholine and gastrin, histamine increases cAMP
- Therefore, H2 blockers inhibit, in addition to histamine, gastrin and acetylcholine mediated acid secretion.
• **Receptors on parietal cells against HCL secretion**
  - These are prostaglandin receptors stimulated by prostaglandins; they inhibit HCL secretion.
  - Prostaglandins also stimulate secretion of mucus, which protects the wall of the stomach from the action of HCL.
  - Therefore, inhibition of prostaglandin synthesis by aspirin increases HCL synthesis & decreases mucus secretion. This predisposes to peptic ulcer.

• **Functions of HCL**
  - Kills ingested bacteria
  - Activates pepsinogen to pepsin & allows its action
  - Maintains iron in the ferrous state to facilitate its absorption
  - Facilitates absorption of calcium
  - Stimulates flow of bile (by stimulating release of secretin)

**The hormone which increase HCL secretion:**

**Gastrin**

• **Characteristics of gastrin**
  - Peptide hormone (half life: 2-3 min).
  - Similar to CCK (The gastrin family of hormones include gastrin & CCK).
  - Found in different lengths: (17, 34, 14 aa …). However, G 17 is the principal form.

• **Gastrin release & catabolism**
  - Released by:
    o G cells in the pyloric antrum of the stomach and upper small intestine.
    o Fetal pancreas (this stops gastrin release after delivery).
    o Some neural structures outside the GIT (e.g. brain, vagus and sciatic nerves).
  - Catabolism: Kidney and small intestine.
- **Stimuli of gastrin release**
  - Gastric distention
  - Luminal peptides and amino acids (e.g. tryptophan & phenylalanine)
  - Vagus (through the neurotransmitter “gastrin releasing peptide” (GRP), not acetylcholine; that is why gastrin is not inhibited by atropine).
  - Calcium ions (hypercalcemia)
  - Epinephrine

- **Inhibitors of gastrin release:**
  - Acid in pyloric antrum (inhibits G cells either directly or through release of somatostatin). This is an example of a negative feedback mechanism.
  - Somatostatin (also inhibits many other hormones).
  - Secretin family of GIT hormones (secretin, GIP, VIP & glucagon).
  - Calcitonin (calcium lowering hormone released by the thyroid gland).

- **Actions of gastrin**
  - **Physiologic actions:**
    - Stimulates gastric acid secretion
    - Stimulates pepsin secretion
    - Trophic effect on the mucosa of the stomach, intestine and colon
    - Stimulates gastric motility
  - **In large doses (non-physiologic actions):**
    - Stimulates pancreatic secretion (the enzymes mainly)
    - Stimulates water & HCO- secretion from pancreatic ducts and biliary ducts
    - Stimulates insulin secretion (following a protein meal)
    - Relaxes the ileo-cecal valve
    - Contracts the lower esophageal sphincter (LES)
    - Stimulates gastric & intestinal motility & slows gastric emptying
Abnormalities associated with high gastrin level:

1- Gastrinoma =“Zollinger Ellison Syndrome”.
   - A tumor (usually in the pancreas) that secretes gastrin excessively
   - Gastrin results in rapid secretion of HCL causing multiple peptic ulcers (in the stomach, esophagus and small intestine)
   - Modalities of treatment include anti-ulcer treatment plus surgery or chemotherapy.

2- Pernicious anemia:
   - This is a severe megaloblastic anemia caused by auto-antibodies that result in failure of parietal cells to secrete the intrinsic factor, which is important for absorption of vitamin B\textsubscript{12}.
   - The parietal cells also fail to secrete HCL; this results in loss of the negative feedback exerted by acid on gastrin causing gastrin excess.

Hormones which decrease HCL secretion

1- Somatostatin: Released from D cells in the pyloric antrum to inhibit gastric acid secretion and gastrin.
   - It is also released from other sites (like intestine, pancreas and hypothalamus) to inhibit other hormones (like growth hormone, insulin, glucagon and many other hormones).

2- Secretin: See control of pancreatic secretion.

3- VIP: Vasoactive intestinal polypeptide is released from GIT, brain & autonomic nerves. It inhibits gastric acid secretion, stimulates intestinal secretion and relaxes smooth muscles in the intestine, blood vessels and bronchioles.

4- Glucagon: See the pancreas in the endocrine system.

5- Enterogastrone: Is thought to be the hormone that is released from the intestine to inhibit gastrin stimulated acid secretion. Its identity is unsettled (may be the peptide YY).
6- **GIP**: Gastric inhibitory peptide is released by K cells in the duodenum in response to luminal glucose or fat.
- Its name refers to its action when administered in high doses (inhibits gastric motility and secretion).
- However, its physiologic role appears to be stimulation of insulin release following ingestion of glucose; that is why it is called the glucose-dependent insulinotropic hormone.

**Other factors that decrease HCL secretion:**

**Vagotony:**
- Cutting the vagus nerve causes loss of the parasympathetic supply to the stomach. This decreases HCL secretion and that is why it is used for treatment of peptic ulcer.
- Vagotony can be:
  - **Truncal** (cutting the nerve supply to the whole abdomen)
  - **Selective** (cutting the branch that supply the whole stomach)
  - **Highly selective** (cutting the branch that supply the acid secreting area at the proximal part of the stomach).
- Vagotony is usually complicated by decreased gastric emptying; this can be treated by pyloroplasty (surgical widening of the pylorus).

**Acute stress (fear):**
- Associated with reduced HCL secretion due to decreased vagal discharge.

**GASTRIC LIPASE**
- This enzyme is released by mucosa of the fundus.
- It causes hydrolysis of triglycerides into monoglycerides and fatty acids.
- Not important except in the absence of pancreatic lipase (its activity = 1/5\textsuperscript{th} of pancreatic lipase activity).
**PEPSIN**
- This enzyme is secreted by peptic cells as pepsinogens (inactive enzymes). Pepsinogens are activated by HCL to pepsin & then by pepsin itself which activates other pepsinogens (auto-activation or auto-catalysis).
- It causes protein digestion (acts in acidic pH (1.5-3.5) - i.e. HCL activates it and provides for it a suitable pH). It is worth noting that pepsin is not essential for protein digestion; unlike proteolytic enzymes of the pancreas.

**RENNIN ENZYME**
- This enzyme is not found in humans, it is found in calf stomach.
- It causes digestion of proteins.

**MUCUS**
- Glycoprotein.
- Protects the stomach from auto-digestion by HCL & pepsin
- For this reason, the mucus layer (aided by bicarbonate ions) are known as “the mucosal barrier.”
- Mucus is stimulated by:
  - Mechanical & chemical irritation
  - Sympathetic & parasympathetic stimulation
  - Prostaglandins

**INTRINSIC FACTOR**
- Glycoprotein secreted by parietal cells to facilitate absorption of vitamin B_{12} at the terminal ileum. It is lost in pernicious anemia (due to autoantibodies attacking parietal cells or the intrinsic factor).

**CONTROL OF GASTRIC SECRETION**
- Controlled by neural & hormonal mechanisms.
- These mechanisms are activated during the following phases: Cephalic phase, gastric phase and intestinal phase.
- **Cephalic phase**
  - When food is in front or within the mouth (not in the stomach).
  - Two neural reflexes are activated:
    1. **Conditioned reflex** (activated by sight, smell, or thought about food)
    2. **Non conditioned reflex** (activated by food in the mouth)
  - Both reflexes are mediated through the vagus nerve.
  - Cutting the vagus nerve abolishes this reflex.

- **Gastric Phase**
  - It is the phase when food reaches the stomach.
  - Here gastric secretion is mediated by both neural & hormonal mechanisms.
    **The neural mechanism:**
    - Distention of the stomach stimulates gastric secretion by long and short reflexes as follows:
      - **Vagovagal reflex** (long reflex mediated by the vagus & integrated in the brain stem. It can be abolished by vagotomy).
      - **Intramural reflex** (short reflex integrated in the submucus plexus within the wall of the stomach).
    **Hormonal mechanism:**
    - Food in the stomach stimulates release of gastrin, which stimulates gastric secretion.
    - **Gastrin stimuli include:** Gastric distention & L-amino acids.

- **Intestinal phase**
  - Activated when chyme reaches the intestine.
  - Here gastric secretion is initially inhibited (due to stimulation of an intestinal hormone that inhibits HCL secretion; this hormone is known as enterogastrone). Then after 1-3 hours, HCL secretion may increase (due to release of gastrin from the intestine).
PEPTIC ULCER

- Defect in the mucosa of the stomach or intestine caused by gastric secretion.
- Patients of peptic ulcer suffer from severe epigastric pain, nausea, vomiting and sometimes gastric bleeding.

Causes of peptic ulcer:

1- Infection of the gastric mucosa with *Helicobacter pylori* bacteria.
   - This is the main cause of peptic ulcer in most cases.
   - The bacteria lives within the mucus layer, it protects itself from the effect of the gastric acid reaching it by releasing the enzyme urease; this enzyme converts urea into ammonia and bicarbonate, both of which are basic substances that neutralize the acid.
   - On the other hand, its presence within the mucus layer protects it from the immune system of the body.
   - Ammonia and the products of leucocytes which attack the bacteria result in disruption of the mucosal barrier or direct damage to the gastric mucosa causing peptic ulcer.

2- Non-steroidal anti-inflammatory drugs (NSAID) like aspirin.
   - These inhibit synthesis of prostaglandins from arachidonic acid.
   - Since prostaglandins inhibit HCL synthesis and increase mucus secretion, then chronic use of aspirin, which inhibits its formation from arachidonic acid, results in increased HCL secretion and decreased mucus production causing peptic ulcer.

3- Zollinger Ellison Syndrome.
   - Described by Zollinger and Ellison in 1955.
   - Caused by a tumor in the pancreas or other part in the GIT.
   - The tumor cells release gastrin (= gastrinoma). This causes excessive secretion of HCL resulting in multiple peptic ulcers.
Medical treatment of peptic ulcer:
- Treatment starts by eradication of the primary cause (e.g. antibiotics against Helicobacter pylori and cessation of NSAID).
- In addition, some of the following drugs should be used for at least 4-6 weeks to allow the ulcer to heal:
  o Drugs that inhibit HCL secretion allow the ulcer to heal:
    ❖ Proton pump inhibitors: Effective drugs in treatment of peptic ulcers. They block the proton pump (the H⁺-K⁺ ATPase pump).
      Example: omeprazole.
    ❖ H₂ blockers: Block histamine receptors type 2 (H₂ receptors).
      Examples: cimetidine, ranitidine and famotidine.
    ❖ Muscarinic blockers: Block the effect of acetylcholine at the muscarinic receptors. However, they are less effective than other drugs.
      Example: pirenzepine.
    ❖ Prostaglandin analogues: Inhibit HCL secretion and induce mucus and bicarbonate secretion.
      Example: Misoprostol.
  o Drugs that neutralize HCL relieve symptoms:
    ❖ Antacids: Are used to neutralize existing acid in the stomach. They are used mainly to relief symptoms.
  o Drugs that cover the ulcer prevent further digestion of the ulcer:
    ❖ Sucralfate: This sucrose octasulphate compound binds to proteins in the ulcer slough, protecting it from further digestion.

Surgical treatment of peptic ulcer
Vagotomy:
- Indicated when there is failure of all types of medical treatment.
- Vagotomy blocks the cephalic phase & part of the gastric phase.
- This decreases HCL secretion, giving chance for the ulcer to heal.
- The problem with vagotomy is the impairment of gastric emptying (see above). That is why pyloroplasty (dilatation of the pylorus) is usually done with the procedure.
- Vagotomy can be tested by insulin injection to induce hypoglycemia because hypoglycemia stimulates the vagus nerve, which increases gastric secretion. Therefore, any increase in gastric secretion following the injection indicates that vagotomy is not successful.

**GASTRIC MOTILITY**

- Many types of movement appear in the stomach as food enters it. These movements allow storage of food for some time with minimal rise in intragastric pressure and facilitate gradual gastric emptying. They include:

1. **Receptive relaxation:**
   - Occurs at the upper part of the stomach to accommodate food with minimal increase in pressure (Laplace law). It is mediated by the vagus.

2. **Peristalsis:**
   - Sweeps down towards the lower part of the stomach to allow chyme to pass through the pylorus. Its frequency is about 3-4 times per min. It is controlled by the basic electrical rhythm (see below).

3. **Migrating Motor Complex (MMC):**
   - Also known as hunger contractions. These are peristaltic waves that occur every 90 minutes during the fasting state (between meals) and disappear upon eating. They pass from the empty stomach through the small intestine, to reach the ileocecal valve.
   - Their exact function is unknown. However, they remove remnants of food & therefore prevent growth of bacteria.
   - The hormone “motilin” which is secreted by upper small intestine during the interdigestive period may be responsible for initiation of MMC.
The basic electrical rhythm (BER):
- These spontaneous rhythmic fluctuations in the membrane potential vary between (-45 & -65 mv). It occurs in smooth muscle of all parts of the GIT except the esophagus and the proximal part of the stomach.
- It is recorded in form of slow waves & spikes. Depolarization in each spike is caused by Ca\(^{++}\) influx & repolarization is caused by K\(^{+}\) efflux.

**Fig 8.11: The basic electrical rhythm**

- The frequency of slow waves (i.e. rate of BER) is 4/min in stomach, 12/min in duodenum, 8/min in ileum, 9/min in cecum and 16/min in sigmoid colon.
- The number of spikes per each wave is increased by acetylcholine and decreased by norepinephrine.
- The function of the BER is co-ordination of peristalsis & other types of GIT motility (This is confirmed by the finding that in its absence peristalsis becomes irregular).

The pyloric sphincter
- An atypical sphincter (since it is open except when peristalsis reaches it).
- It acts with the duodenum and the antral part of the stomach to control gastric emptying.
- When peristalsis reaches the lower part of the stomach, it causes sequential contraction of the antrum followed by the pylorus and then the duodenum.
- The pylorus takes slightly longer time in contraction; this prevents reflux of duodenal contents into the stomach and allows grinding and mixing of solid particles in the stomach.

**Factors affecting gastric emptying**

- Longitudinal mucosal folds in the stomach: Allow rapid emptying of liquids.
- Amount of food: Emptying is faster with higher intra-gastric volume.
- Type of food: Emptying of liquids is faster than solids & emptying of CHO is faster than protein and proteins faster than lipids.
- Osmolarity of chyme: Emptying of hypotonic chyme is faster than hypertonic chyme (this is due to a neural mechanism stimulated by distention or shrinkage of osmoreceptors in duodenum).
- pH of chyme: Emptying of alkaline chyme is faster than acidic (due to a neural mechanism stimulated by chemoreceptors in the duodenum).
- Hormones: Secretin, CCK & GIP decrease gastric emptying. Concerning gastrin, it increases gastric motility; however, it also increases intestinal motility. This increases resistance in the intestine against evacuation of gastric contents. Therefore, the overall effect is reduction in gastric emptying.
- Other factors that decrease emptying include:
  - Distention of the duodenum
  - Vagotomy
  - Emotions like “fear” (unlike excitement, which increases gastric emptying).
VOMITING “or EMESIS”

- This is a protective reflex for expulsion of harmful materials in the stomach forcefully through the mouth.

- It consists of the following components:

  ✷ **Receptors (and their stimuli “emetics”)**

  o Some of the receptors that induce vomiting are situated in the GIT (pharynx, stomach, & duodenum).

  - They are stimulated by chemical irritation, mechanical irritation or over-distention.

  - Other sites that can be stimulated to cause vomiting:

    o The bile ducts, peritoneum, heart and many other organs. Signals from these organs reach the vomiting center in response to certain diseases affecting them; for example, myocardial infarction and obstructive jaundice.

    o Vestibular system: stimulated by motion sickness.

    o The Chemoreceptor trigger zone (CRTZ) on lateral wall of the fourth ventricle in the medulla. It discharges directly to the vomiting center.

      - It is stimulated by circulating chemicals (including drugs). The effects of these chemicals on the CRTZ can be inhibited by serotonin antagonists or dopamine antagonists.

      - It is also stimulated by vestibular stimulation (motion sickness).

    o Frontal lobe: stimulated by psychic stimuli “like shocking sites or smells.”

  (Note: the last 3 stimuli are known as central receptors).

  ✷ **Afferents from the stomach:**

  - Autonomic nerves (sympathetic & vagus)

  ✷ **Vomiting center:**

  - Present bilaterally in the medulla oblongata
- **Efferents:**
  - The cranial nerves and the spinal nerves that supply the effectors

- **Effectors:**
  - All the following effectors participate in the act of vomiting: Abdominal muscles, diaphragm, intestine, stomach, esophagus & mouth.

**The act of vomiting:**
- Vomiting starts with cessation of respiration at mid inspiration (= closure of the glottis & nasopharynx).
- Violent contractions of abdominal muscles & diaphragm occur to squeeze the stomach and increase its pressure.
- Reverse peristalsis occurs to evacuate the upper intestine into the stomach.
- In the mean time: the wall of the stomach relaxes, the lower esophageal sphincter open and the upper esophageal sphincter suddenly open.
- The high intra-gastric pressure allows gastric contents to be expelled through the esophagus to the outside.

**Associated with vomiting:**
- Salivation
- Nausea
- Sweating
- Skin vasoconstriction
- Slowing of the heart rate

**Remember that:** Because vomiting causes slowing of the heart rate, induction of vomiting is used sometimes for treatment of supraventricular tachycardia
QUESTIONS FOR SELF ASSESSMENT-1 (MCQs)

1. Receptive relaxation of the stomach is abolished by:
   a. Ingestion of a heavy meal
   b. Parasympathetic stimulation
   c. Sympathetic stimulation
   d. Vagotomy
   e. Administration of CCK-PZ

2. Saliva is characterized by:
   a. HCO₃⁻ concentration lower than plasma
   b. Presence of proteolytic enzymes
   c. Absence of glucose
   d. pH similar to that of plasma
   e. Hypotonicity relative to plasma

3. Slow waves in smooth muscle of lower part of the stomach are:
   a. Local potentials
   b. Action potentials
   c. Resting membrane potential
   d. Due to action of gastrin
   e. Receptive relaxation electrical activity

4. A patient with gastric ulcer is treated with the drug omeprazole. The basis of omeprazole's inhibition of gastric acid secretion is that it:
   a. Blocks H₂ receptors
   b. Increases intracellular cAMP
   c. Stimulates M₃ receptors
   d. Inhibits the proton pump
   e. Potentiates effects of prostaglandins

5. A patient with Zollinger-Ellison syndrome is expected to have:
   a. Auto-antibodies against parietal cells
   b. Iron deficiency anemia
   c. Multiple peptic ulcers
   d. Insulinoma
   e. Absent mucus barrier of the stomach

6. Gastric emptying is stimulated by:
   a. Fatty meal
   b. Hypertonic fluids
   c. Low pH in the duodenum
   d. Gastric inhibitory peptide
   e. Parasympathetic stimulation

7. Peptic ulcer:
   a. Is caused primarily by excessive secretion of HCl
   b. Can be treated with non steroidal anti-inflammatory drugs like aspirin
   c. Is associated with Helicobacter pylori infection in the majority of patients
   d. Treatment involves reduction of cAMP within the cell
   e. Is caused by H2 receptor blockers
8. **Hydrochloric acid:**
   a. Is secreted by the chief cells
   b. Converts iron from the ferrous state to the ferric state
   c. Activates trypsinogen
   d. Secretion is stimulated by acetylcholine
   e. Is essential for vitamin B12 absorption

9. **The parietal cells of gastric glands:**
   a. Secrete gastrin
   b. Are stimulated by prostaglandin E2
   c. Do not contain carbonic anhydrase
   d. Secrete intrinsic factor
   e. Have H-K ATPase on basolateral membranes

10. **Which of the following statements about gastric emptying is correct?**
    a. Acidification of the antrum decreases gastric emptying
    b. Emptying of solids is faster than liquids
    c. Indigestible food empties during the interdigestive period
    d. CCK accelerates gastric emptying
    e. Enterogastrone increases gastric emptying

11. **Feedback inhibition of gastric acid secretion is achieved by:**
    a. Gasrin
    b. Acetylcholine
    c. Enterogastrone
    d. Somatostatin
    e. Histamine

12. **Gastric emptying increases with an increase in:**
    a. Intra-duodenal osmolarity
    b. Intra-duodenal pH
    c. Intra-gastric volume
    d. Intra-gastric osmolarity
    e. Duodenal fat content

13. **Secondary esophageal peristalsis differs from primary peristalsis in that it is:**
    a. Localized to the esophagus
    b. Preceded by oropharyngeal phase
    c. Involves activation of medullary swallowing centers
    d. Abolished by vagotomy
    e. Results in relaxation of the lower esophageal sphincter

14. **In the buccal stage of swallowing the:**
    a. Mouth should be open
    b. Larynx moves down
    c. Movement is involuntary
    d. Tongue moves upward and backward
    e. Upper esophageal sphincter relaxes

15. **Gastric secretion:**
    a. Is 1 L per day
    b. Contains intrinsic factor that helps in vitamin B6 absorption
c. Is stimulated by gastrin
d. Is inhibited by histamine
e. Converts iron from ferrous to ferric state

16. Opening of the lower esophageal sphincter occurs due to:
   a. Arrival of a peristaltic wave
   b. A vago-vagal reflex.
   c. Stimulation of muscarinic receptors
   d. Stimulation of alpha receptors
   e. A rise in gastric pressure above 15 mmHg

17. H⁺-K⁺ ATPase pumps in an inactive parietal cell is found in the:
   a. Basolateral membrane
   b. Apical membrane
   c. Cytoplasm
   d. Golgi apparatus
   e. Mitochondria

18. Receptive relaxation of the stomach:
   a. Occurs during the cephalic phase
   b. Mediated by the vagus
   c. Causes the stomach to double its volume
   d. Occurs just before vomiting
   e. Occurs in the lower part of the stomach

19. Which of the following statements about saliva is correct:
   a. Volume is about 3 L/day
   b. Produced mainly by the parotid glands
   c. Contains bactericidal substances like lactoferrin
   d. Secretion is stimulated by muscarinic blockers
   e. Secretion is not controlled by hormonal factors

20. Migrating motor complex:
   a. Is a mixing type of movement
   b. Occurs immediately following ingestion of food
   c. Starts in the esophagus
   d. Removes undigested particles from the large intestine
   e. It is initiated during the inter-digestive phase

21. The cephalic phase of gastric secretion:
   a. Depends on purely neural mechanisms
   b. Is associated with receptive relaxation of the stomach
   c. Is mainly due to vagal release of gastrin
   d. Is both neural & hormonal
   e. Depends on conditioned reflexes

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THE EXOCRINE PANCREAS

STRUCTURE

- Consists of lobules. Each lobule consists of acini & ducts.
- The ducts are joined together to form the main pancreatic duct. This opens together with the common bile duct into the duodenum at the ampulla of Vater.
- The opening at the ampulla is guarded by the sphincter of Oddi (choledocho-duodenal sphincter).

**Fig 8.12: The pancreas**

PANCREATIC SECRETION

**Characteristics:**

- Volume: 1.5 L
- Osmolarity: Isotonic
- pH: Alkaline (8) to neutralize gastric acid (together with bile and intestinal secretion)
- Contents: Water, electrolytes (secreted by ductular & centroacinar cells) & digestive enzymes (secreted by acinar cells)
The pancreatic enzymes:
- The main digestive enzymes in the GIT. These enzymes are essential for digestion (i.e. absence of these enzymes impairs digestion and consequently absorption is also impaired).
- The enzymes include:
  - **Enzymes for protein digestion**
    - Produced in an inactive form.
    - Include: Trypsinogen, chymotrypsinogen, proelastase and procarboxypeptidase.
    - Activation occurs as follows: 1st trypsinogen is activated to trypsin in the duodenum by enteropeptidase enzyme (also known as enterokinase), and then trypsin activates the other enzymes (autocatalysis) as follows:
      - Other trypsinogen is activated to trypsin
      - Chymotrypsinogen is activated to chymotrypsin
      - Proelastase is activated to elastase
      - Procarboxypeptidase is activated to carboxypeptidase
  
  Remember that: These enzymes are secreted in inactive form to prevent autodigestion of the pancreas. They are activated within the intestinal lumen, not in the pancreatic duct. Activation within the pancreatic duct is inhibited by a trypsin inhibitor found in the pancreatic juice.
  
  - **Enzymes for carbohydrate digestion**
    - Pancreatic α amylase: Acts on starch.
  
  - **Enzymes for lipid digestion**
    - Pancreatic lipase: For triglycerides
    - Co-lipase: Bound to lipase to increase its activity. It needs activation by trypsin.
    - Cholesterol esterase: For cholesterol esters
    - Phospholipase A₂: For phospholipids. It also needs activation by trypsin.
Enzymes for nucleic acid digestion
- Ribonuclease: For RNA digestion
- Deoxyribonuclease: For DNA digestion

Changes in ionic composition of pancreatic secretion:
- After secretion into the duct lumen, bicarbonate is reabsorbed back in exchange to chloride which is secreted. Therefore high flow rate decreases this exchange resulting in more bicarbonate and less chloride in pancreatic secretion (i.e. bicarbonate & chloride are flow dependent).
- Sodium & potassium concentrations remain constant without difference in concentrations between high or slow rates of secretion (i.e. sodium & potassium are flow independent).

CONTROL OF PANCREATIC SECRETION
- By neural & hormonal mechanisms.
- These mechanisms are activated during the following phases: Cephalic phase, gastric phase & intestinal phase.

Cephalic phase
- It is the phase when food is in front or within the mouth (not in the stomach).
- Two neural reflexes are activated:
  o Conditioned reflex (activated by sight, smell or thoughts about appetizing food).
  o Non-conditioned reflex (activated by presence of food in the mouth).
- Both reflexes are mediated through the vagus nerve.
- The vagus acts on acinar cells to release pancreatic enzymes by two ways: Directly by acting on acinar cells & indirectly by stimulating gastrin release from the stomach (see above).
**Gastric Phase**
- It is the phase when food reaches the stomach.
- Here pancreatic secretion “rich in enzymes” is mediated by both neural & hormonal mechanisms.

**The neural mechanism:** Distention of the stomach stimulates pancreatic secretion by a vagovagal reflex.

**Hormonal mechanism:** Food in the stomach stimulates release of gastrin (through gastric distention &/or L-amino acids). Gastrin stimulates pancreatic secretion rich in enzymes.

**Intestinal phase**
- This is the main phase for pancreatic secretion. It is mediated through hormonal mechanisms. The hormones are released when chyme reaches the small intestine; they are two hormones: Secretin & CCK-PZ.

**SECRETIN**
- Peptide hormone (27aa), released by S cells in the duodenum.
- Similar in structure to VIP, GIP & Glucagon (these hormones constitute the Secretin family).

**History:** Bayliss and Starling in 1902 suggested that a chemical substance released by the small intestine into the blood stimulates pancreatic secretion. This led to the identification of secretin, the first hormone to be discovered.

**Stimuli:**
- Low pH (mainly)
- Amino & fatty acids

**Mechanism of action:**
- Secretin has cell membrane receptors.
- Its effects are mediated via the second messenger “cAMP”.
**Actions:**
- Acts on ductular & centroacinar cells of the pancreas to release water & electrolytes (especially bicarbonate).
- Acts on the biliary tract to release water & electrolytes (it increases flow of bile, i.e. it is choleretic).
- Inhibits gastrin and gastric acid secretion.
- Inhibits intestinal motility.
- Relaxes the lower esophageal sphincter & contracts the ileo-cecal valve.
- Contracts the pyloric sphincter and decreases gastric emptying.
- Augments actions of CCK on the pancreas.

**CCK-PZ (CHOLECYSTOKININ-PANCREOZYMIN)**
- Peptide hormone; similar in structure to gastrin (both hormones constitute the gastrin family)
- Produced by: I cells of the duodenum and by some neurons in the brain and GIT
- Like gastrin it is found in many forms (5, 12, 33, 39, 58 amino acids)

**Stimuli:**
- Luminal amino & fatty acids (mainly)
- Low pH in the duodenum

**Mechanism of action:**
- Has cell membrane receptors.
- Its effects are mediated via “phospholipase C”.

**Actions:**
- Acts on pancreatic acinar cells to stimulate secretion of enzymes.
- Contracts the gall bladder (cholagogue) & relaxes the Oddi sphincter.
- Augments actions of secretin on the pancreas.
- Inhibits gastric emptying.
- Inhibits gastrin and gastric acid secretion (in large doses).
- Relaxes the lower esophageal sphincter & contracts the ileo-cecal valve.
- Contracts the pyloric sphincter (decreases gastric emptying).
- Stimulates intestinal motility.

**ABNORMALITIES OF THE PANCREAS**

**Acute pancreatitis**
- Occurs due to activation of pancreatic enzymes within the pancreatic duct, resulting in autodigestion of the pancreas; as occurs when the common bile duct is obstructed by gallstones.
- Symptoms include severe upper abdominal pain, nausea and vomiting.
- High amount of pancreatic enzymes may enter the blood (e.g. amylase & lipase). Presence of high concentration of these enzymes in the plasma can be used for diagnosis.

**Chronic pancreatitis**
- Characterized by release of low amount of pancreatic enzymes in the duodenum, resulting in maldigestion & malabsorption of protein and fat.
- Large amounts of fat (> 5 grams/day) appear in stool (= fatty stool or steatorrhoea).
THE LIVER AND BILE

THE LIVER

Anatomy:
- Weight: about 1.5 Kg.
- Consists of lobules, each lobule consists of many cellular plates radiating between a central vein & a portal tract.
- Between the cellular columns in each plate are bile canaliculi.
- Between the cellular plates are hepatic sinusoids (lined by endothelial cells & kupffer cells).
- The hepatic sinusoids receive blood supply from both hepatic artery and portal vein (the total liver blood flow = 1.5 L/min; 1L/min from the portal vein & 0.5 L/min from the hepatic artery. Then blood drains to central veins, which drain to hepatic veins and then to the inferior vena cava (IVC).

Fig 8.13: Histology of the Liver
- Between the sinusoids & cellular plates there are spaces of Disse.
- These spaces drain lymph to lymphatic vessels (The liver produces one half of all lymph formed in the body; lymphatic flow= 1 ml/min).
- Because of the large pores in the hepatic sinusoids, they are permeable to both fluid and protein. Therefore large quantities of protein move into the spaces of Disse (Protein concentration in the lymph is only slightly lower than that of the plasma).

**The functional unit:**
- The functional unit of the liver is the **hepatic acinus**. It represents the hepatocytes that lie more near to afferent vessels (i.e. vessels in the portal triads, away from central veins).
- Each acinus can be divided into 3 zones: 1, 2 and 3.
- Zone 1 is the nearest zone to afferent vessels (hepatic arterioles carrying well oxygenated blood). For this reason interruption of hepatic blood flow results in necrosis of cells at zone 3 rather than zone 1 (anoxic damage).

**Fig 8.14: Hepatic acinus**
Functions of the Liver

- Synthesis of plasma proteins (albumin, globulins & fibrinogen).
  - Note that the liver forms α and β globulins (most of which are clotting factors). However, gamma globulins (= the immunoglobulins) are not synthesized by the liver.
- Synthesis & secretion of bile (see functions of bile).
- Metabolism of CHO, proteins, fats and hormones (especially steroid hormones).
- Excretion of end products of metabolism (excreted through bile).
- Storage of glycogen, iron and vitamins (vitamin A, D & B₁₂).
- Detoxification of toxic substances, drugs and ammonia.
  - Note that the liver converts ammonia, which is toxic, to urea, which is non toxic except in very high levels as in renal failure.
- Immunity by Kupffer cells (phagocytic cells derived from monocytes).

**BILE**

- Yellowish to greenish fluid secreted continuously by hepatocytes into the biliary system.

**Characteristics of bile:**

- Color: Golden yellow or greenish fluid
- Taste: Bitter taste
- Osmolarity: Isotonic
- pH: Slightly alkaline
- Contents:
  - Water & electrolytes (K⁺/ Na⁺/ Ca⁺/ HCO₃⁻/ Cl⁻ …)
  - Bile salts
  - Bile pigments (bilirubin)
  - Cholesterol/Phospholipids
  - Alkaline phosphatase enzyme
The gall bladder (Cholecyst)

Characteristics of the gall bladder:
- A pear shaped structure, dark green in color.
- About 10-12 cm in length.
- Connected to the liver and duodenum by the biliary system.

Functions of the gall bladder:
- Storage of bile (Between meals bile is stored in the gall bladder. The full capacity of the gall bladder is about 50 ml. This is released into the duodenum up to 10 times per day (i.e. volume of bile released into the intestine = 0.5 L/day)).
- Concentration of bile (the mucosa of the gall bladder absorbs water).
- Acidification of bile (the mucosa also absorbs bicarbonate).
- Note: The gall bladder also controls release of bile through the cystic & common bile ducts into the duodenum (in response to CCK).

Differences between hepatic bile & gall bladder bile:
- The gall bladder absorbs Na⁺, Cl⁻ & HCO₃⁻ actively, followed by passive water absorption.
- This results in less water, [Na⁺], [Cl⁻], [HCO₃⁻] and pH in bile of the gall bladder compared to hepatic bile; but higher concentrations of the other substances (e.g. bile salts, bile pigment, cholesterol and phospholipids).

Functions of bile:

1- Neutralization of acid chyme
- By the high bicarbonate content in bile (alkaline pH).
- Note that bile, pancreatic secretion and duodenal secretion all act together to neutralize acid in the duodenum.

2- Fat digestion & absorption
- By the Bile salts; the bile salts result in: Emulsification (for fat digestion) & Micelle formation (for fat absorption).
- **Emulsification** = Breakdown of large fat droplets into smaller ones. This facilitates digestion by increasing surface area of fat droplets for the action of pancreatic lipase.

- **Micelles** = Cylindrical structures formed by bile salts and phospholipids in bile. Bile salts are arranged in a way that their hydrophilic parts project to the outside and their hydrophobic parts project to the center inside. Large lipid molecules are enclosed in the center of these micelles. This makes lipids soluble in water & facilitates their transport to the intestinal wall for absorption.

3- **Excretion**

- Bile is an important excretory route for bile pigment (bilirubin), cholesterol, some drugs, some dyes and some inorganic substances.

**Fig 8.15: Emulsification & micelle formation**

**Bile Salts**

- Bile salts are sodium & potassium salts of bile acids.
- Bile acids are formed in the liver from cholesterol as two primary bile acids: Cholic acid & chenodeoxycholic acid.
- They are found conjugated to the amino acids glycine and taurine.
- In the small intestine, bile salts exert the following effects:
  o Participate in fat digestion & absorption
  o Reduce surface tension of fluid in the small intestine.
  o Stimulate CCK (indirectly, by the products of lipid digestion).
- Most of the bile acids (90-95%) are absorbed in the terminal ileum actively to the entero-hepatic circulation (they return to the liver and then re-secreted again in bile). The recycling occurs about 6-10 times every day (twice/meal). The amount of bile acids that recycles is about 2-4g.
- In the large intestine, bacteria deconjugate the primary bile acids & convert them into secondary bile acids as follows:
  o Cholic acid to deoxycholic acid
  o Chenodeoxycholic acid to lithocholic acid.
- Deoxycholic acid is absorbed back to the liver for re-conjugation or secretion whereas most lithocholic acid is excreted in stool.
- The amount of bile acids lost daily in stool is about 0.2-0.4g; this is replaced daily by the liver (i.e. the liver forms only 0.2-0.4 g/day).
- Note: Intestinal bacteria also deconjugate bile pigments into urobilinogens (see RBC destruction in volume 1).

**CONTROL OF BILE**

- By two types of factors:

  **1- Choleretics:**
  - Factors that increase secretion of bile from the liver and its flow within the bile ducts.
  - They include: Bile salts, secretin, vagus, gastrin & glucagon.
  - Note that bile salts recycle through the enterohepatic circulation. This recycling increases flow of bile & decreases synthesis of bile acids.
  - Therefore it is the most important choleretic factor. It is responsible for about 90% of bile flow.
2- Cholagogues:
- Factors that contract the gall bladder & increase flow of bile into the duodenum. They include CCK & vagus. However, sodium sulphate & phosphate are also included.

DISORDERS

1- Gallstones (Cholelithiasis)
- Gallstones are caused by:
  - Bile stasis.
  - Super saturation of bile with cholesterol or excessive calcium ions.
  - Damage or infection of the gall bladder.
- They vary in size and appearance depending on their contents.
- Their types include: Cholesterol stones, pigment stones, or calcium salts stones.
- They may obstruct the common bile duct and the pancreatic duct resulting in obstructive jaundice and pancreatitis respectively.
- Gallstones in the gall bladder are best treated by surgical removal of the gall bladder (cholecystectomy).

2- Cholecystectomy
= Surgical or laparoscopic removal of the gall bladder.
- After cholecystectomy, bile is released constantly into the duodenum (i.e. not following fatty meals as occurs normally).
- This is not going to impair digestion & absorption of fats. However, patients with cholecystectomy are generally advised not to eat diets with high fat content.

3- Jaundice
- Yellowish coloration of the skin, sclera and mucus membranes.
- Due to high bilirubin level in plasma (see jaundice in volume 1).
THE SMALL & LARGE INTESTINE

THE SMALL INTESTINE

- The small intestine is essential for life because it is the most important site for digestion & absorption.
- Removal of a large segment results in malabsorption syndrome.

Anatomy

- The small intestine is formed of three segments: Duodenum = the first 25 cm; jejunum = the first 40% distal to the duodenum & ileum = the remaining 60%, distal to the jejunum.
- The length is about 285 cm (3m) in a living adult subject; however, it elongates after death to reach 7m. The surface area is increased 600 fold to reach 200m² by mucosal folds, villi and microvilli.
- Important histological points:
  - Crypts of Lieberkuhn: At the base of villi. Secrete intestinal secretion
  - Brunner’s glands: In the duodenum. Secrete mucus
  - Peyer’s patches: Lymphoid tissue in the ileum
  - Endocrine cells: Mainly in the duodenum. Secrete GIT hormones like secretin,CCK …

Fig 8.16: The small intestine
INTESTINAL SECRETION

Characteristics:

- Volume: 1L/day
- Osmolarity: Isotonic
- pH: Alkaline
- Contents: Water, electrolytes, mucus & digestive enzymes

The digestive enzymes:

- Enteropeptidase (or enterokinase), which activates trypsinogen
- Peptidases, which complete digestion of protein
- Disaccharidases (sucrase, maltase and lactase), which digest the disaccharides
- Nucleases (RNAase & DNAase), which digest RNA & DNA.

Stimuli for intestinal secretion:

- Neural stimuli: Vagus (for mucus secretion)
- Hormonal stimuli: VIP, Gastrin, CCK & Secretin
- Mechanical irritation
- Chemical irritation

The small intestine is presented with 9 liters of fluid per day as follows:

- 1.5 L from saliva
- 2.5 L from stomach
- 1.5 L from pancreas
- 0.5 L from bile
- 1.0 L from intestine
- 2.0 L from drinking

- It absorbs about 7 L, leaving about 1-2 L to reach the large intestine. The large intestine absorbs 90% of this leaving about 200 ml to be excreted in stool.
THE LARGE INTESTINE (COLON)

Segments:
Cecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum.

- The large intestine differs from the small intestine because it has:
  1- No villi (the surface area is not increased because it is not a major absorptive site)
  2- Higher number of goblet cells (secrete mucus to allow stool movement )
  3- Higher number of intestinal bacteria (the bacteria has many functions, see below)
  4- Haustra (sacculations in the wall of the large intestine)
  5- Shorter length (about 1.5 meter, elongates after death)
  6- Larger diameter
  7- Teniae coli (incomplete longitudinal smooth muscle layer in its wall).

Fig 8.17: The large intestine
Intestinal bacteria (flora)
- Found in all parts of the GIT, but especially in the colon.
- Not pathogenic (i.e. does not cause disease in normal subjects).
- Functions:
  - Antagonize pathogenic bacteria. Therefore, prolonged use of antibiotics changes the normal flora and predisposes to infection of the large intestine “colitis”.
  - Important for normal development of the immune system.
  - Formation of vitamin K, which is needed for formation of some clotting factors in the liver (II, VII, IX & X).
  - Formation of other vitamins like folic acid and some B vitamins. However, this is not important because of the poor absorption at the large intestine.
  - Formation of ammonia (toxic substance) that is absorbed to reach the liver where it is converted into urea (non-toxic). However, patients with liver failure fail to form urea. They get into coma because of ammonia toxicity (= hepatic encephalopathy). That is why management of hepatic failure includes antibiotics (oral streptomycin or neomycin) for eradication of flora (= Sterilization of the bowel).
  - Formation of amines (histamine, tyramine) and gases (hydrogen, hydrogen sulfide, carbon dioxide and methane). These gases (together with the unabsorbed swallowed gas) are excreted as flatus (note that the daily production of gas is 500-1500 ml).
  - Deconjugation of bile acids and bile pigments (revise “bile” above).
INTESTINAL MOTILITY
- There are two types of intestinal motility:
  1- Propulsive movements:
      - Pushes food forward towards the anus (e.g. peristalsis).
  2- Mixing movements:
      - Mixes food with enzymes and exposes it to the intestinal surface for absorption (e.g. segmentation contractions).

MOTILITY OF THE SMALL INTESTINE
- Controlled by the basic electrical rhythm (BER) that originates from pacemaker tissues in the small intestine.
- Its rate is 12 /min in the duodenum and 8/min in the ileum.
- Types of motility:
  1-Migrating motor complex (MMC)
     - Propulsive (described above with gastric motility).
  2-Peristalsis
     - Propulsive (described above with swallowing).
     - Peristalsis in the opposite direction “anti- peristalsis” may occur in vomiting to evacuate the duodenal contents into the stomach.

Fig 8.18: Peristalsis
3-Segmentation contractions
- Ring like contractions of circular muscle layer appearing at regular intervals on the wall of the small intestine. These rings alternate between contraction and relaxation resulting in forward & backward movements of chyme (= mixing movements).
- They are integrated in the myenteric plexus; that is why they persist after cutting the extrinsic innervations of the small intestine.

![Segmentation contractions](image)

**Fig 8.19: Segmentation contractions**

4- Tonic contractions
- Prolonged contractions that isolate one segment of the intestine from another. This decreases movement of chyme and allows absorption.

5- Gastro-ileal reflex
- When food leaves the stomach, the cecum relaxes. This opens the ileocecal valve and allows passage of some chyme into the cecum.
- The reflex is mediated by the vagus.
- Remember that the ileocecal valve is also opened by gastrin and closed by CCK and secretin.
MOTILITY OF THE LARGE INTESTINE
- Also controlled by the BER.
- Frequency of discharge increases from 9/ min in the cecum to 16/ min in the sigmoid colon.
- Types of motility in the large intestine:

1- Segmentation contractions
- Mixing (see above).

2- Peristalsis
- Propulsive (see above).

3- Mass action contraction
- This is a special type of peristalsis (i.e. it is a propulsive movement).
- It is mass movement that propels stool through a long distance in the large intestine (e.g. from the transverse colon to the rectum).
- When stool reaches the rectum, the process of defecation may be initiated.
- Frequency of mass action contraction (and therefore defecation) is one to three times/ day.

Transit time through the small and large intestine
- If a test meal (e.g. barium meal) is followed radiologically, its first part reaches the following regions approximately at the stated time (= transit time):
  - Cecum in 4 hours
  - Hepatic flexure in 6 hours
  - Splenic flexure in 9 hours
  - Pelvic colon in 12 hours
- From the pelvic colon to the rectum it moves slowly. After 3 days, 75% of the meal is excreted in stool; however, total excretion may take more than a week.
CONTROL OF INTESTINAL MOTILITY

- Like other functions of the GIT, it is controlled by neural and hormonal factors.

Neural control:

- Extrinsic nerves:
  - The parasympathetic: increases motility.
  - The sympathetic: decreases motility.
- Intrinsic nerves:
  - The myenteric plexus: acts in integration with the extrinsic nerves. However, it can act independently.

Note: The pacemaker tissues of the BER: control peristalsis.

Hormonal control:

- Intestinal motility is affected by the following hormones & neurotransmitters:
  - Gastrin: stimulates intestinal motility
  - CCK: stimulates intestinal motility
  - Secretin: inhibits intestinal motility
  - Acetylcholine: stimulates motility (contracts intestinal walls and relaxes sphincters)
  - Catecholamine: inhibits motility (relaxes walls and contracts sphincters)
  - Substance P: stimulates intestinal motility (contracts intestinal wall in peristalsis)
  - VIP: relaxes walls and sphincters
  - NO: relaxes walls and sphincters

- Remember that: in peristalsis, acetylcholine and substance P contract the wall of the intestine behind the food whereas NO and VIP relax the wall in front of it.
ABNORMALITIES OF INTESTINAL MOTILITY

Intestinal obstruction

- Two types:
  - Mechanical obstruction
  - Paralytic obstruction (adynamic ileus)

Mechanical obstruction:
- Caused by stool impaction, tumor, stricture, or hernia.
- Characterized by increased peristalsis and distention of bowel proximal to the site of obstruction. This causes severe colicky abdominal pain.
- Blood supply in the distended area is reduced with a risk of perforation.
- Treatment: Surgery

Paralytic (adynamic) ileus
- Occurs following abdominal operations, peritonitis or due to hypokalemia.
- These result in either direct inhibition of smooth muscle or indirect inhibition through increased noradrenergic discharge.
- It is characterized by:
  - Inhibition of peristalsis= no pain
  - Abdominal distention
  - Vomiting
  - Electrolyte disturbance
- Following abdominal operations, peristalsis usually returns after 6-8 h (in the small intestine & then the stomach) and after 2-3 days (in the large intestine).
- Treatment (Medical treatment): Patients should take nothing per mouth, should have nasogastric tube suction of gastric contents and their electrolyte disturbances should be corrected.
DEFECATION

- Spinal reflex initiated by distention of the rectum with feces.
- It results in contraction of the rectum and relaxation of the internal anal sphincter (in response to parasympathetic stimulation).
- This reflex can be facilitated or inhibited by relaxing or contracting the external anal sphincter (Skeletal muscle under voluntary control through the pudendal nerve).
- The pudendal nerve is a somatic nerve originating from the sacral segments S₂, S₃ & S₄.
- The components of this reflex are:
  - **Receptors:** Stretch receptors in the wall of the rectum, stimulated when the rectum is full and its pressure reaches 18 mmHg (e.g. following mass action contraction).
  - **Afferents:** Parasympathetic nerves (pelvic splanchnic nerve).
  - **Center:** Sacral segments (S₂, S₃ & S₄).
  - **Efferents:** Parasympathetic nerves (pelvic splanchnic nerve).
  - **Effectors:** Smooth muscle in the wall of the rectum and smooth muscle of the internal sphincter.
- The response of the reflex is contraction of the wall of the rectum and relaxation of the internal sphincter to allow defecation.
- This is facilitated (in suitable conditions) by relaxing the external sphincter voluntarily. In unsuitable conditions, the subject contracts the external sphincter to inhibit defecation.
- When the pressure in the rectum reaches 55 mmHg, the stool is forced out through the external sphincter in spite of its resistance.
- Note that the sympathetic neurons contract the internal sphincter and relax the wall of the rectum; however, they are not part of the defecation reflex.
**Abnormalities of defecation:**

- Transection of the spinal cord above the sacral segments impairs the descending orders from the brain to the external sphincter (resulting in loss of the voluntary control). However, since the external sphincter is in state of contraction, stool is not evacuated until the rectal pressure reaches 55mm Hg. Here it forces its way out.

**Fig 8.20: The defecation reflex**

![Defecation Reflex Diagram](image)

**The gastro-colic reflex**

- When food enters the **stomach**, the **rectum** contracts to allow defecation.
- This reflex occurs mainly in children who defecate after meals.
- It is not mediated by a neural mechanism.
- The hormone gastrin may be responsible for his reflex.
DIGESTION & ABSORPTION

- Complex substances are broken down into absorbable units in the small intestine.
- The absorbable units enter either the portal blood or the lymphatic system.
- Non-digestible & absorbable units like cellulose & lignin (dietary fiber) are excreted in stool.
- These vegetable products add bulk to stool.
- When they are present in high amount in food (high fiber diet), they decrease incidence of colonic cancers, diabetes mellitus, ischemic heart disease and other problems.

CARBOHYDRATES

CHO Digestion

- Types of CHO in diet:
  - Monosaccharides:
    - Glucose
    - Fructose
  - Disaccharides:
    - Maltose (2 glucose)
    - Trehalose (2 glucose)
    - Sucrose (glucose + fructose)
    - Lactose (glucose + galactose)
  - Polysaccharides (glucose polymers):
    - Starch
    - Derivatives of starch (Amylose, amylopectin)
    - Glycogen
- Digestive enzymes:
  In the mouth: Salivary α amylase (acts on polysaccharides "starch")
  In the stomach: No specific enzyme. Salivary α amylase is inhibited (by the low pH).
  In the intestine: Pancreatic α amylase (also acts on starch).
Note: Salivary α amylase may resume its activity in the intestine (suitable pH)
- Products of starch digestion by α amylase enzymes:
  1- Disaccharides: maltose
  2- Trisaccharides: maltotriose
  3- Short polymers: α dextrins
- Further digestion requires the following intestinal enzymes found in the brush border:
  o α dextrinase: Acts on alpha dextrins, maltose & maltotriose
  o Maltase: Acts on maltose to give glucose + glucose
  o Sucrase: Acts on sucrose to give glucose + fructose
  o Lactase: Acts on lactose to give glucose + galactose
  o Trehalase: Acts on trehalose to give glucose + glucose

**CHO Absorption**
- Only occurs for the monosaccharides (e.g. glucose, galactose …)
- Absorption is almost 100%
- The absorbed units enter portal circulation

**Glucose absorption:**
- Co transported with sodium
  - Na⁺ facilitates glucose absorption & vice versa.
- Water follows sodium; that is why oral rehydration solutions (ORS) are used for treatment of diarrhea. These solutions contain salt and sugar.
- Transporters of glucose and sodium:
  1- On luminal membrane (carriers for co-transport to inside the cell):
     o Sodium-glucose transporters 1 & 2 (SGLT1 & SGLT2)
  2- On basolateral membrane (carriers for facilitated diffusion to the ISF):
     o Glucose transporters 1 & 2 (GLUT1 & GLUT2)

- Remember that: Glucose transporters are also found in the cells of the proximal convoluted tubules in the kidney for reabsorption of sodium and glucose (see chapter 9).
- Glucose transporters are also found in other cells in the body. They are seven types; among these types, only GLUT-4 is sensitive to insulin (found in fat & muscle cells).

**Galactose absorption:** Similar to glucose (i.e. co transported with sodium “secondary active transport”)

**Fructose absorption:** Facilitated diffusion

**Pentose absorption:** Produced from metabolism of nucleic acids. Absorbed by simple diffusion.

**Abnormalities of CHO digestion & absorption**
- Deficiency of the digestive enzymes in the intestinal brush border (by a congenital or acquired cause) results in diarrhea, abdominal distention and flatulence. This usually follows ingestion of a carbohydrate meal and its breakdown by the intestinal bacteria resulting in increased number of osmotic particles (causing diarrhea) and excessive release of gases (causing abdominal distention & flatulence).
- A good example is **lactose intolerance** due to deficiency of lactase enzymes. Here symptoms follow ingestion of milk.
- The condition is treated by avoidance of milk and use of yogurt, which contains bacterial lactase.
PROTEINS

Protein Digestion
- Sources of protein:
  - Diet
  - GIT secretions & desquamated cells.
- Digestive enzymes:
  - In the mouth: No enzyme for digestion.
  - In the stomach: Pepsin, gelatinase and rennin (See gastric secretion).
  - In the intestine: Pancreatic endopeptidases (Trypsin, chymotrypsin, and elastase) and pancreatic exopeptidase (Carboxypeptidases (A & B)). Then further digestion occurs by proteolytic enzymes found in the brush border (aminopeptidase, carboxypeptidase, endopeptidase and dipeptidase).
- Products of protein digestion:
  - Free amino acids
  - Dipeptides and tripeptides
- These are further digested by peptidases in the cytoplasm of cells.

Protein Absorption
- About 95-98% of proteins are digested & absorbed.
- The absorbed units enter portal circulation.

Absorption of free amino acids:
  - Co transport with sodium (mainly)

Absorption of dipeptides & tripeptides:
  - By a mechanism involving hydrogen ions.

Complete proteins (undigested):
  - Occurs in infants for IgA antibodies in milk by endocytosis.
Abnormalities of protein digestion & absorption
- Absorption of foreign proteins induces antibody formation; this explains allergy to certain types of food.
- Congenital defects in the mechanisms of amino acid absorption result in inborn errors of metabolism. Examples include: Hartnup disease & Cystinuria.

LIPIDS

Lipid Digestion
- Lipids in diet:
  - Triglycerides & cholesteryl esters
- Digestive enzymes:
  - In the mouth:
    - Lingual lipase (acts on triglycerides).
  - In the stomach:
    - Gastric lipase.
  - In the intestine: (from the pancreas and from the liver)
    - From the pancreas:
      - Pancreatic lipase & Colipase (revise contents of pancreatic secretion)
      - Bile salt activated lipase
      - Cholesteryl ester hydrolase
    - From the liver:
      - Bile salts, which cause emulsification and micelle formation (see functions of bile).

Lipid Absorption
- More than 95% of fats are absorbed in adults, but less than that in infants.
Most fats are absorbed by passive diffusion. However, carriers may be involved.

The absorbed units either enter portal circulation or lymphatics as follows:

- Fats entering the portal blood have carbons $< (10-12)$ e.g. short chain free fatty acids (FFAs).
- Fats entering the lymphatics have carbons $> (10-12)$ e.g. long chain free fatty acids and cholesterol.

Before entering the lymphatics, the long chain fatty acids and cholesterol are re-esterified within the cytoplasm of intestinal cells and become coated with protein & phospholipids to form chylomicrons.

Chylomicrons are released to lymphatics by exocytosis.

**Abnormalities of fat digestion & absorption**

**Steatorrhoea (fatty stool):**

- Loss of more than 5 grams of fat in stool per day.
- Steatorrhoea is caused by conditions that impair release of pancreatic lipase or bile salts into the small intestine.
- For example: Chronic pancreatitis & obstruction of the common bile duct.
- Stool is usually bulky, offensive and difficult to flush, because of fats.

(Note that the total weight of normal stool is about 80-200 g/day but 75% of this amount is water; also there are other constituents not dietary in origin like bacteria & desquamated cells)

**ABSORPTION OF ELECTROLYTES**

**Sodium:**

- Absorbed throughout the small & large intestines, actively by the action of the Na$^+$-K$^+$ ATPase pumps on the basolateral membranes of intestinal cells.
- Glucose facilitates absorption of sodium on the apical membranes (through the SGLTs, see above).
- Other substances that are co-transported with sodium on the apical membranes include: galactose, mannose, amino acids, lactate, iodide, bile acids and some short chain fatty acids).

**Chloride:**
- **Absorbed** passively with sodium and possibly actively in exchange to bicarbonate.
- **Secreted** to the intestinal lumen through chloride channels.
- Enters enterocytes from ISF by (Na-K-2Cl) co transporters on the basolateral membranes.
- Part of the cholera toxin enters enterocytes & increases cAMP. This results in activation of the chloride channels through a protein kinase.
- The activation causes severe watery diarrhea because it increases chloride secretion, decreases NaCl absorption and increases water loss.

**Potassium:**
- **Secreted** into the intestinal lumen by diffusion or active secretion.
- Aldosterone increases K⁺ secretion in the colon (by increasing Na⁺-K⁺ ATPase pump activity in the basolateral membranes of intestinal cells).
- In the distal colon some K⁺ is **absorbed** back by H⁺-K⁺ ATPase pump in the luminal membrane.
- Chronic diarrhea decreases this absorption resulting in loss of K⁺ (= hypokalemia = paralytic ileus).
- See iron absorption in volume 1 & calcium absorption below in the endocrine system.
<table>
<thead>
<tr>
<th>QUESTIONS FOR SELF ASSESSMENT-2 (MCQS)</th>
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<tbody>
<tr>
<td><strong>1-</strong> Facilitated diffusion is used for absorption of:</td>
</tr>
<tr>
<td>a- Glucose</td>
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<td>b- Galactose</td>
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<td>c- Fructose</td>
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<td>d- Pentose</td>
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<td>e- Lactose</td>
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<td><strong>2-</strong> The hormone secretin:</td>
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<td>a- Is stimulated by acid in the duodenum</td>
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<td>b- Is produced by the pancreas</td>
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<td>c- Stimulates contraction of the gall bladder</td>
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<td>d- Stimulates secretion of pancreatic enzymes</td>
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<td>e- Stimulates gastric emptying</td>
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<td><strong>3-</strong> The large intestine differs from the small intestine because:</td>
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<tr>
<td>a- It is a site for absorption of water and electrolytes</td>
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<td>b- It moves its food contents by peristalsis</td>
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<td>c- It has lower number of goblet cells</td>
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<td>d- Its longitudinal muscle layer is incomplete</td>
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<td>e- It is not supplied by the vagus nerve</td>
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<td><strong>4-</strong> When compared with bile in the common hepatic duct, bile in the gall bladder contains lower concentration of:</td>
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<tr>
<td>a- Bile salts</td>
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<td>b- Bile pigments</td>
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<td>c- Sodium ions</td>
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<td>d- Hydrogen ions</td>
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<td>e- Cholesterol</td>
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<td><strong>5-</strong> Long chain fatty acids, after being processed within mucosal cells of the intestine, are:</td>
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<td>a- Extruded back to intestinal lumen</td>
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<td>b- Released directly into portal circulation</td>
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<td>c- Released to lymphatics in form of chylomicrons</td>
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<td>d- Stored within the cells</td>
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<td>e- Catabolised immediately for release of energy</td>
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<td><strong>6-</strong> Paralytic ileus is:</td>
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<td>a- Caused by hypokalemia</td>
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<td>b- Characterized by excessive peristalsis</td>
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<td>c- Improved following discharge of noradrenaline</td>
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<td>d- Often painful</td>
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<td>e- Best treated by surgical operation</td>
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<td><strong>7-</strong> Peristaltic contractions</td>
</tr>
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<td>a- Are propulsive movements</td>
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<td>b- Depend on extrinsic innervation</td>
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<td>c- Occur in the absence of the myenteric plexus</td>
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<td>d- In the small intestine are abolished by vagotomy</td>
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<td>e- Are increased by sympathetic stimulation</td>
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</table>
8- **Control of bile secretion depends on:**
   a- Vagal stimulation especially during the intestinal phase
   b- CCK which relaxes the gall bladder to receive bile
   c- Enterohepatic circulation of bile acids
   d- High rate of bile acid formation in the liver
   e- Secretin which causes contraction of the gall bladder

9- **Digestion of lipids:**
   a- Occurs mainly in the large intestine
   b- Requires bile pigment
   c- Must be preceded by emulsification
   d- Requires a lipid soluble enzyme
   e- Is impaired in absence of both gastric and lingual lipase

10- **Defecation:**
   a- Is exclusively an involuntary reflex
   b- Is initiated by distension of the rectum
   c- Is mediated via sympathetic neurons
   d- Stops permanently after spinal cord transaction at L2
   e- Usually occurs when rectal pressure reaches 55 mmHg

11- **Removal of the terminal ileum results in:**
   a- Decreased glucose absorption in large intestine
   b- Increased fat absorption in small intestine
   c- Decreased hepatic formation of bile acids
   d- Increased water content of feces
   e- Prolonged constipation

12- **Bile:**
   a- Is secreted by the gall bladder
   b- Contains lipase for digestion of lipids
   c- Is acidic due to bile acids
   d- Release is stimulated by CCK
   e- Becomes diluted in the gall bladder

13- **Concerning pancreatitis, which of the following findings is correct?**
   a- Diarrhoea with high concentration of amylase in stool
   b- Constipation with low concentration of lipase in intestinal lumen
   c- Steatorrhoea with high concentration of amylase in serum
   d- Low concentrations of both amylase in lipase in serum
   e- High concentrations of both amylase in lipase in intestinal lumen

14- **Bile salts:**
   a- Are synthesized from fatty acids
   b- Are absorbed in the duodenum
   c- Increases surface tension of intestinal fluid
   d- Increases surface area of fat droplets
   e- Are totally absorbed to the enterohepatic circulation

15- **The gastro-colic reflex:**
   a- Is a neural reflex
b- Causes relaxation of the external anal sphincter
c- Usually follows a mass action contraction of large intestine
d- Occurs after release of gastric contents in the duodenum
e- Is more common in neonates than adults

16- The following enzyme is essential for protein digestion:
   a- Alpha amylase
   b- Lingual lipase
   c- Pepsin
   d- Trypsin
   e- Alkaline phosphatase

17- Water and electrolyte in the GI tract are:
   a- Derived mainly from ingested fluids
   b- Absorbed mainly in the large intestine
   c- Equilibrated with GI secretions at the stomach
   d- Absorbed mainly in the jejunum
   e- Absorbed in response to activity of GI hormones

18- The following vitamin is absorbed primarily by diffusion:
   a- Vitamin C
   b- Folic acid
   c- Vitamin D
   d- Vitamin B12
   e- Niacin

19- Pancreatic secretion rich in bicarbonate is released in response to:
   a- CCK
   b- Vagal stimulation
   c- Glucagon
   d- Gastrin
   e- Secretin

20- Which of the following is directly activated by trypsin:
   a- Enterokinase
   b- Co-lipase
   c- Pepsinogen
   d- Pancreatic lipase
   e- Alpha amylase

21- Bile salts are
   a- Synthesized from hemoglobin
   b- Absorbed in terminal ileum
   c- Form chylomicrons within the enterocytes
   d- Responsible for the color of stool
   50% are absorbed to the enterohepatic circulation

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CHAPTER (9)
THE RENAL SYSTEM

STRUCTURE & FUNCTION

- The renal system consists of the following structures:
  - 2 kidneys, 2 ureters, urinary bladder & urethra.

**Fig 9.1: The renal system**

- The kidneys are "bean shaped" retroperitoneal structures.
- They are located on each side of the vertebral column, approximately at the level of T12 to L3.
- In a normal adult, each kidney is about 10 cm long, 5.5 cm in width and about 3 cm thick, weighing 150 grams.
- The upper parts of the kidneys are partially protected by the eleventh and twelfth ribs, and each whole kidney is surrounded by two layers of fat.
- The right kidney sits just below the liver, the left below the diaphragm and adjacent to the spleen. Therefore, the right kidney is slightly lower than the left one.
The medial side of each kidney is concave. On the concavity there is an opening known as the renal hilum. This admits the renal artery, the renal vein, the renal nerves (mostly sympathetic) and the ureter.

- The outer portion of the kidney is called the renal cortex. This lies immediately beneath the renal capsule (fibrous tissue).

**Fig 9.2: The kidney**

- The renal medulla lies deep to the cortex. It is divided into about 10 conical structures known as the renal pyramids.
- Each pyramid together with the associated overlying cortex forms a renal lobe (supplied by an interlobar artery).
- The tip of each pyramid (called a papilla) empties into a minor calyx. Each minor calyx empties into a major calyx. The major calices empty into the renal pelvis. The pelvis transmits urine to the urinary bladder through the ureter.
Fig 9.3: The minor and major calices

RENAL BLOOD VESSELS
- From the abdominal aorta the blood supply to the kidney comes through and then drained by the following blood vessels (look at fig 9.4 & match the vessels with the numbers):
  1. Renal artery
  2. Interlobar arteries
  3. Arcuate arteries
  4. Interlobular arteries
  5. Afferent arteriole
  6. Glomerular capillaries
  7. Efferent arteriole
  8. Peritubular capillaries
  9. Interlobular veins
 10. Arcuate veins
 11. Interlobar veins
 12. Renal vein

Remember that: Peritubular capillaries in the Juxtamedullary nephrons (see below) form U shaped capillaries known as vasa recta. These long and straight capillaries play an important role in concentration of urine.
RENAL BLOOD FLOW (RBF)

= 1.2 L/min. This is about 20-25% of the cardiac output.
- It is directed mainly to the cortex (90% to the cortex and only 10% to the medulla).
- This low blood flow to the medulla maintains its high osmolarity.
- The renal blood flow is autoregulated (i.e. it is maintained constant in spite of the changes in mean arterial pressure between 80-180 mmHg).
- This autoregulation is explained by:
  • Myogenic response (response from smooth muscle in walls of renal blood vessels)
  • Humoral factors (factors mixed with blood like NO & Angiotensin 2)
- The RBF is also regulated by the following neural & hormonal factors:
  o Sympathetic stimulation: decreases RBF by constricting afferent arterioles.
  o Catecholamines: decrease RBF by constricting afferent arterioles.
  o Dopamine: increases RBF by causing vasodilatation.
  o Angiotensin II: decreases RBF by constricting mainly the efferent arterioles.
  o ADH (Vasopressin): decreases RBF by causing vasoconstriction.
  o Prostaglandins: some of these local hormones are vasodilators (PGI₂, PGE₂) & others are vasoconstrictors (thromboxane A₂).

Therefore, chronic use of aspirin, which inhibits prostaglandin synthesis, affects renal blood flow & renal function.

- The renal blood flow can be measured by:
  o Flow meter devices.
  o Fick principle (using clearance of para-aminohippuric acid (PAH), (see below).
FUNCTIONS OF THE KIDNEY

1. Excretion of waste products (e.g. urea, uric acid …)
2. Control of ECF volume (by excretion of more or less water in urine)
3. Control of ECF osmolarity (by regulation of sodium and water excretion)
4. Control of ECF electrolytes (by regulation of electrolyte excretion in urine)
5. Control of B.P. (long term effect / see control of blood pressure)
6. Control of pH (see acid base balance)
7. Endocrine function:
   - Synthesis and secretion of erythropoietin
   - Activation of vitamin D
   - Release of renin enzyme into the blood

THE NEPHRON

= The functional unit of the kidney.
- There are about 1.3 million nephrons in each human kidney. Each nephron is about 45-65 mm in length, consisting of a glomerulus and tubules.
- The Glomerulus is a tuft of capillaries enclosed within a Bowman’s capsule. It is supplied by an afferent arteriole and drained by an efferent arteriole. Its diameter is about 200µm and its function is filtration.
- The tubules are specialized for reabsorption and secretion.
- They include:
  - The proximal convoluted tubule (PCT)
  - The loop of Henle (LH)
  - The distal convoluted tubule (DCT)
  - The collecting ducts (CDs)
- All glomeruli are found in the cortex. Most of them are found higher up in the cortex whereas some of them are located in juxtaposition to the medulla. Accordingly there are two types of nephrons:
  
  o **Cortical nephrons:**
  
    - About 85% of all nephrons. Their glomeruli are found higher up in the cortex. They are characterized by short loops of Henle.
  
  o **Juxtamedullary nephrons:**
  
    - About 15% of all nephrons. Their glomeruli are located close to the medulla. They are characterized by very long loops of Henle. They play an important role in concentration of urine.

**Fig 9.5 The nephron**

- Fig 9.6 Types of nephrons
**Important points in histology of nephrons**
- The wall of glomerular capillaries consists of endothelial cells resting on a basement membrane and surrounded by epithelial cells of Bowman's capsule. These 3 layers (endothelium, basement membrane, and epithelium) form the filtration membrane through which plasma is filtered.  
- Each layer in the filtration membrane has a special characteristic:
  - The endothelial cells of glomerular capillaries are fenestrated. The fenestrations are 70-90 nm in diameter.
  - The basement membrane is negatively charged. This is due to presence of sialoproteins.
  - The epithelial cells of Bowman's capsule have foot processes that interdigitate with each other leaving slits between them. For this reason, they are called podocytes. The slits are about 25 nm in diameter.

**Fig 9.7 The filtration membrane**

- Cells of the proximal convoluted tubules are characterized by:
  - Microvilli on the luminal surface forming brush border
  - Large number of mitochondria to provide energy for active transport
  - Tight junctions at the apical side between the cells

- Cells of the thin limbs of the loops of Henle are:
  - Attenuated and flat cells.
- Cells of the thick limbs of the loops of Henle are characterized by:
  o Cuboid shape, with some invaginations on the basilar membrane
  o Large number of mitochondria to provide energy for transport
- Cells of the distal convoluted tubules are characterized by:
  o A few microvilli and mitochondria
- Cells of the collecting ducts are two types:
  o Principal cells (also known as “the collecting duct cells”)
    - Higher in number (= about 75% of all cells)
    - Contain receptors for the hormones: ADH, aldosterone, cortisol, PTH, calcitonin, catecholamines (β) and ANP (the papillary part of the collecting duct).
  o Intercalated cells
    - Less in number but contain more organelles
    - Play an important role in pH control (secrete H⁺ or HCO₃⁻ ions)

Remember that: Cells of the proximal convoluted tubules also contain receptors for: PTH, Angiotensin II and catecholamines (mainly α receptors).
- Some cells of the distal convoluted tubules, together with other cells, form the Juxtaglomerular apparatus.

**Fig 9.8 The Juxta-glomerular apparatus**
- These cells of the distal convoluted tubules are close to the afferent arteriole (they are called the macula densa cells).
- They form the Juxta-glomerular apparatus together with cells of the afferent arteriole "Juxta-glomerular cells" and “Lacis cells.”
- Lacis cells are mesangial cells lying outside the glomerulus. Their function is unknown.
- The apparatus secretes the enzyme renin in response to:
  - Hyponatremia
  - Renal ischemia (e.g. due to hypotension or hypovolemia)
  - Sympathetic stimulation.
- Renin converts angiotensinogen (a plasma protein produced by the liver) into angiotensin I (deca peptide).
- Angiotensin I is converted to angiotensin II (octa peptide) by the angiotensin converting enzyme (ACE) produced by endothelial cells in pulmonary capillaries.
- Angiotensin II plays an important role in control of ECF volume and blood pressure (causes vasoconstriction, stimulates the hormones ADH and aldosterone, stimulates thirst, activates the sympathetic and directly stimulates sodium reabsorption at the PCT).

**FORMATION OF URINE**
- Urine is formed by: (filtration) at the glomerulus & (reabsorption & secretion) by the tubules.

**glomerular filtration**
- It is the transport of fluid and crystalloid from glomerular capillaries to Bowman’s space.
- The filtrate is similar to plasma. However, it does not contain proteins. (i.e. filtrate = plasma – proteins).
The rate of glomerular filtration is known as the glomerular filtration rate (GFR). Normal GFR = 125 ml/min in an average adult male. It is less in females (by about 10%).

**CONTROL OF THE GFR**

\[ \text{GFR} = k_f ((\text{HP}_{GC} - \text{HP}_T) - (\text{OP}_{GC} - \text{OP}_T)) \]

Where:
- \( k_f \) = Glomerular filtration coefficient. Depends on permeability & effective surface area.
- \( \text{HP}_{GC} \) & \( \text{HP}_T \) = Hydrostatic pressure of glomerular capillaries and hydrostatic pressure of Bowman’s capsule respectively.
- \( \text{OP}_{GC} \) & \( \text{OP}_T \) = Oncotic pressure of glomerular capillaries & oncotic pressure of Bowman’s capsule respectively.

**From the above formula, the GFR is determined by these factors:**

1. **Hydrostatic pressure of glomerular capillaries (HP\(_{GC}\))**
   - For filtration
     - \( 45-60 \text{ mmHg} \) (higher than hydrostatic pressure of systemic capillaries which is about \( 15-35 \text{ mmHg} \)).
   - This is because:
     a. Glomerular capillaries are drained by arterioles not venules. (The arterioles have high hydrostatic pressures; whereas the venules have low pressures; therefore, the higher resistance in the arterioles elevates the \( \text{HP}_{GC} \)).
     b. Another explanation is the fact that renal blood vessels are short and straight. This ensures transmission of the high hydrostatic pressure from the abdominal aorta towards the glomerular capillaries.

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2- Oncotic Pressure of glomerular capillaries (OP_{GC})
   - It is the osmotic pressure of plasma proteins (mainly albumin).
   - Against filtration
   - = 20 - 25 mmHg at afferent arteriolar end. This increases to 35 mmHg at efferent arteriolar end (because proteins become highly concentrated after filtration of about one fifth of the plasma).

3- Hydrostatic pressure of Bowman's space (HP_T)
   - Against filtration. = 10 mmHg (increased in urinary tract obstruction).

4- Oncotic Pressure of Bowman's space (OP_T)
   - = Zero (because proteins are not filtered to the Bowman's space).

5- Permeability of the membrane
   - Allows free passage of particles < 4 nm in diameter
   - Prevents passage of particles > 8 nm in diameter
   - Between (4-8 nm) passage depends on:
     1. Electrical charge: (particles can not pass if negatively charged)
     2. Shape: (particles cannot pass if irregular in shape)

6- Surface area of the membrane (SA)
   - = 0.8 m² (for both kidneys)
   - Increases or decreases by contraction or relaxation of mesangial cells.
     - Contraction of mesangial cells by Angiotensin 2, endothelin, ADH, histamine, leukotrienes and catecholamine decreases the SA whereas their relaxation by ANP, cAMP and Dopamine increases the SA.

The filtration pressure can be measured as follows:
- At the end of glomerular capillaries near the afferent arteriole:
  Filtration pressure = HP_{GC} - (OP_{GC} + HP_T) = 45 - (25 + 10) = 10 mmHg
- At the end of glomerular capillaries near the efferent arteriole:
  Filtration pressure = 45 - (35 + 10) = 0, indicating that filtration occurs normally at the first part of glomerular capillaries.
The GFR is affected by:

Changes in $HP_{GC}$ by:
- Changes in blood pressure: The blood pressure does not affect the GFR unless the mean arterial pressure is above or below the autoregulation range (i.e. < 80 or > 180 mmHg).
- Afferent arteriolar constriction: Decreases the GFR (by decreasing the $HP_{GC}$).
- Efferent arteriolar constriction: May be mild constriction (Increases the GFR by increasing the $HP_{GC}$) or severe constriction (Decreases the $HP_{GC}$ & the GFR).

Changes in $OP_{GC}$ by:
- Hypoproteinemia: Increases the GFR (by decreasing the $OP_{GC}$).
- Dehydration: Decreases the GFR (by increasing the $OP_{GC}$).

Changes in $HP_T$ by:
- Edema of the kidney: Distention of the kidney within its tough capsule increases the hydrostatic pressure within the tubules and decreases GFR.
- Obstruction of the urinary tract: Decreases the GFR (by increasing the $HP_T$).
Changes in $O_{PT}$
- Glomerulonephritis: Results in filtration of proteins into the Bowman’s space (by causing loss of the negative charges in the basement membrane). This increases the GFR by increasing the $O_{PT}$.

Changes in permeability
- Glomerulonephritis: Increases the GFR.

Changes in surface area
- Removal of one kidney decreases the surface area and therefore the GFR.
- Contraction or relaxation of mesangial cells affects the GFR by decreasing or increasing the surface area respectively (read about factors affecting mesangial cells above).

Changes in renal blood flow
- The renal blood flow is normally autoregulated. However, when increased it increases the GFR and when decreased decreases the GFR.

The Tubuloglomerular feedback
- When the tubular flow rate increases at the distal part of the nephron, GFR decreases. The macula densa cells are the sensor for this feedback & the response is adjusted by constricting the afferent arteriole by a mediator (most probably ATP).
- On the other hand, when GFR increases, tubular reabsorption also increases (this is called “Glomerulotubular balance”).

MEASUREMENT OF THE GFR
- By measuring clearance of substances with the following characteristics:
  - Non toxic
  - Not metabolized, stored or produced by the kidney
- Freely filtered
- Not reabsorbed by the renal tubules
- Not secreted by the renal tubules

- Since the substance (X for example) is not reabsorbed or secreted by renal tubules:

  It’s Filtration = Excretion

  \[ \text{GFR} \times P_x = U_x \times V \]

  \[ \text{GFR} = \frac{U_x \times V}{P_x} \]

  This is the formula of clearance

\( P_x \) = plasma concentration of \( x \)

\( U_x \) = urine concentration of \( x \)

\( V \) = urine flow rate (or urine volume per unit time)

- Examples of substances used to measure the GFR:
  - Inulin: fructose polymer administered by intravenous (I.V.) infusion (see below)
  - Creatinine: produced from creatine kinase (phosphocreatine) in muscles (see below)
  - Iohexol: a contrast agent (known as omnipaque); used recently as alternative to inulin.
  - Radioisotopes: (e.g. \(^{51}\text{Cr- EDTA}\))

**CLEARANCE**

- Defined as the volume of plasma, which is completely cleared of a substance per unit time.

- Clearance of any substance is measured by the formula \( C_x = \frac{U_x \times V}{P_x} \)

- It can be used for:
  - Measurement of GFR (by inulin or creatinine clearance).
  - Measurement of renal blood flow (by PAH clearance).
  - Assessment of renal function
Measurement of GFR using inulin clearance:
1- Inulin is given by continuous intravenous (I.V.) infusion until its level in plasma becomes constant.
2- A blood sample is taken to measure its concentration in plasma ($P_x$).
3- Urine is collected for certain time (usually 24 hours) to measure urine flow rate ($V$) and a sample is taken to measure inulin concentration in urine ($U_x$).
4- The formula of clearance is applied to measure the GFR as follows: $GFR = \frac{U_xV}{P_x}$.

Remember that:
- Inulin is the ideal substance for measurement of the GFR because it is freely filtered, not reabsorbed or secreted. However, the method is time consuming, needs I.V. infusion of inulin and accurate collection of timed-urine samples.
- The classical method for measuring inulin clearance involves continuous I.V. infusion of inulin until its level in plasma becomes constant; however, an alternative method of administration (a single bolus dose) gives comparable results, especially in children.

Measurement of GFR using creatinine clearance:
1- Urine is collected for 24 hours to measure urine flow rate ($V$) and a urine sample is taken to measure creatinine concentration in urine ($U_x$).
2- A blood sample is taken to measure creatinine concentration in plasma ($P_x$).
3- The formula of clearance is applied to measure GFR ($= \frac{U_xV}{P_x}$).

Remember that:
- Creatinine does not need I.V. injection because it is produced endogenously from phosphocreatine in muscles. This advantage makes it more practical in measuring the GFR.
- The disadvantage of creatinine is its slight secretion by the proximal convoluted tubules. This tends to give higher value for GFR. However, the method used for measuring creatinine in plasma gives higher results. This corrects the error and gives almost true GFR results.

**Measurement of renal blood flow using PAH clearance:**

- Blood flow to organs is usually measured by the Fick principle.
- The principle states, “the amount of a substance consumed or added by an organ in a given time equals the arterio-venous difference in concentration times the blood flow to the organ.”
- In summary: \( Q = ([A] - [V]) \times \text{Blood flow} \) (where \( Q \) is the amount consumed & the \([A] - [V]\) is the arterio-venous difference in concentration).
- Therefore: \( \text{Blood flow} = Q / ([A] - [V]) \)
- Substances used in measurement of renal blood flow should be:
  - Non toxic
  - Not metabolized, stored or produced by the kidney
  - Do not affect RBF
  - Highly secreted to the extent that its concentration in renal veins = 0 (or, alternatively, the concentrations in renal artery and vein can be measured).
- The para aminohippuric acid (PAH) is an example of a substance that is highly secreted by renal tubules (secreted excessively by the PCT).
- The mechanism of secretion is an active mechanism (i.e. have an upper limit for secretion). That is why PAH concentration in renal vein = zero only when infused in small dose.
- When PAH concentration in renal vein is zero, this indicates that the entire amount consumed by the kidney (\( Q \)) is excreted in urine (i.e. \( Q = \text{Excretion} = U_{PAH} \times V \)).
- By applying Fick's principle (Blood flow = Q/[A] – [V]):
  \[ \text{Blood flow} = U_{PAH} \times V/[A] – \text{zero} \]
- Since PAH is measured in plasma, then the concentration in artery “[A]” is actually a concentration in plasma “\(P_{PAH}^{\text{plasma}}\)”; and the obtained measurement is plasma flow rather than blood flow.
- Therefore: Effective renal plasma flow = \(U_{PAH} \times V/\text{P}_{PAH}\) \(= \) Formula of clearance for PAH
- The obtained measurement is the effective renal plasma flow (ERPF= 625 ml/min) since not all renal plasma flow is filtered in the tubules. About 10% of the renal plasma flow (supplies the capsule and the fats around the kidney) is not included in the measurement.
- Therefore the total renal plasma flow (RPF) can be measured from the ERPF as follows: RPF= ERPF /90% or RPF= ERPF x 100/90= 700 ml/min
- Now the renal blood flow (RBF) can be calculated from the (RPF) as follows: RBF = RPF x 100/100-PCV.

**Filtration fraction**
- Filtration fraction = GFR/RPF = 125/700 = 0.16-0.2.
- This indicates that one fifth of plasma is filtered every minute
- The filtration fraction is used as an index for glomerular function.

**Clearance of other substances**
- **Glucose clearance:**
  - Equals zero as long as glucose is not excreted in urine (read below).
  - When glucose concentration in plasma exceeds a certain value (the renal threshold “180mg/dL”); the excess glucose starts to appear in urine (because it is not reabsorbed). Therefore, glucose clearance rises as glucose level in plasma is increased; until it approaches the value of inulin clearance.
**Fig 9.10: Comparison between inulin and glucose clearance**

![Graph comparing inulin and glucose clearance](image)

- **PAH clearance:**
  - Equals the renal plasma flow because PAH is highly secreted in the PCT. The mechanism of secretion is an active process (i.e. it has an upper limit of secretion at which all the carriers are saturated ($T_m^{PAH}$)); that is why it is absent in veins when given in a small dose, but it appears when given in larger doses. For this reason, PAH clearance decreases as its plasma concentration rises.
  - In very high plasma level, PAH clearance may reach inulin clearance.

**Fig 9.11: Comparison between inulin clearance and PAH clearance**

![Graph comparing inulin clearance and PAH clearance](image)
- **Free water clearance (C\textsubscript{water}) & osmolar clearance (C\textsubscript{OSM}):**
  - C\textsubscript{water} is the volume of plasma that is completely cleared of free water per unit time. It is the difference between urine volume and clearance of osmoles (C\textsubscript{water} = V – U\textsubscript{OSM} V/P\textsubscript{OSM}) where “V” is urine flow rate.
  - C\textsubscript{OSM} = the amount of water necessary to excrete the osmotic load in a urine that is isotonic with plasma.
  - Free water clearance can be used as an indicator of how water is regulated. A free water clearance of zero means the kidney is producing isotonic urine. Values greater than zero imply that the kidney is producing dilute urine (through excretion of solute-free water). Values less than zero imply that the kidney is conserving water.
  - For example, during maximum antidiuresis with excess ADH, C\textsubscript{water} = -1.9 L/d whereas during absence of ADH C\textsubscript{water} = 20.9 L/day.

**Notes to remember about clearance:**
- Clearance ranges between "0" for totally reabsorbed substances & "625 ml/min" for highly secreted ones. Clearance of of 125 ml/min indicates that a substance is neither absorbed, nor secreted (look at the following table).

**Table 9.1: Clearance of substances with different characteristics:**

<table>
<thead>
<tr>
<th>Characteristic of the substance</th>
<th>Clearance (ml/min)</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totally reabsorbed</td>
<td>0</td>
<td>Glucose</td>
</tr>
<tr>
<td>Not reabsorbed or secreted</td>
<td>125 = GFR</td>
<td>Inulin</td>
</tr>
<tr>
<td>Highly secreted</td>
<td>625 = renal plasma flow</td>
<td>PAH</td>
</tr>
<tr>
<td>Partially reabsorbed</td>
<td>less than 125 &amp; more than 0</td>
<td>Urea</td>
</tr>
<tr>
<td>Partially secreted</td>
<td>more than 125 and less than 625</td>
<td>Potassium</td>
</tr>
</tbody>
</table>
TUBULAR FUNCTION

- Generally, the renal tubules perform the following functions:
  o Reabsorption: Transport of a substance from the tubular lumen to the blood in peritubular capillaries through or between the tubular cells.
  o Secretion: Transport of a substance in the opposite direction (from the peritubular capillaries to the tubular lumen).
- By these 2 processes the filtrate is changed into urine.

Fig 9.12: Reabsorption and secretion

Note: Transport of solutes and water between the tubular cells (through the tight junctions) is known as "paracellular transport" whereas through the cells is known as "transcellular transport."

- The mechanisms of transport may be active or passive. They include:
  1. Simple diffusion (down chemical & electrical gradient; across ion channels; without use of carriers or consumption of energy).
  2. Facilitated diffusion (down chemical & electrical gradient; with use of carriers but without consumption of energy).
  3. Primary active transport (against chemical or electrical gradient; with use of carriers and consumption of energy).
4. Secondary active transport (involves indirect consumption of energy and uses one of two types of carriers: symport (for co-transport with another substance in the same direction) & antiport (for transport with another substance in the opposite direction)).

5. Endocytosis (active transport for small proteins and peptides in the PCT).
   - Here are examples for reabsorption and secretion of some important substances:

**WATER REABSORPTION**

- Volume of water filtered into the Bowman's capsule = 180 L/day.
- Volume of water excreted in urine normally = 1-1.5 L/day.
- In abnormal conditions urine volume may be as low as 0.5 L/day (e.g. due to ADH excess) or as high as 23 L/day (e.g. due to ADH deficiency).
- Most of the filtered water is reabsorbed passively by the renal tubules through special water channels (aquaporins) as follows:

**PCT**

- Reabsorbs 60-70% of filtered water.
- Water moves passively (following Na⁺ reabsorption) through “aquaporin-1 channels”.
- The filtered fluid remains isotonic.

**Loop of Henle**

- Reabsorbs about 15-20% of filtered water at the thin descending limb (through aquaporin-1 channels). The ascending limbs are
  - The thin descending limb reabsorbs water but not solute. The filtrate becomes hypertonic.
  - The thin ascending limb reabsorbs solute passively but not water. The filtrate starts to be diluted.
The thick ascending limb reabsorbs solute actively but not water. The filtrate becomes hypotonic; for this reason, the thick ascending limb is known as the diluting segment.

DCT
- Relatively impermeable to water.
- Reabsorbs 5% of filtered fluid.
- Solute is reabsorbed in excess of water. Therefore, the filtered fluid is further diluted (remains hypotonic).

CDs
- Water reabsorption is hormonally dependent according to the needs of the body.
- ADH stimulates reabsorption of about 7-13% of filtered water.
- It stimulates insertion of water protein channels (aquaporin II) to the luminal membrane to allow passive water reabsorption (water moves from the hypotonic fluid in the tubules to the cells and then to the hypertonic medulla).

Mechanism of ADH action:
- ADH binds to $V_2$ receptors on the basolateral membrane of principal cells
- This activates adenylate cyclase enzyme resulting in hydrolysis of ATP to cAMP
- cAMP activates protein kinase A
- The protein kinase A activates translocation of aquaporin-2 channels from intracellular vesicles to the apical membrane
- Water moves passively through the aquaporin-2 channels

- In presence of high level of ADH (Syndrome of inappropriate ADH secretion “SIADH”), urine becomes highly concentrated. Its volume is only about 0.5 L/day and its osmolarity may reach 1400 mosm/Kg.
- In absence of ADH (Diabetes Insipidus), large volume of diluted urine is excreted. Urine volume may reach 23 L/day and its osmolarity is only about 30 mosm/L.

- There are 2 types of diabetes insipidus (DI): Nephrogenic & neurogenic
  - Nephrogenic DI: due to a defect in either V₂ receptors or aquaporin-2 channels. This type does not respond to treatment with ADH agonist.
  - Neurogenic DI: due a defect in synthesis or release of ADH from the CNS. It responds to treatment with ADH agonist.

**Remember that:**

- In SIADH: Plasma is diluted whereas urine is highly concentrated.
- In DI: Plasma is concentrated whereas urine is highly diluted (in spite of dehydration).
- In addition to aquaporins 1 & 2; humans have aquaporin 5 & 9 in extra-renal tissues.

**Fig 9.13: Water reabsorption**
SODIUM REABSORPTION

- Filtered into the Bowman's capsule: \([Na] \times GFR = 26000\) mmol/day. Excreted in urine: \([Na] \times \text{urine volume per day} = 150\) mmol/day.
- Sodium excretion may be as low as 1 mmol/day or less (on a low salt diet) or as high as 400 mmol/day or more (on a high salt diet).
- Most of the filtered sodium is reabsorbed by the renal tubules as follows:
  - PCT: Reabsorbs 60-70% of the filtered Na⁺.
  - Reabsorption occurs actively by Na⁺ -K⁺ ATPase pump on the basolateral membrane.
  - The pump creates low sodium concentration in the tubular cells by taking 2 potassium ions to inside and extruding 3 sodium ions to the interstitium. This allows passive sodium diffusion through the luminal membrane down its chemical and electrical gradients. However, the overall process is active transport, not passive transport.
  - Water follows Na⁺ (Osmosis) to the interstitium; then from the interstitium or peritubular space, water and sodium enter capillaries by solvent drag.
  - Some substances are co-transported with Na⁺ (through the luminal membrane):  
    - Glucose
    - Amino acids
    - Phosphate
    - Organic acids (e.g. lactate)
    - Bicarbonate (unlike the above, through the basolateral membrane)
  - On the other hand, some substances are antiported with Na⁺:
    - H⁺ ions
    - Ammonium (NH₄⁺)
Loop of Henle
- Reabsorbs 20-25% of filtered Na⁺.
- The thin descending limb does not reabsorb sodium.
- The thin ascending limb reabsorbs sodium passively.
- The thick ascending limb reabsorbs sodium actively (by 1Na⁺, 1K⁺ & 2Cl⁻ co-transport pump on the luminal membrane).

DCT & CDs
- Na reabsorption is hormonally dependent according to the body needs.
- Mineralocorticoids (e.g. aldosterone) act on intracellular receptors in principal cells to stimulate Na⁺ reabsorption and K⁺ secretion.

Mechanism of aldosterone action:
- Aldosterone binds to cytoplasmic receptors.
- The receptor-hormone complex moves towards the nucleus where it stimulates transcription of mRNA, mRNA is translated into proteins.
- The proteins result in rapid effects (within 10-30 min) and later effects.
- The rapid effects include:
  - Activation of pre-existing epithelial sodium channels (ENaCs); thus increasing the permeability of the luminal membrane to sodium.
  - Activation of pre-existing Na⁺-K⁺ pumps; this decreases intra-cellular sodium to allow its entry from the lumen to the cells.
- The later effects include:
  - Increased number of ENaCs
  - Increased number of Na⁺-K⁺ pumps

Other hormones affecting sodium excretion:
- Atrial natriuretic peptide: decreases sodium reabsorption (acts in CDs).
- Glucocorticoids (e.g. cortisol): have mineralocorticoid effect (in CDs).
- Angiotensin II: causes sodium reabsorption (acts in PCT).
- Local factors (PGE₂, IL-1 & Endothelin): cause natriuresis.
Fig 9.14: Sodium reabsorption

Conditions associated with abnormal sodium excretion:

- **Primary & secondary hyperaldosteronism:**
  - Primary hyperaldosteronism (Conn’s syndrome) is due to adenoma in the adrenal cortex secreting excess aldosterone.
  - It is characterized by sodium retention, hypertension, & hypokalemia.
  - It is not characterized by edema. This is due to “aldosterone escape phenomenon” caused by secretion of ANP (read about aldosterone in the endocrine system).
  - Secondary hyperaldosteronism, on the other hand, is characterized by sodium retention and edema. It is associated with nephrotic syndrome, heart failure and liver cirrhosis.

- **Primary adrenal insufficiency (Addison’s disease):**
  - Due to destruction of adrenal cortex (by tuberculosis or auto antibodies).
- The resulting features (tiredness, hypoglycemia, hyponatremia, hypotension & hyperkalemia) are due to deficiency of both mineralocorticoids and glucocorticoids.

- **Bartter’s syndrome**
  - Occurs due to congenital defect in NaCl reabsorption in the thick ascending limb of the loop of Henle. The resulting loss of sodium chloride in urine causes hypovolemia. Hypovolemia causes secondary stimulation of the renin-angiotensin-aldosterone system resulting in hypokalemia and metabolic alkalosis. (Remember that: there is no hypertension in spite of the high renin and aldosterone).

- **Liddle’s syndrome**
  - Occurs due to a gene mutation that causes prolonged action of the epithelial sodium channels (ENaCs). This causes sodium retention and hypertension associated with excessive loss of potassium. The most important feature is the low level of renin and aldosterone in plasma (i.e. hypertension with low renin and aldosterone).

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**POTASSIUM HANDLING**

- Filtered into the Bowman's capsule= ([K⁺] in plasma x GFR) = 600 mmol/day. Excreted in urine= ([K⁺] in urine x urine volume per day) = 90 mmol/day. However, the amount excreted varies according to the intake (input = output). Potassium is reabsorbed & secreted in the renal tubules as follows:
  - **PCT**
    - Reabsorbs 60-70% (by an active mechanism).
  - **Loop of Henle**
    - Reabsorbs about 20% actively in the thick ascending limb by the (1Na⁺, 1K⁺ & 2Cl⁻ co-transporters).
DCT & CDs

- Here there is potassium secretion by the principal cells “the collecting duct cells.” Secretion of $K^+$ is hormonally dependent (depends on aldosterone). Aldosterone stimulates $Na^+$ reabsorption and $K^+$ secretion.

Mechanism of $K^+$ secretion:

- Potassium is secreted down its electrochemical gradient from the principal cells to the tubular lumen (through the apical membranes).
- The chemical gradient is created actively by the “$Na^+-K^+$ ATPase pumps” on the basolateral membranes which increase potassium concentration inside the cells (activated by aldosterone).
- The electrical gradient occurs because the tubular lumen is negative compared with the cells (Note: the negativity inside the cells is decreased by $Na^+$ reabsorption; that is why $Na^+$ reabsorption facilitates $K^+$ secretion (= an electrical coupling)).

Fig 9.15: Potassium reabsorption and secretion

Factors affecting $K^+$ secretion:

- Dietary $K^+$
- Secretion is increased by high $K^+$ intake & decreased by low intake.
- This is due to alterations in plasma level of potassium.
  o Plasma K⁺
  - Secretion is increased in hyperkalemia & decreased in hypokalemia.
  - This is explained by the direct effect of potassium on aldosterone secretion. It is also explained by direct effects of potassium ions on the secretory cells in the kidney.
    o Aldosterone
      - Secretion is increased by aldosterone.
      - This is explained by the effect of aldosterone on the principal cells.
    o Tubular flow rate
      - Secretion is increased when the tubular flow rate is increased.
      - This is because the rapid flow of tubular fluid maintains low potassium concentration in the lumen (i.e. maintains the chemical gradient for K⁺ secretion).
    o Sodium concentration in the tubular fluid
      - High sodium concentration [Na⁺] in the tubular fluid increases potassium secretion. This can be explained by the high tubular flow rate when [Na⁺] is high and by the facilitation of K⁺ secretion by Na⁺ reabsorption (read mechanism of K secretion).
    o pH
      - Secretion is increased in alkalosis and decreased in acidosis.
      - This is explained by the competition between H⁺ & K⁺ for exchange with sodium in the tubular fluid. In acidosis H⁺ is secreted more than potassium & in alkalosis K⁺ is secreted more than H⁺.
  o Diuretics
    - Most types of diuretics increase potassium secretion (read about diuretics below). This occurs either directly (by inhibiting the 1Na⁺, 1K⁺ & 2Cl⁻ pump) or indirectly (by increasing the tubular flow rate).
GLUCOSE REABSORPTION

- The amount filtered depends on the concentration of glucose in plasma (filtered load = [glucose] in plasma x GFR).
- The amount reabsorbed has an upper limit.
- This limit is never reached normally; however, when glucose level is very high, the limit is exceeded and glucose appears in urine.
- Reabsorption occurs almost totally in the PCT by:
  - Secondary active transport on the luminal membrane (Co-transport with Na⁺ to allow entry of glucose into PCT cells)
  - Then glucose enters the interstitium by facilitated diffusion on the basolateral membrane.
- The carriers for the co-transport are: Sodium- Glucose transporters 2 (SGLT 2)
- The carriers for facilitated diffusion: Glucose transporters 2 (GLUT 2).

Fig 9.16: Glucose transporters
Remember that:
- Glucose transporters are also found in the intestine.
- In rats, SGLT-1 & GLUT-1 are also found in the terminal portions of the PCT.
- Among the 7 types of glucose transporters in humans (from 1 to 7), only GLUT-4 responds to insulin and allow entry of glucose in insulin sensitive cells (e.g. muscle and fat cells).
- The transport of glucose can be inhibited by phlorhizin (a plant sugar that competes with glucose for the transporters).

**The tubular transport maximum for glucose (Tm\textsubscript{G})**
- Tm\textsubscript{G} is the maximum rate of glucose that can be transported by carriers in the PCT per unit time.
  \[= 375 \text{ mg/min in males or } =300 \text{ mg/min in females.}\]
- This value is never reached when glucose concentration is normal.
- For example, the normal glucose level in plasma = 80 mg/dL and its rate of transport at the PCT = GFR x [glucose]; = 125 ml/min x 80 mg/100ml; = 125 ml/min x 0.80 mg/ml; = 100 mg/min (i.e. less than T max for glucose).

**Calculation of Tmax for glucose**
- The T max can be calculated by subtracting the excretion from the filtered load. \[\text{Tmax} = \text{Filtered load} - \text{Excretion}\]

**Example:**
Calculate Tmax for glucose in a patient whose GFR= 125 ml/min, [glucose] in plasma= 360mg/dL, urine flow rate= 1ml/min and [glucose] in urine= 50 mg/ml

**Answer:**
\[\text{Tmax} = (360 \text{ mg/100 ml} \times 125 \text{ ml/min}) - (1 \text{ ml/min} \times 50 \text{ mg/ml})\]
\[= 450 \text{ mg/min} - 50 \text{ mg/min} = 400 \text{ mg/min}\]
The renal threshold for glucose
- The level of glucose in the plasma at which all glucose carriers in the PCT are saturated (= 180 mg/dL in veins or 200 mg/dL in arteries).
- At this level the filtered load of glucose is equivalent to the TmG (the upper limit of transport) and above this level glucose appears in urine.
- However, when calculating the actual level of glucose in plasma, which gives a filtered load that equals the TmG, it is found to be higher than 180 mg/dL:
  \[
  \text{Filtered load} = \text{GFR} \times \text{Plasma concentration}
  \]
  \[
  \text{Plasma concentration} = \frac{\text{Filtered load (or } TmG \text{ at this case)}}{\text{GFR}}
  \]
  \[
  \text{Plasma concentration} = \frac{375 \text{ mg/min}}{125 \text{ ml/min}} = 3 \text{ mg/ml} = 300 \text{ mg/dL}
  \]
- The difference between the calculated renal threshold & the true one is related to the avidity with which the glucose transporters bind glucose (some nephrons reabsorb small amount of glucose whereas others can reabsorb large amount. Tmax represents the average reabsorptive capacity of all nephrons).

TUBULAR SECRETION
- Certain substances are lost from the body by secretion in the renal tubules (leaves the blood to enter the lumen through the tubular cells in the kidney).
- Examples include:
  - Potassium
  - Hydrogen
  - Ammonia
  - Phosphate
- Uric acid
- PAH
- Creatinine
- Penicillin
- 5-hydroxyindolacetic acid
- Sulfonphthalein dyes

**DIURETICS**
- Include chemical substances and drugs that block sodium (and therefore water) reabsorption to increase urine volume.
- Types include:
  - **Loop diuretics:**
    - Inhibit the (1Na⁺, 1K⁺ & 2Cl⁻ co-transporters) in the thick ascending limb of the loop of Henle. Example: Frusemide “Lasix”.
  - **Thiazide diuretics:**
    - Inhibit sodium reabsorption at the early portion of the DCT (inhibit the Na⁺/Cl⁻ co-transporter at this site". Example: Chlorothiazide.
  - **Potassium sparing diuretics:**
    - Antagonize the action of aldosterone (e.g. spironolactone); or inhibit the ENaCs (e.g. amiloride).
  - **Carbonic anhydrase inhibitors:**
    - Inhibit carbonic anhydrase enzyme. This decreases bicarbonate formation and reabsorption and therefore decreases sodium reabsorption and hydrogen secretion. Example: Acetazolamide “Diamox”.
  - **Osmotic diuretics:**
    - Un-reabsorbed substances in the renal tubules exert an osmotic effect to trap water. This decreases Na⁺ concentration in the filtrate and thus
decreases its reabsorption. Examples: Manitol, excess glucose and excess urea.

- **Other diuretics:**
  - Water: excess water expands plasma volume & decreases osmolarity; therefore inhibits ADH causing water diuresis.
  - Alcohol (e.g. ethanol): inhibits ADH.
  - Caffeine: increases GFR & decreases sodium reabsorption.
  - Acidifying salts (Calcium chloride “CaCl₂” & Ammonium chloride “NH₄Cl”): Acidify ECF and urine. The anion (Cl⁻) binds Na⁺ in urine preventing its Reabsorption. This causes mild diuresis. They are used to promote excretion of ionizable drugs & poisons.

### CONCENTRATION OF URINE

- Depends on the action of ADH, which is responsible for the final adjustment of urine volume and osmolarity at the collecting ducts.
- At the absence of ADH: about 87% of filtered water is reabsorbed but urine volume is still high (about 23 L/day) and its osmolarity is very low (about 30 mosm/L).
- At the presence of excess ADH: urine volume is very low (about 0.5 L/day) and its osmolarity is very high (may reach 1400 mosm/day).
- As mentioned above, the filtrate, which reaches the collecting ducts, is hypotonic. At the absence of ADH, the filtrate is excreted as hypotonic whereas at its presence, the filtrate is concentrated by osmosis (movement of water from area of lower concentration to area of higher concentration). This means that the action of ADH depends on presence of hypertonic medulla.
- There is a gradient of increasing osmolarity along the medullary pyramids (starting from 300 mosm/L at the cortex to 1400 mosm/L at the deepest
parts of the medulla in humans; or even more than 2000 mosm/L in some animals).

- Hypertonicity in the medulla is created and maintained by many factors; without these factors, urine can never be concentrated. In summary: Together with ADH, these factors are responsible for excretion of concentrated urine.

- The factors include:

1- **The counter current system**

- Counter current transfer is the passive transfer of a substance from a fluid to another through a semi permeable membrane. It occurs when an inflow of fluid runs parallel to, counter to and in close proximity to an outflow.

- It is found at many sites in the body:
  
  o **The legs**
  - Between arteries and veins; to control core body temperature in cold weather.
  - Heat is transferred from the descending arteries to the ascending veins; to keep the body warm and the feet cold.

  o **The testes**
  - Between arteries and veins in the pampiniform plexus; to supply the testes with high amount of testosterone & to conserve the low temperature at the scrotum.
  - Testosterone, which is synthesized within the testes, diffuses from the draining veins to the supplying arteries.

  o **The kidney**
  - Here the counter current system plays an important role in concentration of urine.
  - The counter current system is found at two sites:
a- The loop of Henle (the counter current multiplier): Creates hypertonicity
b- The vasa recta (the counter current exchanger): Maintains hypertonicity

**a- The loop of Henle (the counter current multiplier):**
- The counter current system is formed by the descending and the ascending limbs of the loop of Henle.
- The thin descending limb is permeable to water not to solute.
- The thin ascending & the thick ascending limbs are not permeable to water. However, they multiply solutes in the medulla (passively and actively).
- Therefore they create hypertonicity of the medulla.

**Fig 9.17: The counter current multiplier**
b- The vasa recta (the counter current exchanger):
- The counter current system is formed by the descending and the ascending limbs of the vasa recta.
- The descending limb allows passive influx of solutes and efflux of water.
- The ascending limb (which is fenestrated) allows passive efflux of solutes and influx of water.
- By this exchange, water is diverted a way from the deepest parts of the medulla (so as not to wash out the solutes); whereas the solutes recycle between the interstitium of the medulla and the vasa recta (to maintain hypertonicity).

**Fig 9.18: The counter current exchanger**

2- The low blood flow to the medulla
- The medulla receives only 10% of the whole renal blood flow.
- This is important to maintain hypertonicity of the medulla because the high blood flow may wash out the solutes.
3- Urea recycling between the medulla and the tubules
- A high protein diet increases the ability of the kidney to concentrate urine for a limited time.
- That is because urea (an end product of protein metabolism) recycles between the tubules and the interstitium of the medulla for some time before complete excretion.
- About 50% of the filtered urea is reabsorbed in the PCT & about 10% is excreted in urine. The remaining 40% is reabsorbed in the collecting ducts (at the presence of ADH) to the interstitium of the medulla and then diffuses passively through the thin ascending limb of the loop of Henle into the tubular lumen to recycle again; part of this is excreted and the remainder is reabsorbed to repeat the circulation until all the amount is excreted. Therefore, urea circulation between the interstitium and the tubules increases hypertonicity of the medulla.

**Fig 9.19: Urea recycling between the interstitium & the tubules**
THE MICTURITION REFLEX

- It is a visceral reflex; integrated in the spinal cord and influenced by the higher centers. Components of the reflex are:

  a- Receptors
  - These are stretch receptors situated on the smooth muscle in the wall of the bladder. They are stimulated by stretch when urine volume reaches 400 ml (however, the first urge to void is felt at a volume of about 150 ml).
  - At lower volumes the receptors are not stimulated because the pressure inside the urinary bladder “intravesical pressure” is maintained constant by relaxation (or plasticity) of the wall of the bladder.
  - The relaxation increases the diameter and therefore decreases the intravesical pressure (according to the Laplace law: Pressure α 1/radius).

  b- Afferent
  - Sensory neurons in the parasympathetic nerves (pelvic nerves).

  c- Center
  - The center is found at the sacral segments (S₂, S₃ & S₄).

  d- Efferent
  - Motor neurons in the parasympathetic nerves (pelvic nerves).

  e- Effectors
  - The smooth muscle in the wall of the bladder “detrusor muscle” (which contracts) & the smooth muscle of the internal sphincter (which relaxes).

Remember that: Although the sympathetic supplies the detrusor muscle and the internal sphincter, it does not participate in the micturition reflex.
  - Relaxation of muscles of the pelvic floor facilitates micturition.
  - The reflex of micturition can be initiated even before complete filling of the bladder by contraction of the abdominal muscles voluntarily to raise the intra-abdominal pressure.
Effect of the higher centers:
- Descending tracts from the brain may facilitate or inhibit micturition.
- Facilitatory areas are found in the pons and posterior hypothalamus whereas an inhibitory area is found in the midbrain.
- Voluntary orders from the cerebral cortex acting on the external sphincter (skeletal muscle guarding the bladder neck) allow or inhibit micturition.
- In suitable conditions the subject relaxes the external sphincter voluntarily to allow micturition whereas in unsuitable conditions he contracts it to inhibit micturition.
- The voluntary orders from the higher centers leave the sacral segments to reach the external sphincter through the pudendal nerve ($S_2$, $S_3$ & $S_4$).

**Fig 9.20: The micturition reflex**

![Diagram of the micturition reflex](image_url)
Abnormalities of micturition:

- **Automatic bladder**
  - When the full bladder empties involuntarily (no voluntary control).
  - Occurs due to spinal cord damage above $S_2$ resulting in interruption of the descending tracts from the brain. This causes loss of the voluntary control.
  - The micturition reflex is intact (because all components are present). Therefore bladder filling is followed immediately (automatically) by reflex emptying.
  - Patients can be trained to induce micturition (before the automatic emptying) by scratching the inner aspect of the thigh. In these patients the afferent impulses irradiate in the whole sacral segments causing micturition (through a mass reflex).

- **Atonic bladder**
  - When the full bladder does not contract (atonic). This occurs due to damage to the parasympathetic nerves or the sacral segments.
  - The micturition reflex is lost. Therefore filling is not followed by emptying (no contraction in the bladder wall).
  - In this form of urine retention, the high pressure within the bladder may force some droplets of urine to pass out (a condition known as overflow incontinence).

- **Enuresis (or bed wetting)**
  - Most children remain dry at night by the age of three to five years. However, unintentional discharge of urine during sleep may occur in children who cannot keep the external sphincter closed during sleep (but the micturition reflex is intact).
The core of this may be unknown (primary enuresis) or may be associated with problems like diabetes mellitus, diabetes insipidus, epilepsy and urinary tract infection (secondary enuresis). Emotional stress was reported in some cases.
- Most affected children retain the ability to control the sphincter at older age.

### ABNORMALITIES ASSOCIATED WITH RENAL DISEASES

1. **Proteinuria (in glomerulonephritis & nephrotic syndrome)**
   - Loss of albumin in urine due to glomerular damage or loss of the negative charges in the glomerular basement membrane.

2. **Decreased GFR with increased urine volume (in renal failure)**
   - GFR is decreased due to loss of acting glomeruli whereas urine volume is increased due to defective reabsorption of salts; the salts cause osmotic diuresis.

3. **Loss of concentrating & diluting power of the kidney (in renal failure)**
   - Due to loss of functioning nephrons & loss of hypertonicity of the medulla that results from defective counter current multiplier and exchanger.

4. **Uremia (in renal failure)**
   - Rise in blood urea due to failure in its excretion. The high urea causes (nausea, vomiting, mental confusion, convulsions & coma).
   - It should be treated by dialysis (hemodialysis or peritoneal dialysis).

5. **Activation of the renin-angiotensin-aldosterone system (in renal failure)**
   - Renal is released due to renal ischemia or hyponatremia.

6. **Hypertension (in renal failure)**
   - Due to activation of the renin-angiotensin-aldosterone system.

7. **Hypocalcemia (in renal failure)**
   - Due to failure of the kidney to activate vitamin D.
- Hypocalcemia results in secondary stimulation of the parathyroid hormone (PTH) from the parathyroid gland.
- PTH causes abnormalities in bone (= renal osteodystrophy).

8- Anemia (in renal failure) or polycythemia (in renal tumors)
- Due to abnormal synthesis of erythropoietin hormone by the kidney.
- The anemia is "Normocytic normochromic anemia".

9- Acidosis (in renal failure)
- Due to failure of the kidney to secrete hydrogen ions, reabsorb bicarbonate and synthesize ammonia.

10- Hematuria (due to stones or tumors)
- Presence of blood in urine.

11- Pyuria (in urinary tract infections "U.T.I.")
- Presence of pus in urine.
- Diagnosed when there are 10 or more neutrophils, detected by high power field microscopy, in midstream urine.
ACID BASE BALANCE

Normal pH
- pH = - log [H] = 7.4 ± 0.05.
- [H+] = 40 nmol/L or 0.00004 mmol/L (in arterial blood).
- pH less than 7.35 = Acidosis & more than 7.45 = Alkalosis.
- pH above 7.7 or below 7.0 is incompatible with life

Sources of acid in the body
- The body produces large amount of H+ every day. Sources of H+ include:
  1- Carbon dioxide (Volatile acid)
     - From metabolism of fats, proteins & carbohydrates.
     - CO₂ produces about 12,500 mmol of H⁺/day.
  2- Fixed acids (H₂SO₄, H₃PO₄)
     - From metabolism of phospholipids and amino acids containing sulphur (methionine, cystine) or phosphorus (phosphoserine).
     - Produce 50-100 mmol of H⁺/day.
  3- Organic acids (acetoacetic acid, lactic acid,...)
     - From metabolism of fats & carbohydrates
     - Give Small amount of H⁺. However, in abnormal conditions (e.g. diabetic ketoacidosis & exercise) large amount of hydrogen ions are produced.
  4- Ingestion of acidifying salts (NH₄Cl, CaCl₂)
     - The anions of these salts react with water to give acids; thus adding small amount of acid to the body.
  5- Failure of diseased kidneys to excrete normal amount of acid
     - Renal failure is a known cause of acidosis.

Sources of alkali
1- Loss of gastric acid
- After vomiting or naso-gastric tube suction of gastric contents, parietal cells of the stomach increase secretion of HCL into the gastric lumen.
- For each H⁺ secreted to gastric lumen, HCO₃⁻ is secreted to the blood; that is why alkalosis follows loss of gastric acid.

2- Ingestion of alkali
- Ingestion of alkalinizing salts (e.g. sodium bicarbonate “NaHCO₃”).
- Ingestion of fruits (rich source of NaHCO₃ and KHCO₃).

CONTROL OF pH

- Control of ECF pH is important for:
  - Normal enzyme function
  - Normal neuronal function
- Mechanisms for control of pH include:
  - Buffers (act immediately for very rapid control)
  - The respiratory system (acts in seconds to minutes for less rapid control)
  - The renal system (acts in hours to days for long term control)

The buffers
- A buffer is defined as a chemical substance that has the ability to bind or release H⁺ in solution, thus keeping the pH of the solution relatively constant despite the addition of considerable quantities of acid or base.
- Or it can be defined as a chemical substance formed of weak acid & alkali, acts to resist changes in pH.

Examples of Buffers in body fluids
- In the blood
  - Bicarbonate
  - Proteins
  - Hemoglobin
- In the interstitium
  - Bicarbonate
- In the cells
  - Proteins
  - Phosphate
- In urine
  - Bicarbonate
  - Ammonia
  - Phosphate

**Henderson-Hasselbalch Equation (= the equation of buffers)**

\[
\text{pH} = \text{pK} + \log \frac{[\text{base}]}{[\text{acid}]}
\]

- This equation is obtained as follows:
  - From the general equation for a buffer system: \( \text{HA} = H^+ + A^- \) (Where HA is un-dissociated acid & A^- is any anion or base)
  - By the law of mass action:
    Equation constant = Concentration of products / reactants
    \( K = \frac{[H]}{[A]} \) (Where K is the equation constant)
  - By taking - log:
    - \( \log K = - \log [H] + \log [A] / [HA] \)
    - \( \log [H] = - \log K + \log [A] / [HA] \)
    - \( \text{pH} = \text{pK} + \log [\text{base}] / [\text{acid}] \)
  - From the equation, the most effective buffer is expected to have equal concentrations of base and acid.
  - This means that \( [A] / [HA] = 1 \)
  - Since log 1 = zero, the equation will be (pK = pH).
  - Therefore a buffer system is regarded to be effective when:
    - Its pK is near to pH.
    - Its concentration is high.
**Bicarbonate buffer**

- $\text{H}_2\text{CO}_3 = \text{H}^+ + \text{HCO}_3^-$
- From H-H equation: $\text{pH} = \text{pK} + \log \left[\text{HCO}_3^-\right] / \left[\text{H}_2\text{CO}_3\right]$
- $\text{pK} = 6.1$ & $\text{H}_2\text{CO}_3$ is found at equilibrium with $\text{CO}_2$
- Therefore: $\text{pH} = 6.1 + \log \left[\text{HCO}_3^-\right] / \left[\text{CO}_2\right]$
- The solubility of $\text{CO}_2 = 0.0301 \text{ mmol/L/mmHg}$
- Therefore: $\text{pH} = 6.1 + \log \left[\text{HCO}_3^-\right] / 0.03 \times \text{Pco}_2$

**Example:**

Calculate pH of a patient whose $\text{PaCO}_2 = 10 \text{ mmHg}$ and plasma $\left[\text{HCO}_3^-\right] = 12 \text{ mmol/L}$

**Answer:**

$\text{pH}= 6.1 + \log 12/ 0.03x10= 6.1 + \log 40= 6.1 + 1.6= 7.7$

---

**Remember that:** $\text{pK}$ of bicarbonate $= 6.1$ (not near to pH). In spite of this, the bicarbonate buffer is an important buffer in ECF because:

1. Concentration in plasma is high.
2. The acid "$\text{CO}_2$" can be controlled by respiration & the base "$\text{HCO}_3^-$" can be controlled by the kidney.
3. CO2 produced daily by metabolism is not buffered by "$\text{HCO}_3^-\$". It diffuses inside RBCs where it reacts to give $\text{H}^+$ that is buffered by Hb.

- The bicarbonate buffer acts by shifting this reaction ($\text{H}_2\text{CO}_3 = \text{H}^+ + \text{HCO}_3^-$) to the right or left; e.g. addition of acid ($\text{H}^+$) causes left shift with formation of $\text{H}_2\text{CO}_3$ and this gives $\text{H}_2\text{O} + \text{CO}_2$; then $\text{CO}_2$ is excreted by the lung to keep pH constant.
- On the other hand, addition of alkali ($\text{HCO}_3^-$) causes consumption of ($\text{H}^+$), this causes right shift with dissociation of $\text{H}_2\text{CO}_3$ to more $\text{H}^+$ & $\text{HCO}_3^-$. The $\text{HCO}_3^-$ is excreted in urine by the kidney to keep pH constant.
**Protein buffer**
- Proteins have two dissociated groups that act as buffers:
  - Carboxyl group (RCOOH = RCOO⁻ + H⁺)
  - Amino group (RNH₃ = RNH₂ + H⁺)
- But these contribute little to the buffering capacity in the blood.

**Hemoglobin buffer**
- In addition to the two ionizable groups in its protein part “globin,” hemoglobin has another ionizable group (imidazole group) that is found in the amino acid histidine.
- There are 38 residues of histidine in each molecule of Hb. In addition, concentration of Hb is high. That is why Hb has 6 times the buffering capacity of proteins.

**Remember about the Hb buffer:** Deoxyhemoglobin as a buffer is better than oxyhemoglobin. That is because the imidazole group in deoxyHb dissociates less than in oxyHb; making deoxyHb a weaker acid & therefore a better buffer.

**Phosphate buffer**
- Dihydrophosphate is a weak acid that dissociates as follows:
  \[ \text{H}_2\text{PO}_4^- = \text{H}^+ + \text{HPO}_4^{2-} \]
- The buffer equation for dihydrophosphate is as follows:
  \[ \text{pH} = \text{pK} + \log \left( \frac{[\text{HPO}_4^{2-}]}{[\text{H}_2\text{PO}_4^-]} \right) \]
- pK = 6.8
- It is more important in ICF than ECF (because its concentration is higher in ICF).
- It is also important in urine where it buffers hydrogen ions secreted excessively in cases of acidosis.
**The respiratory system**
- Acts within seconds to minutes.
- There are 2 types of chemoreceptors:
  - Peripheral: Stimulated by low \( \text{Po}_2 \), high \( \text{P} \text{co}_2 \) & low pH (in plasma)
  - Central: Stimulated by high \( \text{Pco}_2 \) & low pH (in CSF)
- Stimulation of the chemoreceptors (e.g. by the low pH) results in stimulation of the respiratory center which causes hyperventilation. This results in washout of \( \text{CO}_2 \) and correction of the low pH.
- On the other hand, high pH decreases stimulation of the chemoreceptors and this eventually causes hypoventilation resulting in accumulation of \( \text{CO}_2 \) and correction of the high pH.

**The renal system**
- The kidney participates in acid base balance by:
  1. Reabsorption of \( \text{HCO}_3^- \)
  2. Synthesis of new \( \text{HCO}_3^- \)
  3. Secretion of \( \text{H}^+ \)

1. **Reabsorption of \( \text{HCO}_3^- \)**
   - Filtered \( \text{HCO}_3^- \) reacts with secreted \( \text{H}^+ \) at the brush border of the PCT as follows: \( \text{HCO}_3^- + \text{H}^+ \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}_2\text{O} + \text{CO}_2 \)
   - Then \( \text{CO}_2 \) diffuses inside PCT cells.
   - This reversible reaction between water and carbon dioxide proceeds at the presence of carbonic anhydrase enzyme.
   - In addition to the kidney, carbonic anhydrase enzyme is also found in RBCs, saliva, parietal cells, lung, pancreas and other sites.
   - Inhibition of this enzyme by certain drugs like sulphonamides (e.g. acetazolamide) has a mild diuretic effect.
- Inside the PCT cells:
  \[ \text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^- \]
  - \( \text{H}^+ \) is secreted to the lumen (antiported with Na\(^+\)).
  - \( \text{HCO}_3^- \) enters the interstitium (co-transported with Na\(^+\)).
  - At the collecting ducts, \( \text{HCO}_3^- \) is exchanged with Cl\(^-\) through the basolateral membrane.

**Remember that:** reabsorption of \( \text{HCO}_3^- \) is almost 100% when the pH of urine is < 6.5

**Fig 9.21: Reabsorption of \( \text{HCO}_3^- \)**

2- **Synthesis of new \( \text{HCO}_3^- \)**
- Inside PCT cells, bicarbonate is formed from the reaction between \( \text{CO}_2 \) & water (here \( \text{CO}_2 \) is produced by metabolism within the cells). Bicarbonate is also formed from the amino acid glutamine during ammonia formation:
  \[
  \text{Glutamine} + \text{water} \xrightarrow{\text{glutaminase}} \text{alpha ketoglutaric acid} + \text{NH}_3 \xrightarrow{\text{decarboxylation}} \text{HCO}_3^- 
  \]
Remember that:
- Ammonia is an important buffer in urine. It is formed in the kidney (PCT) from the amino acid glutamine, which is synthesized in the liver. It is also formed by de-amination of glutamic acid & other amino acids.
- It is converted to ammonium ion (NH₄⁺) and excreted as ammonium chloride (NH₄Cl) in urine.

3- Secretion of hydrogen
- In the PCT, hydrogen secretion occurs by the following mechanisms:
  a- Antiported with Na⁺
  b- H⁺ - ATPase pump (less important)
- In the collecting ducts (intercalated cells) hydrogen secretion occurs by:
  a- H⁺ ATPase pump
  b- Antiported with K⁺
- Cells cannot secrete hydrogen ions if pH of urine < 4.5 (the limiting pH).
- Therefore, there are buffers in urine that prevent decrease of urine pH to less than 4.5; these include:
  o Phosphate buffer (HPO₄²⁻ + H⁺ ↔ H₂PO₄⁻)___________pK = 6.8
  o Ammonia (NH₃ + H⁺ ↔ NH₄⁺)___________________pK = 9.0
- Acid buffered by phosphate in urine is known as “titratable acid (TA)”.
- TA is defined as the amount of NaOH that must be added to urine to raise its pH back to that of plasma.
- Net acid excretion per day equals (TA - NH₄⁺ - HCO₃⁻) x urine flow rate

ACID BASE DISTURBANCES
- Low pH (acidosis) is caused by:
  o High CO₂ (Due to a respiratory problem)
  o Low HCO₃⁻ (Due to a metabolic cause)
- High pH (alkalosis) is caused by:
  o Low CO₂ (Due to a respiratory problem)
  o High HCO₃⁻ (Due to a metabolic problem)
- Therefore there are 4 types of acid base disturbances:
  a- Metabolic acidosis (due to low HCO₃⁻)
  b- Metabolic alkalosis (due to high HCO₃⁻)
  c- Respiratory acidosis (due to high CO₂)
  d- Respiratory alkalosis (due to low CO₂)
- Uncompensated versus compensated acid base disturbance
- On acute presentation, the acid base problem is usually uncompensated (i.e. the compensatory mechanisms are not fully activated).
- On chronic presentation (after a few days), the compensatory mechanisms are fully activated.
- Generally, respiratory acidosis and alkalosis require renal compensation whereas metabolic acidosis and alkalosis require both renal and respiratory compensation (unless the cause of the metabolic problem is renal failure).
- The renal compensation:
  ❖ As mentioned above, in acidosis there is increased:
  1- Reabsorption of bicarbonate
  2- Synthesis of new bicarbonate
  3- Secretion of hydrogen ions
  4- Synthesis of ammonia from glutamine & excretion of ammonium chloride in urine
  5- Lower ratio of HPO₄²⁻ to H₂ PO₄⁻ in urine (because the secreted hydrogen ions convert HPO₄²⁻ to H₂ PO₄⁻ thus increasing the H₂ PO₄⁻ and decreasing the ratio).
  ❖ In alkalosis, all the above compensatory mechanisms are inhibited.
- The respiratory compensation:
- As mentioned above, there is hyperventilation in acidosis (resulting in lower PCO$_2$) and hypoventilation in alkalosis (resulting in higher PCO$_2$).

1- Metabolic acidosis
- Causes:
  o Failure to excrete acids (renal failure)
  o Formation of high amounts of acids (diabetic ketoacidosis, lactic acidosis)
  o Loss of base (diarrhea)
- Characterized by:
  o Low pH & low bicarbonate
- Compensation:
  o Buffers
  o Respiratory system (hyperventilation)= low PCO$_2$
  o Renal system (see the renal compensation above)

2- Metabolic alkalosis
- Causes:
  o Loss of gastric acid: (vomiting or naso-gastric tube suction)
  o Ingestion of alkali
  o Diuretics
- Characterized by:
  o High pH & high bicarbonate
- Compensation:
  o Buffers
  o Respiratory system (hypoventilation)= high PCO$_2$
  o Renal system
3- **Respiratory acidosis**
- Causes:
  - Respiratory center depression by drugs or trauma
  - Paralysis of respiratory muscles
  - Diseases of the lung
- Characterized by:
  - Low pH & high PCO$_2$
- Compensation:
  - Buffers & renal system (the respiratory system is the cause)

4- **Respiratory alkalosis**
- Causes:
  - Hysteria (hyperventilation)
- Characterized by:
  - High pH & low PCO$_2$
- Compensation:
  - Buffers & renal system (the respiratory system is the cause)

**Fig 9.22: Compensation of acid base disturbances**
EVALUATION OF ACID BASE STATUS

[1] Measurement of the following in the plasma:
- pH
- PCO₂
- HCO₃⁻
- These give idea about the type of acid base disturbance and state of compensation.

- The anion gap is the difference between the sum of anions and cations in ECF.

\[
\text{Anion gap} = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-])
\]
- Note that Na & K = 95% of cations whereas Cl⁻ & HCO₃⁻ = 86% of anions.
- Therefore, the gap represents the unmeasured anions like phosphate, sulphate and organic acids (e.g. lactate and ketones).
- Normal value = 8-16 mmol/L (average= 12 mmol/L).
- The anion gap is used to differentiate between the causes of metabolic acidosis.
- When it is high, specific causes can be considered; and those, which cause normal or low anion gap, can be excluded.
- Causes of high anion gap:
  - Diabetic ketoacidosis "DKA"
  - Severe exercise (lactic acidosis)
  - Alcohol toxicity
  - Aspirin toxicity
- Causes of normal anion gap:
  - Carbonic anhydrase inhibition (acetazolamide)
  - Ingestion of ammonium chloride
- Diarrhoea (loss of bicarbonate)
- Renal loss of bicarbonate (renal tubular acidosis)

- Causes of low anion gap:
  - Rare but may occur when there is high positively charged
  proteins (e.g. in multiple myeloma).

[3] The base excess
- Refers to the amount of cid or base required to restore the pH of one liter
  of blood to normal at a PCO₂ of 40 mmHg.
- The base is positive "excess" in alkalosis and negative "deficit" in
  acidosis.
- Normal range from -2 to +2 meq/L.
- Examples:
  - A base excess of -10 meq/L indicates severe metabolic acidosis
  - A base excess of + 10 meq/L indicates severe metabolic
    alkalosis.
- The term and concept were first introduced by Astrup and Siggaard
  Andersen in 1958.
QUESTIONS FOR SELF ASSESSMENT-3 (MCQS)

1. Water reabsorption occurs primarily in the:
   a. Proximal convoluted tubules
   b. Thin ascending loop of Henle
   c. Thin descending loop of Henle
   d. Collecting ducts
   e. Distal convoluted tubules

2. The glomerular filtration rate is:
   a. Increased by sympathetic stimulation
   b. Higher in females than males
   c. Measured by PAH clearance
   d. Directly proportional to renal blood flow
   e. About 23 L/day in patients with diabetes insipidus

3. Oxygen consumption by the kidney:
   a. Is greater in the medulla than the cortex
   b. Is inversely proportional to renal blood flow
   c. Increases with afferent arteriolar constriction
   d. Reflects active transport of solutes
   e. Is controlled by ADH

4. Glucose transport across the luminal membrane in the PCT:
   a. Is insulin dependent
   b. Is antiported with hydrogen
   c. Depends on GLUT type 2
   d. Is decreased in diabetes mellitus
   e. Is co transported with sodium

5. A patient with high anion gap is likely to have high plasma concentration of:
   a. Sodium
   b. Chloride
   c. Potassium
   d. Bicarbonate
   e. Lactate

6. Use the following data to calculate Tmax for glucose:
   GFR= 125 ml/min
   Plasma glucose= 400 mg/dL
   Glucose excretion= 100 mg/min
   a. 300 mg/min
   b. 400 mg/min
   c. 500 mg/min
   d. 375 mg/min
   e. 275 mg/min

7. The plasma concentration at which a substance starts to appear in the urine is known as the:
   a. Excretion fraction
   b. Filtration fraction
c. Effective plasma flow
d. Transport maximum (Tmax)
e. Renal threshold

8. Most of hydrogen secreted in the PCT is buffered by:
   a. Ammonia
   b. Monohydrophosphate
c. Dihydrophosphate
d. Filtered protein
e. Bicarbonate

9. Under the effect of ADH, the filtrate becomes isotonic in the:
   a. Descending limb of the loop of Henle
   b. Ascending limb of the loop of Henle
c. Cortical collecting ducts
d. Medullary collecting ducts
e. Renal pelvis

10. Calculate renal clearance of a substance if its plasma concentration= 0.5 mg/dL, its urine concentration= 35 mg/dL and urine volume= 1ml/min.
    a. 5 ml/min
    b. 7 ml/min
c. 30 ml/min
d. 35.5 ml/min
e. 70 ml/min

11. The PCT in the kidney reabsorbs almost all of the filtered:
    a. Sodium
    b. Potassium
c. Chloride
d. Glucose
e. Water

12. Transport of sodium through basolateral membranes of thick ascending limbs of Henle loops occurs mainly by:
    a. \(1\text{Na}^+\cdot1\text{K}^+\cdot2\text{Cl}^-\) cotransport pump
    b. \(\text{Na}^+\cdot\text{K}^+\) pumps
c. Solvent drag
d. Simple diffusion
e. \(\text{Na}^+\cdot\text{H}^+\) antiport

13. The "counter-current multiplier" in the kidney is:
    a. Responsible for maintenance of hypertonicity of renal medulla
    b. Formed by the juxtaglomerular apparatus
c. Found in other parts of the body
d. Dependent on slow blood flow through the vasa recta
e. Found in less than 20% of all nephrons in the kidney

14. Titratable acidity in urine is:
    a. Equal to the amount of base that raises its pH to 7.0
    b. Equal to amount of acid that reduces its pH to 1.0
c. Buffered by ammonia
d. Buffered by phosphate  
e. Equal to net acid excretion

15. Clearance of which of the following measures the GFR:
   a. Urea  
   b. Uric acid  
   c. Inulin  
   d. PAH  
   e. Cotinine

16. In a patient with chronic renal failure there is reduction in:
   a. Anion gap  
   b. Acid excretion  
   c. Fractional excretion of sodium  
   d. Free water clearance  
   e. Calcium concentration in plasma

17. In absence of ADH, sodium concentration is lowest at the:
   a. Proximal convoluted tubule  
   b. Distal convoluted tubule  
   c. Cortical collecting duct  
   d. Thick ascending limb of loop of Henle  
   e. Medullary collecting duct

18. The GFR is increased by:
   a. Contraction of mesangial cells  
   b. Stimulation of renal nerves  
   c. Efferent arteriolar constriction  
   d. Compression of renal capsule  
   e. Activation of juxta-glomerular apparatus

19. Secretion of H⁺ in the PCT is primarily associated with reabsorption of:
   a. Potassium  
   b. Bicarbonate  
   c. Chloride  
   d. Glucose  
   e. Calcium

20. Clearance of a substance that appears in the renal artery but not the renal vein equals:
   a. Renal blood flow  
   b. Glomerular filtration rate  
   c. Glucose clearance  
   d. Renal plasma flow  
   e. Free water clearance

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21. Ammonia (NH₃) in the kidney:
   a. Is synthesized in the collecting ducts
   b. Reduces bicarbonate concentration in filtrate
   c. Decreases urine pH
   d. Is classified as titratable acid
   e. Is increased in response to respiratory acidosis

22. The renal blood flow is:
   a. Measured by creatinine clearance
   b. Increased by Antidiuretic hormone
   c. Increased by parasympathetic stimulation
   d. Greater in the renal cortex than the renal medulla
   e. Increased by chronic use of use of aspirin

23. The following substance is secreted by the renal tubules:
   a. Uric acid
   b. Calcium
   c. Inulin
   d. Ammonium
   e. Glucose

24. Secretion of potassium in the distal tubules is increased by:
   a. Anti-diuretic hormone
   b. Acidosis
   c. Hypokalaemia
   d. Loop diuretics
   e. Slow fluid tubular flow rate

25. As plasma glucose concentration rises from 100 to 160 mg/dL, its:
   a. Filtered load increases
   b. Transport maximum increases
   c. Clearance increases
   d. Excretion increases
   e. Renal transporters decrease

26. Concentration of this substance at the beginning of the PCT is almost equal to its concentration at the end of the PCT:
   a. Inulin
   b. Creatinine
   c. Bicarbonate
   d. Sodium
   e. Phosphate

27. In presence of ADH, the tubular fluid leaving the:
   a. PCT is hypotonic
   b. Ascending loop of Henle is hyperotonic
   c. DCT is isotonic
   d. Collecting duct is hypertonic
   e. Descending loop of Henle is hypotonic

28. Hypokalaemia is associated with:
   a. Renal failure
   b. Hypoventilation
29. Which of the following is reabsorbed actively in the proximal convoluted tubules:
   a. Water
   b. Hydrogen ions
   c. Sodium ions
   d. Creatinine
   e. Carbon dioxide

30. Which of these statements about micturition reflex is correct; it is:
   a. Facilitated by sympathetic activation
   b. Never initiated unless urine volume reaches 400 ml
   c. Present in paraplegic patients
   d. Absent in children
   e. Mediated by both sympathetic and parasympathetic neurons

31. Excretion of concentrated urine is more likely when:
   a. $1\text{Na}^+-1\text{K}^+-2\text{Cl}^-$ co-transport pump in the loop of Henle is inhibited
   b. $\text{Na}^+-\text{K}^+$ pump in the loop of Henle is activated
   c. Tubular flow rate in the loop of Henle is increased
   d. The glomerular filtration rate is increased
   e. ADH receptors in the collecting ducts are blocked

32. When blood glucose concentration is 300 mg/dl, the following is most likely to be higher than normal
   a. pH of the blood
   b. Inulin clearance
   c. Urine flow rate
   d. Renal threshold for glucose
   e. Sodium concentration in plasma

33. Atrial natriuretic peptide decreases sodium reabsorption at the:
   a. Proximal convoluted tubule
   b. Loop of Henle
   c. Distal convoluted tubule
   d. Cortical collecting duct
   e. Medullary collecting duct

34. Metabolic acidosis with hypokalemia is likely to develop due to:
   a. Vomiting
   b. Hyperventilation
   c. Diabetes insipidus
   d. Diarrhoea
   e. Renal failure

35. In a patient with compensated metabolic acidosis, which of the following is most likely to be correct:
   a. Bicarbonate concentration in plasma= 24 mmol/L
   b. Partial pressure of carbon dioxide in arterial blood= 20 mmol/L
   c. pH of urine is=6.5
d. pH of the plasma = 7.4
e. Ratio of HPO$_4^{--}$ to H$_2$PO$_4^{-}$ = 10

36. **In chronic compensated Respiratory acidosis:**
   a. Urine pH becomes less than 4.0
   b. Plasma pH becomes more than 7.4
   c. The partial pressure of carbon dioxide in the arterial blood is decreased
   d. Ammonia production by the kidney is increased
   e. Potassium secretion by the kidney is increased

37. **Which of the following statements about principal cells in the kidney is correct:**
   a. Found in the loop of Henle
   b. Secrete ammonia
   c. Secrete hydrogen ions
   d. Secrete potassium ions
   e. Have 1Na-1K-2Cl co transporters

38. **Aldosterone:**
   a. Causes water retention through aquaporin 2 in the distal nephron
   b. Activates H$^+$ ATPase pumps in the proximal convoluted tubules
   c. Excess causes edema due to sodium retention followed by water
   d. Increases secretion of renin enzyme by the juxtaglomerular cells
   e. Activates the Na/K ATPase pumps of principal cells

39. **Which of the following has the highest renal clearance:**
   a. Calcium
   b. Glucose
   c. Sodium
   d. Potassium
   e. Creatinine

40. **Which of the following is an important buffer in the interstitial fluid:**
   a. Proteins
   b. Bicarbonate
   c. Hemoglobin
   d. Phosphate
   e. Ammonia

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CHAPTER (10)
THE ENDOCRINE SYSTEM

INTRODUCTION

The Endocrine glands
- The endocrine glands are ductless glands that release hormones directly into the blood to act on target cells. Examples are mentioned in this figure:

Fig 10.1: The endocrine glands

Endocrine glands essential for life
- Some of the endocrine glands are essential for life because deficiency of their hormones causes death in a short time. These include:
  - The anterior lobe of the pituitary gland (releases adrenocorticotropic hormone “ACTH”)
  - The adrenal cortex (releases “cortisol”)
  - The parathyroid gland (releases parathyroid hormone “PTH”)

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**Organs with endocrine function**

- Certain organs contain endocrine cells that synthesize and release hormones, thus adding an endocrine function to these organs. Examples:
  - The hypothalamus (see below)
  - The kidney (releases erythropoietin)
  - The heart (releases atrial natriuretic peptide “ANP”)
  - The GIT (releases gastrin, secretin, CCK …)
  - The skin (releases vitamin D)
  - The adipose tissue (releases leptin)
  - The liver (releases insulin like growth factors “IGF”)
  - The placenta (releases estrogens, progesterone, hCG, hCS …)

**Hormones**

- Hormones are chemical substances released by endocrine glands or organs to act on specific target cells. After release in tissue fluid, they act through one or more of these types of signaling:
  - Enter blood to act on distant target cells (endocrine action)
  - Act on neighbouring cells (paracrine action)
  - Act on the same cell that produced it (autocrine action)

**Fig 10.2: Patterns of hormonal signaling**

![Diagram of hormonal signaling](image)
Chemical structure of hormones
- Generally, hormones are either derived from amino acids (= water-soluble) or from cholesterol (lipid-soluble).
  - Examples for hormones derived from amino acids:
    o One amino acid: Catecholamines & melatonin
    o Two amino acids: thyroid hormones
    o Eight amino acids: Angiotensin II
    o Nine amino acids: ADH & oxytocin
    o Polypeptides & proteins: GIT hormones, pancreatic hormones, all hypothalamic releasing hormones, PTH, calcitonin, growth hormone, prolactin, ACTH, hCS, ANP, leptin ...
    o Glycoproteins: LH, FSH, TSH & hCG
  - Examples for hormones derived from cholesterol:
    o Steroid hormones (containing the steroid nucleus “4 rings”): the hormones, which are released by the adrenal cortex & the gonads (Aldosterone, cortisol, adrenal androgens, testosterone, estrogens & progesterone).
    o Secosteroid hormone (containing the steroid nucleus but one ring is open): Vitamin D.
- Remember that: Local hormones like prostaglandins are lipid soluble but derived from fatty acids “arachidonic acid” not cholesterol.

Transport of hormones in plasma
- Lipid soluble hormones like thyroid & steroid hormones circulate in plasma in two forms:
  - Free form (usually conjugated in case of steroid hormones to be water soluble)
  - Protein bound (to albumin or globulin “α”)
- The free form is the active form of the hormone.
- The protein-bound form is inactive; it acts as a storage form (not excreted in urine).
- The protein-bound form is not filtered through the glomeruli in the kidney; that is why it stays for longer time in the circulation.

**Sites of catabolism**
- The principal sites of hormonal destruction are:
  - The liver
  - The kidney
  - Other tissues (e.g. adipose tissue)
- Generally, steroid hormones are destroyed mainly in the liver (and to a lesser extent in the kidney) whereas peptide hormones are destroyed mainly in the kidney.
- The products of hormonal catabolism (the metabolites) are excreted in urine & bile.

**Half-life**
- The time required for half of a hormone to be metabolized or eliminated by the body.
- Generally, the half-life of peptide hormones is less than steroid & thyroid hormones (with a few exceptions).
- Glycoprotein hormones have longer half-life than other peptide hormones. This is because the carbohydrate groups in the glycoproteins decrease their rate of metabolism.
- A higher percentage of protein bound fraction of a hormone indicates a longer half-life.

**Receptors**
- The receptors for hormones are proteins, located either on:
  - The cell membrane
  - Inside the cell (the nucleus or the cytoplasm)
- Generally, receptors for the peptide hormones are attached to the cell membrane (= cell membrane associated receptors) whereas receptors for the steroid hormones are found in the cytoplasm or the nucleus (= intracellular receptors).
- Exception to this general rule: The thyroid hormones (which are synthesized from the amino acid tyrosine) have intracellular receptors.
- Cell membrane receptors are integral proteins; they have three regions “or domains”:
  - Extracellular domains: the residues which are exposed to the outside of the cell (= the N-terminal of the protein).
    - These bind the hormone.
  - Transmembrane domains: the hydrophobic parts of the protein; serve to anchor the receptor in the membrane.
    - May be simple or complex (e.g., the protein which binds GTP or GDP “i.e. the G-protein” spans the cell membrane 7 times).
  - Cytoplasmic or intracellular domains: the tails or loops of the receptor that are within the cytoplasm (The C-terminal of the protein). These lead to formation of second messengers (see below).

Mechanism of hormonal action
- Peptide hormones: Binding of a hormone to its cell membrane receptor initiates a series of events, which lead to generation of “second messengers” within the cell. The second messengers then trigger a series of reactions that alter the physiologic state of the cell.
- Steroid hormones: Act by binding of a hormone to a cytoplasmic receptor. Then the hormone/receptor complex enters the nucleus and binds to specific sites at the DNA. It acts as a transcription factor that modulates gene expression.
Functions
- Most hormones regulate metabolic processes; however, they have additional effects on various organs of the body.
- Generally, the name of each hormone indicates one of its major functions (e.g. growth hormone, anti-diuretic hormone, angiotensin II, prolactin, thyroid-stimulating hormone …)

Control
- Many endocrine glands (e.g. the thyroid, the adrenal cortex & the gonads) are controlled by the master gland in the body (the pituitary gland). Release of hormones from these glands is stimulated or inhibited by other hormones released from the pituitary. However, hormones of the pituitary are also controlled by other hormones released by the brain structure which is found immediately above the pituitary gland,” the hypothalamus.” This is known as “the hypothalmo-pituitary axis.”
- Certain factors (environmental, nutritional, ions …) act directly on the hypothalamus to stimulate or inhibit its hormones.
- Similar factors act on the other glands, which are not controlled by the hypothalamo-pituitary axis (like the parathyroid gland, the pancreas and the adrenal medulla) to activate or suppress their secretions.
- Most hormones in the body are controlled by “a negative feedback mechanism.” (When a system’s output acts on the system input, resulting in its attenuation). Here a hormone (e.g. secreted from the thyroid) acts on the hormone that stimulates its release (secreted from the pituitary) & inhibits further release of that hormone & therefore, its own release.
- Few hormones are controlled by “a positive feedback mechanism.” (When a system’s output acts on the system input, resulting in its amplification). Here the hormone stimulates its own release.
- Examples of positive feedback mechanism include oxytocin, angiotensin II & LH in females (just before ovulation).

**The second messengers of peptide hormones**
- The second messengers are components of the signal transduction cascades. Here a hormonal signal results in series of biochemical reactions within the cell carried by enzymes. These enzymes are activated by the second messengers, which include:
  - cAMP “cyclic adenosine monophosphate”
    - For ADH, LH, FSH, TSH, ACTH, PTH, calcitonin, glucagon, catecholamines …
    - The hormone binding activates a G-protein (GDP or GTP-bound protein).
    - The protein activates the enzyme adenylyl cyclase.
    - This enzyme catalyzes formation of cAMP from ATP.
    - cAMP activates certain proteins within the cell (e.g. protein kinase A).
    - This phosphorylates other proteins (enzymes) to exert the effect of the hormone.
- Tyrosine kinase
  - For oxytocin, growth hormone, prolactin, insulin & erythropoietin.
  - The hormone binding causes conformational changes in the receptor.
  - The intracellular domain of the receptor, which becomes a tyrosine kinase, phosphorylates itself or other proteins to exert effects.

**Fig 10.4: The second messengers of peptide hormones**

- Inositol-triphosphate (IP$_3$), diacylglycerol (DAG) & calcium
  - For GnRH, TRH, catecholamines, angiotesin II and ADH.
  - The hormone binding activates a G-protein (GDP or GTP-bound protein).
  - The protein activates the enzyme phospholipase C.
This results in hydrolysis of phosphatidyl-inositol-4,5-diphosphate (PIP$_2$) into two second messengers:
  - inositol-1,4,5-triphosphate (IP$_3$) & diacyl-glycerol (DAG).
  - IP$_3$ triggers release of calcium from the sarcoplasmic reticulum.
  - Calcium ions bind to a calcium modulatory protein, calmodulin, which binds to and activates the calmodulin-dependent kinase.
  - DAG acts through activation of protein kinase C.
  - cGMP “cyclic guanosine monophosphate”
    - For atrial natriuretic peptide “ANP” (also for local signals like nitric oxide)
    - The hormone binding causes conformational changes in the receptor.
    - This activates guanylyl cyclase & results in formation of cGMP.
    - cGMP activates the cGMP-dependent protein kinase (also protein kinase A) to exert effects.

**THE PITUITARY GLAND**

- Small gland (1g) situated in the hypophyseal fossa “sella turcica” at the base of the skull, below the brain.
- Consists of two lobes: anterior and posterior lobes (in animals there is an additional intermediate lobe).
- The anterior lobe synthesizes and releases hormones whereas the posterior lobe does not synthesize hormones. It stores hormones that have been synthesized in the hypothalamus.

**The neuro-endocrine relationship**

- The endocrine system acts in close relation with the nervous system to control the metabolic functions of the body. There are many examples describing this relationship. One of these is the direct anatomical and physiological connection between the hypothalamus (= neural structure) and the pituitary (= endocrine gland).
- Through this connection, the hypothalamus controls the activity of the pituitary gland (by releasing and inhibitory hormones); and the pituitary controls the activity of many other endocrine glands in the body (by trophic “or tropic” hormones).
- The hypothalamus is connected to the pituitary gland in two ways.
  - **Neural connection:** between the hypothalamus and the posterior pituitary. Here hormones from the hypothalamus are transmitted through axons of neurons to be stored in the posterior pituitary gland.
  - **Vascular connection:** between the hypothalamus and the anterior pituitary. Here releasing and inhibitory hormones from the hypothalamus are sent through portal blood vessels to control activity of the anterior pituitary gland.

**Fig 10.5: The hypothalamic-pituitary connections**

![Diagram of hypothalamic-pituitary connections]

**Note:**
- The intermediate lobe in animals secretes melanocyte stimulating hormone (MSH). This lobe (and therefore its hormone) are not found in humans. However, ACTH acts as a melanocyte stimulating hormone. This is because it has a similar chemical structure to MSH since it comes from the same large precursor molecule “pro-opiomelanocortin”.

*The core of medical physiology (vol 2) ed 2*
- Acidophils in the anterior lobe secrete GH and PRL; basophils secrete FSH, LH, TSH and ACTH whereas chromophobes are inactive.
- Some of the anterior pituitary hormones are tropic hormones since they act on other endocrine glands to increase cellularity, vascularity and secretion of these glands. These are:
  
  - TSH (acts on the thyroid gland; also known as thyrotropin).
  - ACTH (acts on the adrenal cortex; also known as corticotropin).
  - FSH and LH (act on the gonads; also known as gonadotropins).
- In addition, GH can also be regarded as a tropic hormone because it exerts comparable effects on the liver (see below).
- Look at these differences between the two lobes of the pituitary gland:

**Table 10.1: Differences between the anterior and posterior lobes**

<table>
<thead>
<tr>
<th>Difference</th>
<th>Anterior lobe</th>
<th>Posterior lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryological origin</td>
<td>From roof of pharynx “Rathke's pouch” (i.e. glandular in origin)</td>
<td>From floor of third ventricle (i.e. neural in origin)</td>
</tr>
<tr>
<td>Types of cells</td>
<td>Acidophils (40%), basophils (10%) and chromophobes (50%)</td>
<td>Modified astrocytes (pituicytes) and nerve endings</td>
</tr>
<tr>
<td>Hypothalamic connection</td>
<td>Vascular: (Hypothalamo-hypophyseal portal vessels)</td>
<td>Neural: (H-h neural tracts)</td>
</tr>
<tr>
<td>Function</td>
<td>Synthesizes hormones</td>
<td>Stores hormones</td>
</tr>
<tr>
<td>Hormones</td>
<td>1- Growth hormone (GH)</td>
<td>1- Anti-diuretic hormone (ADH)</td>
</tr>
<tr>
<td></td>
<td>2- Prolactin (PRL)</td>
<td>2- Oxytocin</td>
</tr>
<tr>
<td></td>
<td>3- Adrenocorticotropic hormone</td>
<td>4- Thyroid stimulating hormone</td>
</tr>
<tr>
<td></td>
<td>4- Thyroid stimulating hormone</td>
<td>5- Follicle stimulating hormone</td>
</tr>
<tr>
<td></td>
<td>5- Follicle stimulating hormone</td>
<td>6- Luteinizing hormone</td>
</tr>
<tr>
<td></td>
<td>6- Luteinizing hormone</td>
<td></td>
</tr>
</tbody>
</table>
HORMONES OF THE ANTERIOR PITUITARY

GROWTH HORMONE (GH)

Characteristics of human growth hormone (hGH)
- Peptide hormone (191 amino acids) in a single chain.
- Molecular weight: 22,000 (22 k)
- Species specific (i.e. human growth hormone (hGH) differs from GH of other species).
- Half life: (about 20 min).
- About 50% of the hormone is bound to a plasma protein (the protein is a large fragment of GH receptor).

Control
- From the hypothalamus by:
  - Growth hormone releasing hormone (GHRH)
  - Growth hormone inhibitory hormone (GHIH); also known as somatostatin.
- Negative feedback mechanism by GH itself or by somatomedins (see below).
- GH stimuli:
  - Hypoglycemia, fasting, starvation
  - 2-Deoxyglucose (blocks catabolism of glucose 6 phosphate causing intracellular glucose deficiency)
  - Sleep (Non REM)
  - Stress
  - Exercise
  - Protein intake (increase in circulating levels of certain amino acids like arginine)
  - Glucagon, estrogens and androgens
  - L-Dopa, α adrenergics and their agonists
- GH inhibitors:
  - REM sleep
  - Free fatty acids
  - I.V. glucose
  - Cortisol
  - Growth hormone
  - Medroxyprogesterone

Somatomedins:
- These are insulin like growth factors “IGF” produced by the liver and other tissues in response to GH. The principal somatomedins in humans are:
  - Insulin-like growth factor-I (IGF-I, or somatomedin C)
  - Insulin-like growth factor II (IGF-II)
- They mediate the effects of GH on skeletal tissues (stimulate growth of bone & cartilage), stimulate protein synthesis & exert some insulin like activity.

**Fig 10.6: Control of GH**
-Effects of GH

- Promotion of growth:
  - GH promotes growth directly in most tissues and indirectly in skeletal tissues (through somatomedins).

- Metabolism of protein:
  - GH is an anabolic hormone. It stimulates protein synthesis (i.e. exerts +ve nitrogen and phosphorus balance). Therefore, it decreases the level of blood urea and amino acids.

- Metabolism of fat:
  - GH causes lipolysis (mobilization of adipose tissue). This increases free fatty acids (FFAs) in the plasma.

- Metabolism of CHO:
  - GH causes hyperglycemia by increasing hepatic glucose output (gluconeogenesis & glycogenolysis) and antagonizing actions of insulin in muscles and adipose tissues. Therefore, it has both diabetogenic effect (by increasing the level of glucose in plasma) and ketogenic effect (by increasing the level of FFAs in plasma).
    - Remember that GH increases both glucose and FFAs in plasma; however, it prevents utilization of glucose by antagonizing the effects of insulin. Therefore, it shifts the metabolism towards utilization of FFAs and sparing glucose as a source of energy for the brain.

- Metabolism of electrolytes:
  - GH increases absorption of calcium & phosphate in the intestine (through activation of vitamin D) and decreases excretion of sodium and potassium by the kidney; because these electrolytes are needed by the growing tissues.

- Lactogenic effect:
  - Because it is similar in chemical structure to prolactin.
Remember that:

The polypeptide hormone “ghrelin,” which is produced by the hypothalamus and the stomach to stimulate appetite, has marked growth hormone stimulating activity.

Abnormalities

- **GH excess before puberty = gigantism**
  - Excess GH before puberty causes gigantism. Here the size of viscera and the length of bones are increased. Patients have tall stature because the abnormality occurred before closure of the epiphyseal plates (which occurs at puberty due to estrogens).

- **GH excess after puberty = acromegaly**
  - Excess GH after puberty causes acromegaly. Here the size of viscera is increased but the length of bones is not increased because the abnormality occurred after closure of the epiphyseal plates. However, bones at the acral “peripheral” parts of the body are increased in size. These include bones of hands and feet. In addition, soft bones in the face like the malar and frontal bones are increased in size. The size of the lower jaw is also increased (= prognathism). These changes produce the characteristic acromegalic facies.

Remember about GH excess:

- It is caused by pituitary adenomas (tumors secreting GH).
- It is associated with increased lean body mass (increased protein) and decreased body fat.
- It is associated with increased excretion of hydroxyproline in urine, which indicates either high collagen destruction or synthesis (here it indicates increased collagen synthesis).
- May be associated with diabetes mellitus resistant to insulin treatment.
- **GH deficiency before puberty = dwarfism**
  - Deficiency of GH before puberty causes [dwarfism](characterized by short stature with intact mental function) whereas deficiency of GH after puberty causes minor metabolic abnormalities and increased sensitivity to insulin.
  - Causes of GH deficiency include:
    - Pituitary tumors
    - Deficiency of GH releasing hormone or IGF-I
    - GH receptor defect (Laron syndrome); here the level of GH in plasma is not low.

**Other causes of short stature**
- Short stature is also caused by:
  - **Hormonal causes (before puberty):**
    - Deficiency of insulin during childhood (diabetes mellitus- type I).
    - Deficiency of thyroid hormones during childhood (cretinism; associated with mental retardation).
    - Excess estrogens during childhood causing early closure of epiphyses (precocious puberty).
  - **Non-hormonal causes:**
    - Chromosomal abnormalities (e.g. Turner’s syndrome)
      - Lack of one X chromosome (XO pattern); characterized by female appearance, short stature & ovarian agenesis
    - Gene defects (e.g. achondroplasia)
      - Common cause of short stature; inherited as autosomal dominant
      - Characterized by short limbs & normal trunk
    - Other causes
      - Constitutional
      - Malnutrition
      - Psychological causes
PROLACTIN (PRL)

Characteristics
- Peptide hormone (199 amino acids) in a single folded chain.
- Similar in structure to growth hormone and human chorionic somatomammotropin (hCS).
- Half life: (20 min).
- In addition to the anterior pituitary, it is also secreted by the endometrium & the placenta.

Control
- From the hypothalamus by:
  - Prolactin releasing hormone (PRLRH)
  - Prolactin inhibitory hormone (PRLIH); also known as dopamine.
  
Note: PRLIH is more dominant than PRLRH. That is why cutting the pituitary stalk increases release of PRL while decreasing release of other anterior pituitary hormones.
- Negative feedback mechanism by PRL.
- Stimuli of PRL:
  - Pregnancy (& estrogens)
  - Suckling “stimulation of the nipple”; (Note: lactation without nursing is a stimulus)
  - Sleep
  - Stress (& hypoglycemia)
  - Exercise
  - Thyroid releasing hormone “TRH” (& hypothyroidism)
  - Dopamine antagonists (e.g. phenothiazines)
- Inhibitors of PRL:
  - L-dopa
  - Dopamine agonists (e.g. bromocriptine)
Fig 10.7: Control of PRL

Effects of PRL
- Growth of mammary glands (During pregnancy, together with estrogen & progesterone)
- Production of milk (Starts after delivery. This action is inhibited during pregnancy by estrogen & progesterone).
- Inhibition of gonadotrophins (resulting in loss of menstrual cycle during lactation)

Abnormalities
- **PRL excess:**
  - Caused by pituitary tumors (chromophobes adenoma).
  - Characterized by:
    - Infertility in both males and females due to inhibition of gonadotropin effects.
    - Amenorrhoea in females (absence of the menstrual cycle).
    - Impotence & loss of lipido in males.
    - Osteoporosis in females (due to low estrogens resulting from the inhibition of gonadotropins).
    - Galactorrhoea (milk production).
ADRENO-CORTICOTROPHIC HORMONE (ACTH)

Characteristics
- A single chain polypeptide (39 amino acids); synthesized from pro-opiomelanocortin in the anterior pituitary.
- Half life: (5-15 min); with “unknown” site of catabolism.

Control
- From the hypothalamus by corticotrophin releasing hormone (CRH).
- Negative feedback mechanism by ACTH itself and cortisol from the adrenal cortex.
- Diurnal (or circadian) rhythm: Increases in the morning and decreases at night.

Remember that:

<table>
<thead>
<tr>
<th>About 75% of ACTH secretion during the day occurs in the morning. This is regulated by the suprachiasmatic nuclei of the hypothalamus (= the biological clock).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimuli = all types of stress: (physical stress “exercise”, emotional stress “fear”, hypoglycemia, cold exposure and pain.</td>
</tr>
<tr>
<td>- The above stimuli activate the median eminence of the hypothalamus to increase CRH by the neurons of the paraventricular nucleus; then CRH stimulates ACTH secretion.</td>
</tr>
</tbody>
</table>

Effects of ACTH
- Trophic effect on the adrenal cortex: Increases cellularity, vascularity and secretion of cortisol from the adrenal cortex.
- Increases the responsiveness of the adrenal cortex to subsequent doses of ACTH. Therefore patients with hypopituitarism or those on chronic treatment with cortisol-like drugs “e.g. prednisolone” (both are not secreting cortisol) fail to respond immediately to ACTH injections or re-secretion after stopping the treatment.
- Pigmentation of the skin (The melanocyte stimulating hormone “MSH” is not found in humans; however, ACTH takes over its action and stimulates the melanocytes to increase melanin production (This is because ACTH is synthesized from the same large precursor molecule of MSH in animals “pro-opiomelanocortin”).

**Fig 10.8: Control of cortisol and ACTH**

![Diagram of the control of cortisol and ACTH](image)

**Abnormalities**

- **Excess ACTH:**
  - Caused by:
    - Pituitary tumors that secrete ACTH (= cortisol excess of secondary Cushing’s syndrome)
    - Lung tumors that secrete ACTH (= cortisol excess of ectopic Cushing’s syndrome)
    - Adrenal problems causing cortisol deficiency due to loss of the negative feedback on the pituitary (= Primary Addison’s disease)
- **Deficiency of ACTH:**
  - Caused by:
    - Pituitary tumors, which destroy the cells that secrete ACTH (decreased cortisol secretion from the adrenal cortex = secondary Addison’s disease)
    - Diseases of the adrenal cortex that cause excessive cortisol secretion (= primary Cushing’s disease) are associated with low ACTH due to the negative feedback mechanism.

**THYROID STIMULATING HORMONE (TSH)**

**Characteristics**
- Glycoprotein (211 amino acids) consisting of two subunits: alpha & beta.
- Other glycoprotein hormones that have similar alpha subunits but differ in the beta ones are FSH, LH and hCG (see the reproductive system).
- Half life: (60 min), catabolized mainly in the kidney and to a lesser extent in the liver.

**Control**
- From the hypothalamus by thyroid releasing hormone (TRH).
- Negative feedback mechanism by TSH itself (short loop –ve feedback) & by the thyroid hormones from the thyroid gland (long loop –ve feedback).
  - Stimuli: Cold
  - Inhibitors: Heat and stress
- Glucocorticoids, dopamine and somatostatin also inhibit TSH secretion. However, they are not involved in its physiological control.

**Effects**
- Trophic effect on the thyroid gland: Increases cellularity, vascularity and secretion of thyroid hormones from the thyroid gland.
Abnormalities

- **TSH excess**
  - Caused by:
    - Pituitary tumors that secrete TSH (= high T\textsubscript{3} & T\textsubscript{4} = secondary hyperthyroidism)
    - Thyroid diseases that decrease T\textsubscript{3} & T\textsubscript{4} secretion (= primary hypothyroidism)

- **TSH deficiency**
  - Caused by:
    - Pituitary tumors that decrease T\textsubscript{3} & T\textsubscript{4} secretion (= secondary hypothyroidism)
    - Thyroid diseases that increase T\textsubscript{3} & T\textsubscript{4} secretion (= primary hyperthyroidism)

FOLLICLE STIMULATING HORMONE (FSH) & LEUTINIZING HORMONE (LH)

Characteristics
- Known as gonadotrophins “or gonadotropins” because of their trophic effects on the gonads.
- They are glycoproteins. Each consists of 2 subunits: alpha & beta (similar to TSH & hCG).
- Half life: FSH= 3 hours and LH= 1 hour.

Control
- From the hypothalamus by the gonadotrophin releasing hormone (GnRH).
- Negative feedback mechanism by FSH and LH and by the sex hormones that are released from the gonads in response to them (estrogens, progesterone and testosterone).
• Release of GnRH starts at puberty (after maturation of the CNS) and then the release of FSH and LH starts following that (see the reproductive system). Therefore FSH & LH are almost absent before puberty.

• Inhibitors: Stress and Prolactin (possibly inhibits their effects at the level of the ovary)

Actions
• Trophic effect on the gonads: Increase vascularity, cellularity and secretion of sex hormones from the gonads in both males and females.
• Control of gonadal functions: production of sperms in males and the menstrual cycle including ovulation in females (see the reproductive system).

Abnormalities
- Gonadotrophin excess
  - Results in "precocious puberty" if occurred before puberty.
- Gonadotrophin deficiency
  - Delays onset of puberty (if occurred before puberty) & results in infertility (if occurred after puberty).

PITUITARY INSUFFICIENCY (PAN-HYPOPITUITARISM)
Causes:
• Tumors (e.g. craniopharyngioma or pituitary tumors)
• Surgical removal of the pituitary (for eradication of a tumor)
• Sheehan’s syndrome (pituitary infarction following postpartum hemorrhage, due to severe vasoconstriction as a body response to shock)
• Infiltration of the pituitary (e.g. by iron as in hemochromatosis)
• Infections (e.g. tuberculosis or meningitis)
**Features:**
- (Combined features of hypothyroidism, Addison’s disease, hypogonadism & low GH)
  - Skin pallor due to loss of the melanocyte stimulating activity of ACTH
  - Intolerance to cold due to decreased rate of metabolism caused by low TSH GH & ACTH
  - Loss of menstrual cycle in females due to low LH & FSH
  - Failure of lactation due to low prolactin
  - Hypoglycemia & increased sensitivity to insulin (due to low GH & ACTH which antagonize insulin). Hypopituitarism improves diabetes mellitus.
  - Increased sensitivity to stress (due to low ACTH)
  - Atrophy of some endocrine glands (e.g. gonads & adrenal cortex (zona fasciculata & zona reticularis, but not zona glomerulosa)
  - Polyuria due to absence of ADH; However, this is not very severe because the decreased metabolism is associated with decrease in the osmotic load that should be excreted

Remember that:

<table>
<thead>
<tr>
<th>- The following are not features of pituitary insufficiency:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Salt &amp; water depletion (hypovolemia shock); because aldosterone secretion is maintained</td>
</tr>
<tr>
<td>- Fatal hypoglycemia</td>
</tr>
<tr>
<td>- Loss of weight</td>
</tr>
</tbody>
</table>

**Treatment:**
- Hormone replacement as follows:
  - Glucocorticoids (in form of hydrocortisone) & thyroid hormones.
  - Sex hormones (testosterone in males & estrogen in females).
  - Growth hormone (for children).
HORMONES OF THE POSTERIOR PITUITARY

ANTIDIURETIC HORMONE (ADH)

Characteristics
- Also known as vasopressin (or arginine-vasopressin “AVP” to differentiate it from lysine-vasopressin of pigs).
- Nona-peptide (9 amino acids)
- Half life: 18 min
- Synthesized in hypothalamus in the:
  o Supra-optic nucleus (SON): the main site of ADH synthesis
  o Paraventricular nucleus (PVN): synthesis occurs to a lesser extent
- Transmitted through axons in the hypothalamo-hypophseal neural tracts (bound to neurophysin II) to be stored in the posterior pituitary.
- Synthesized also in other locations like the gonads and the adrenal cortex (but the function & the significance of this secretion are unknown).

Control
- Release of this hormone is stimulated by:
  ▪ Hyperosmolarity
    - Detected by osmoreceptors located at the hypothalamus and connected to the cell bodies of the SON & PVN through dendrites.
    - The osmoreceptors contain isotonic fluid; when the osmolarity of ECF is increased, the osmoreceptors shrink due to osmosis; this pulls the dendrites causing mechanical stimulation for the release of ADH.
  ▪ Hypovolemia
    - The volume of ECF is detected by volume receptors located at the great veins near the heart (the lower pressure side of the circulation); these send tonic inhibitory discharge through the vagus to inhibit release of ADH.
Hypovolemia results in less stretch of the volume receptors and therefore less inhibition of ADH release.

- **Hypotension**
  - The blood pressure is detected by baroreceptors located at the aortic arch and the carotid bifurcation (high-pressure side of the circulation). These receptors respond to elevation in blood pressure by sending inhibitory discharge to the cardiovascular centers in the medulla (to control blood pressure) and to the hypothalamus (to inhibit release of ADH).
  - Hypotension causes less stimulation of the receptors & therefore less inhibition of ADH.

- **Angiotensin II**
  - This octa-peptide (8 amino acids) hormone is synthesized in the blood from angiotensinogen, a plasma protein synthesized in the liver, following release of renin from the Juxta-glomerular apparatus in the kidney (see the section of adrenal cortex). Angiotensin II stimulates release of ADH.

- **Drugs**
  - Include: barbiturates, clofibrate, nicotine and morphine.

- **Inhibitors of ADH include:**
  - Hypo-osmolarity
  - Hypertension
  - Hypervolemia
  - Alcohol

**Receptors**

- Vasopressin has two types of cell membrane receptors:
  - $V_1$ receptors ($V_{1A}$ & $V_{1B}$):
    - $V_{1A}$ (in the blood vessels, liver & brain)
    - $V_{1B}$ (in the anterior pituitary)
    - Both act through Ca$^{++}$ as a second messenger
o V₂ receptors:
  o In the collecting ducts (and distal part of the DCTs)
  o Act through cAMP as a second messenger

Effects
- Water retention:
  - ADH acts on V₂ receptors in the distal part of the distal convoluted tubules “DCT” and the collecting ducts “CDs” in the kidney causing water retention (through insertion of aquaporin II on the luminal membrane, see the renal system).
  - It facilitates reabsorption of 7-13% of the filtrate in the kidney.

- Vasoconstriction:
  - ADH does not cause vasoconstriction when it is present in normal level in the circulation except in the vasa recta. However, in high levels (e.g. in response to hemorrhage) it causes vasoconstriction (through V₁ receptors) resulting in elevation of the B.P.

- Other effects
  - Glycogenolysis in the liver (through V₁α receptors)
  - Neurotransmitter in the brain and spinal cord (through V₁α receptors)
  - Release of ACTH from the anterior pituitary (through V₁B receptors)

Abnormalities
- **ADH deficiency: “diabetes insipidus”**
  - Results in polyuria and excessive thirst (urine volume may reach up to 23 L/day).
  - The condition is known as diabetes insipidus (DI).
  - It may result from a problem in the hypothalamus (neurogenic DI) or a problem in the kidney (nephrogenic DI).
- The neurogenic type is caused by trauma, tumors or diseases affecting the hypothalamus. It can be treated by synthetic ADH (desmopressin “DDAVP”) given by nasal inhalation.
- The nephrogenic type can be inherited (sex-linked for defective V$_2$ receptors or autosomal for abnormal aquaporin II) or can be caused by drugs (e.g. demeclocycline & lithium).

  ▪ **Excessive ADH secretion: “SIADH”**
    - Excessive ADH causes abnormal water retention.
    - This results in oliguria (reduction in urine volume), hypertension, and edema. The condition is known as syndrome of inappropriate ADH secretion (SIADH).
    - It is caused by head trauma, pneumonia, lung tumors, pancreatitis, and drugs like chlorpropamide, cyclophosphamide & carbamazepine.
    - It can be treated by drugs that decrease the sensitivity of the renal receptors to ADH (e.g. demeclocycline).

**Notice that:** Polyuria in diabetes insipidus is decreased by removal of the anterior pituitary; because the rate of metabolism (induced by TSH, ACTH & GH) is decreased. This decreases the metabolic products and therefore the osmotic load that should be excreted in urine.

**OXYTOCIN**

**Characteristics**
- Nona-peptide (9 amino acids); half-life: (1-4 min).
- Synthesized in hypothalamus mainly in the paraventricular nucleus (PVN) and to a lesser extent in the supra-optic nucleus (SON) & stored in the posterior pituitary (it is transmitted bound to neurophysin I through the neural tracts).
- It is synthesized in other locations like the gonads and adrenal cortex.
Control

- Positive feedback mechanism through neuro-endocrine reflexes stimulated by:
  - **Suckling** (stimulation of touch receptors around the nipple with the mouth of the baby during suckling results in discharge of impulses that activate the PVN & the SON in the hypothalamus, this stimulates release of stored oxytocin in the posterior pituitary. Oxytocin causes ejection of milk & the baby sucks the milk, and at the same time, causes more stimulation and therefore more release of oxytocin)
  - **Labor** (towards the end of pregnancy, the fetal head descends into the pelvis and starts to stimulate touch receptors at the cervix of the uterus, afferent impulses ascend to stimulate release of oxytocin. Oxytocin causes contraction of the uterus, the fetus descends more, his head dilates the uterine cervix, and at the same time, causes more stimulation of receptors and more release of oxytocin until delivery)
- Other stimuli: Stress & coitus (genital stimulation)
- Inhibitors: Alcohol

Effects

- Milk ejection: Acts on myoepithelial cells in the breast tissue causing ejection of milk.
- Contraction of the uterus: Contracts the smooth muscle in the uterus during labor. This effect is facilitated by estrogens and inhibited by progesterone.
- Other minor effects (when stimulated by coitus):
  - Helps in contraction of the uterus to facilitate movement of sperms
  - Helps in contraction of the vas deferens to facilitate ejaculation

Clinical points: Clinical abnormalities related to oxytocin are not known. A synthetic oxytocin (Syntocinon®) is used clinically to initiate labor.
QUESTIONS FOR SELF ASSESSMENT-4 (MCQS)

1- The following hormone is not released by the hypothalamus:
   a. Growth hormone
   b. Adrenocorticotrophic hormone
   c. Dopamine
   d. Thyroxin
   e. Insulinotropic hormone

2- Which of the following hormones induces milk synthesis?
   a. Oxytocin
   b. Prolactin
   c. Thyroxin
   d. FSH
   e. ACTH

3- Growth hormone:
   a. Stimulates lipogenesis
   b. Secretion is lowered during fasting
   c. Secretion is increased during sleep
   d. Is a steroid hormone
   e. Is released from basophils of the pituitary

4- Deficiency of which of the following hormones results in short stature with mental retardation?
   a. Insulin
   b. Growth hormone
   c. Prolactin
   d. Thyroid hormones
   e. Vasopressin

5- Acromegaly is a condition produced by:
   a. Arginine vasopressin deficiency
   b. Excess growth hormone
   c. Excess secretion of oxytocin
   d. Destruction of the adrenal gland
   e. Deficiency of somatomedin C

6- ACTH is released:
   a. During REM sleep
   b. After trauma
   c. After food intake
   d. During corticosteroid therapy
   e. From acidophil cells of anterior pituitary

7- Prolactin:
   a. Is not found in males
   b. Is secreted by acidophils of the white blood cells
   c. Antagonizes effects of gonadotropins
   d. Is increased in Sheehan’s syndrome
   e. Inhibits secretion of estrogen during pregnancy
8- Growth hormone is:
   a. Catabolic
   b. Hypoglycemic
   c. Anti-ketogenic
   d. Lipogenic
   e. Lactogenic

9- Hormones synthesized in acidophils of the pituitary include:
   a. Prolactin releasing hormone
   b. Growth hormone
   c. Follicle stimulating hormone
   d. Adrenocorticotrophic hormone
   e. Thyroid releasing hormone

10- In cases of deficiency, replacement of the hormone secreted by this gland is essential for life:
   a. Thyroid
   b. Pituitary
   c. Adrenal cortex
   d. Testes
   e. Pancreas

11- Secretion of antidiuretic hormone (ADH) is inhibited by:
   a. Standing
   b. Hyperosmolarity
   c. Hypotension
   d. Hypovolemia
   e. Alcohol

12- Physiological effects of ADH include:
   a. Raising peripheral resistance
   b. Increasing blood viscosity
   c. Skin vasoconstriction
   d. Increasing urine osmolarity
   e. Decreasing rate of sweating

13- Growth hormone:
   a. Receptors are cytoplasmic
   b. Synthesis is from cholesterol
   c. Effects on bone are indirect
   d. Secretion is increased during REM sleep
   e. Inhibition is by dopamine

14- Growth hormone differs from prolactin in that, it is:
   a. A protein hormone
   b. Released from acidophils of the anterior pituitary
   c. Stimulated by stress
   d. Inhibited by dopamine
   e. Not increased during pregnancy

15- Following transection of the pituitary stalk, plasma concentration of this hormone remains constant:
   a. GH
b. TRH
c. FSH
d. ADH
e. Cortisol

16- Excessive production of growth hormone in a 9-year old boy results in:
a. Acromegaly
b. Paget’s disease of bone
c. Short stature
d. Increased glucose tolerance
e. Positive nitrogen balance

17- A pituitary adenoma in a 45-year-old man, that excessively secretes prolactin, may result in:
a. Infertility
b. Diabetes mellitus
c. Renal stones
d. Female hair distribution
e. Goiter

18- Cutting the connection between the pituitary and the hypothalamus increases secretion of:
a. Oxytocin
b. Insulin
c. Growth hormone
d. Prolactin
e. ACTH

19- Which of the following statements about hormones is correct?
a. Neuro-hormones are released by glands to act on neurons
b. Autocrine hormones act on cells of the autonomic nerves system
c. All hormones act through second messengers
d. All hormones have both endocrine and paracrine effects
e. Effects include synthesis of specific proteins in the target cell

20- The anterior pituitary:
a. Is neural in origin
b. Is derived as down-growth from floor of 3rd ventricle
c. Is connected to hypothalamus by neural tracts
d. Hormones are regulated by neuro-hormones secreted from hypothalamus
e. Hormones are released during stress

21- ACTH:
a. Decreases the conversion of cholesterol to pregnenolone in adrenal cortex
b. Stimulates glucocorticoid secretion
c. Is released in response to hyperglycaemia
d. Is secreted continuously throughout the day
e. Level is decreased in adrenalectomized animal

22- The basophilic cells of the adenohypophysis secrete:
a. TSH
b. Somatostatin
c. Oxytocin
d. Gonadotrophins relating hormone
e. Growth hormone

23- Growth hormone:
   a. Decreases somatomedin formation in the liver
   b. Stimulates glucose entry into cells
   c. Increases free fatty acids in the blood
   d. Decreases the level of ketone bodies in the blood
   e. Stimulates the growth of bones in the fetus

24- The action of trophic hormones released by the anterior pituitary on their target glands include:
   a. Reducing the blood flow
   b. Decreasing the size of the gland
   c. Increasing the synthesis of specific hormone
   d. Reducing antibody formation against specific hormone
   e. Decreasing cyclic AMP production

25- In an adult with a pituitary tumor producing excessive amounts of ACTH:
   a. Production of adrenal androgens is decreased due to consumption of cholesterol
   b. Blood pressure is increased due to increased secretion of aldosterone
   c. Blood sugar is decreased due to increased secretion of insulin
   d. Total body weight is decreased due to higher rate of metabolism
   e. Glomerular filtration rate is decreased due to higher secretion of cortisol

26- Which of the following hormones is not a glycoprotein:
   a. TSH
   b. CRH
   c. FSH
   d. LH
   e. HCG

27- Oxytocin is:
   a. Synthesized in the posterior pituitary
   b. Regulated by positive feed back mechanism
   c. A known cause of galactorrhoea
   d. Synthesized from cholesterol
   e. Antagonized by progesterone

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THE THYROID GLAND

Structure of the thyroid gland
- The thyroid gland is the largest endocrine gland in the body; weighing about (20-25g). It lies on the trachea at the anterior aspect of the neck and moves with swallowing.
- In the embryo, at the 3\textsuperscript{rd} or 4\textsuperscript{th} week of pregnancy, the thyroid originates from the floor of the pharynx at the base of the tongue, at a point latter indicated by the foramen cecum. Subsequently the thyroid descends to its position through the thyroglossal cyst.
- It consists of two lobes that are connected by the thyroid isthmus. In addition, an extra pyramidal lobe may be found sometimes.
- Concerning its histology, it is made up of multiple acini (or follicles). Each follicle is surrounded by a single layer of cells and filled with a protein material (known as the colloid).
- The type of protein in the colloid is known as the thyroglobulin.
- The activity of the gland is indicated by:
  - The amount of colloid (abundant when the gland is inactive, small amount when it is active)
  - The shape of follicular cells (flat when the gland is inactive, columnar when it is active)

Fig 10.9: The thyroid gland
- The thyroid gland synthesizes the following hormones:
  - Thyroid hormones “T₃ and T₄” (by the follicular cells- see below)
  - Calcitonin (by the parafollicular cells “clear cells” - see control of Ca⁺⁺)

**THYROID HORMONES**

**Characteristics**
- The thyroid hormones are two types:
  a- T₃ (Tri-iodothyronine)
  b- T₄ (tetra-iodothronine or thyroxine)
- T₃ is about 3 to 5 times more active than T₄.
- Each hormone is synthesized from two molecules of tyrosine and 3 or 4 atoms of iodide.

**Steps of thyroid hormone synthesis**
1. **Iodide trapping by the follicular cells:**
   - The “I⁻/Na⁺ symporters” pump iodide into thyroid cells against electrical & chemical gradients; co-transported with Na⁺ (these symporters are stimulated by TSH).
   - Iodide trapping also occurs in other tissues including: (salivary glands, gastric mucosa, placenta, ciliary body of the eye, choroid plexus & mammary glands). However, the physiological significance is unknown.
   - To maintain normal thyroid function, the minimum daily requirement of iodine intake is about 150 µg/day.

2. **Oxidation of iodide into iodine inside the follicular cells:**
   - Iodide (I⁻) is converted to iodine (I₂).
   - This is catalyzed by the enzyme thyroid peroxidase.
   - Then iodine diffuses to the colloid down its chemical and electrical gradients.
3. **Synthesis of thyroglobulin by the follicular cells**

   – Glycoprotein made up of two subunits (MWt = 660,000).
   
   – Each molecule contains 123 tyrosine residues (but only 4-8 are involved in synthesis of Hs).
   
   – It is secreted into the colloid by exocytosis.

4. **Iodination**

   – Iodine is added to the tyrosine residues in thyroglobulin (to carbon number 3 &/or 5). This gives either mono-iodo-tyrosine “MIT” &/or di-iodo-tyrosine “DIT” residues.
   
   – Iodination occurs as the iodine & thyroglobulin are transported through the cell membrane towards the colloid and it is catalyzed by the enzyme thyroid peroxidase.

5. **Coupling (Condensation) inside the colloid**

   – Coupling of the iodinated tyrosine residues within the thyroglobulin.
   
   – Also catalyzed by the enzyme thyroid peroxidase.
   
   – Tyrosine + tyrosine = “thyronine”; and the iodine molecules are also summated as follows:
     
     - MIT + DIT = T₃  (= 7%)
     - DIT + DIT = T₄  (= 35%)
     - DIT + MIT = reverse T₃ “RT₃”  (= trace)
     - Uncoupled residues “MIT & DIT” (= 56%).

6. **Release of thyroid hormones**

   – The colloid is ingested by the follicular cells by the process of endocytosis. The iodinated residues are detached from thyroglobulin by the lysosomal enzymes: (proteases); giving T₃, T₄, RT₃, MIT & DIT.
   
   – T₃, T₄ & RT₃ are released to the blood as well as the rest of the thyroglobulin.
–Iodine in MIT & DIT is extracted by iodotyrosine deiodinase enzyme for re-utilization in thyroid hormone synthesis.

–This de-iodination is an important source of iodine; therefore deficiency of the enzyme iodotyrosine de-iodinase results in loss of the iodine in MIT & DIT in urine.

**Fig 10.10: The thyroid hormones**

![Thyroid Hormones Diagram](image)

7. **Peripheral conversion of T₄ into T₃**

–About one third of T₄ (thyroxine) is converted to T₃ by de-iodinase enzymes found in peripheral tissues including the liver, kidney and brain.

–Note that the thyroid gland secretes only 13% of the circulating T₃. The rest is formed by peripheral de-iodination. Similarly, most of RT₃ in the plasma is formed by peripheral de-iodination.

–Certain conditions may cause fluctuation in de-iodination, resulting in rise of RT₃ and depression in T₃. They include selenium deficiency (because the de-iodinase enzymes are selenium dependent), hypercatabolic states
(burn, trauma, advanced cancer, liver cirrhosis, renal failure & myocardial infarction) and the fasting states.

– Remember that: in the above states the low T3 guards against rapid loss of calories and protein.

**Thyroid hormones in the plasma**

- The average normal level in the plasma:
  - \([T_3] = 2.3 \text{ nmol/L}\)
  - \([T_4] \text{ "thyroxine"} = 103 \text{ nmol/L}\)
- Both hormones are found in the circulation in the two forms:
  - Free form (the active form that carries out the functions).
  - Protein bound form (inactive form not filtered in the kidney, acts as storage form).
- About 99.98% of \(T_4\) is bound to proteins whereas about 99.8% of \(T_3\) is bound to proteins.
- The binding proteins are:
  1. Thyroxine binding globulin (TBG)
     - Has the highest affinity to bind thyroxine
     - It carries about 67% of all \(T_4\) and 46% of all \(T_3\) in plasma
  2. Thyroxine binding albumin (TBA)
     - Has the highest capacity “available sites” to bind thyroid hormones
     - It carries about 13% of all \(T_4\) and 53% of all \(T_3\) in plasma
  3. Thyroxine binding pre albumin (TBPA or Transthyretin)
     - It carries about 20% of all \(T_4\) and 1% of all \(T_3\) in plasma

**Note:**

- Albumin has the highest concentration in the plasma and it stays for longer time in the circulation (Half-life for TBA = 13 days, TBG = 5 days and TBPA = 2 days).
Alterations in the level of the binding proteins (e.g. TBG) result in changes in the level of total hormone (the free + the protein bound fractions); however, plasma TSH and the free hormone are normal; and the patient remains euthyroid.

E.g. Elevation in TBG level causes reduction in the free fraction; resulting in elevation of TSH (due to loss of the –ve feedback mechanism). TSH stimulates secretion of more thyroid hormones. Therefore a new equilibrium is reached where TSH and thyroid hormone secretion return to normal (euthyroid) but the total hormone is increased.

Remember that: in hypo or hyperthyroidism, plasma TSH and the free hormone level are abnormal.

Factors that increase TBG (= increase total hormone) include:
- Pregnancy
- Contraceptive pills (containing estrogen)
- Certain drugs (clofibrate, tranquilizers …)

Factors that decrease TBG (= decrease total hormone) include:
- Androgens
- Glucocorticoids

Drugs that inhibit binding of TBG to thyroid hormones (= decrease total hormone) include:
- Aspirin
- Phenytoin

The half-life of each hormone:
- $T_3$ = 1.5 days (It is less bound to proteins and more active than $T_4$)
- $T_4$ = 6-7 days (It is more bound to proteins and less active than $T_3$)

Sites of metabolism:
- Liver (conjugated and excreted in bile)
- Kidney (and other tissues).
Control of thyroid hormones

- By the hypothalamo-pituitary axis
  - The hypothalamus secretes thyroid releasing hormone (TRH); the anterior pituitary responds by secreting thyroid stimulating hormone (TSH); then the thyroid gland secretes thyroid hormones (see TSH in the section of the pituitary gland).
  - The thyroid hormones exert a negative feedback effect on the pituitary and hypothalamus.
  - TRH is stimulated by cold exposure and inhibited by hot exposure and stress.

Fig 10.11: Control of thyroid hormones

Mechanism of thyroid hormone action

- Receptors for thyroid hormones are intracellular DNA-binding proteins that function as transcription factors, very similar to the receptors for steroid hormones.
- The hormone enters target cells through membrane transporter proteins (facilitated diffusion).
- In the cytoplasm, T₄ is converted to T₃ by the enzyme 5’ de-iodinase.
- Once inside the nucleus, T₃ binds its receptor.
- The hormone-receptor complex interacts with specific sequences of DNA to modulate gene expression, either by stimulating or inhibiting transcription of specific genes.
- Thyroxine (T₄) has not been shown to alter gene transcription although it can bind to the nuclear receptor with much less affinity than triiodothyronine.
- Therefore, it is likely that it serves as a pro-hormone with essentially all actions of thyroid hormone at the transcriptional level caused by triiodothyronine.

**Fig 10.12: Mechanism of thyroid hormone action**
**Effects of thyroid hormones**

1- Calorigenic action:
- Thyroid hormones increase oxygen consumption of most tissues in the body. This is because they increase the rate of metabolism and the activity of Na\(^+\)-K\(^+\) ATPase pump. Exceptions include adult brain, anterior pituitary, testes, uterus, and lymph nodes.

Note: oxygen and glucose uptake by the brain are normal in hypo and hyperthyroidism.

2- Effect on metabolism:

**Protein:**
- Thyroid hormones increase both protein catabolism (in high levels) and increase protein anabolism (in low to moderate levels).
- The increased protein catabolism may partly explain the proximal myopathy (muscle weakness) seen in thyrotoxicosis.
- In hypothyroidism, a variety of proteins and polysaccharides accumulate in the skin producing the characteristic puffiness of the skin (= myxedema). However, it is also associated with myopathy.

**Fat:**
- Thyroid hormones increase mobilization of fat & decrease cholesterol level in plasma.
- They decrease cholesterol because they increase formation of LDL receptors in the liver cells; thus increasing hepatic uptake of cholesterol to be excreted in bile.

**CHO:**
- Increase absorption of carbohydrates in the GIT.
- In hyperthyroidism, the plasma glucose level rises and then descends rapidly following ingestion of a carbohydrate meal (= lag storage curve in glucose tolerance test “GTT”). It also increases degradation of
insulin & potentiates the glycogenolytic effects of catecholamines; thus making diabetes worse.

**Vitamins:**
- Because of their effects on metabolism, they increase the need for vitamins.
- They convert carotene to vitamin A in the liver.
- In hypothyroidism, carotene accumulates in plasma (carotenemia) causing yellowish coloration of the skin but not the scleras (this differentiates it from jaundice).

3- **Growth:**
- Thyroid hormones are needed for normal growth and skeletal maturation. In addition, they potentiate the effects of growth hormone on tissues.
- Hypothyroidism in children results in stunted growth.

4- **CVS:**
- Thyroid hormones have the following effects on the cardiovascular system:
  - Increase heart rate (because they increase number & affinity of β1 receptors to catecholamines. They also increase α myosin heavy chains, G proteins, Na⁺-K⁺ ATPase pump and some K⁺ channels). Note: α myosin heavy chains have more ATPase activity and therefore higher speed of contraction than β myosin heavy chains.
  - Increase stroke volume (because they increase contractility of the heart by increasing number & affinity of β1 receptors to catecholamines. They also increase α myosin heavy chains, G proteins, Na⁺-K⁺ ATPase pump and some K⁺ channels).
  - Increase the cardiac output (because they increase the heart rate & the stroke volume).
- Increase the systolic blood pressure (because they increase the cardiac output).
- Vasodilatation (because they increase the metabolic rate and therefore heat production).
- Decrease the diastolic blood pressure (because they cause skin vasodilatation and therefore decrease the peripheral resistance).
- Increase the pulse pressure (because they increase the systolic & decrease the diastolic).

5- GIT:
- Increase appetite and increase intestinal motility.
- Hypothyroid patients suffer from constipation whereas hyperthyroid patients suffer from diarrhea.

6- CNS:
- Increase development of the brain in children (especially the cerebral cortex, basal ganglia and cochlea). That is why hypothyroidism in children causes mental retardation, motor rigidity, and deafness.
- Increase mentation in adults (partly due to increased responsiveness to catecholamines).
- Thyroid hormones are needed for normal reaction time in stretch reflexes.

7- Other effects:
- Increase milk synthesis.
- Essential for normal menstruation and fertility; therefore hypo and hyperthyroidism are associated with abnormal menstruation.

Abnormalities

Hyperthyroidism (or thyrotoxicosis)
- Primary hyperthyroidism is caused by toxic tumors, inflammation, drugs, or autoantibodies that activate the thyroid.
- When the cause is “long acting thyroid stimulating antibodies” (LATS antibodies), acting on TSH receptors of the thyroid gland (i.e. thyroid stimulating antibodies), hyperthyroidism is called “Graves’ disease”. Unlike other causes of hyperthyroidism, Graves' disease is characterized by eye signs (see below).
- Secondary hyperthyroidism is caused by pituitary tumors that increase production of TSH.
- Features of hyperthyroidism (see effects of thyroid hormones) include:
  - Increased metabolism = increased heat production = intolerance to hot
  - Increased heart rate, SV, COP, systolic B.P. and pulse pressure. Decreased diastolic B.P.
  - Irritability and nervousness
  - Increased appetite (hyperphagia)
  - Diarrhea and weight loss
  - Fine tremor
  - Warm, soft skin and sweating
  - Eye signs (only in Graves’ disease which is the commonest cause of thyrotoxicosis):
    - Lid retraction (= retraction of the upper eyelid; allowing appearance of the whitish sclera above the cornea. Normally, the upper sclera cannot be seen).
    - Lid lag (= delay in movement of the upper eyelid when looking to an object descending from above to downwards. This sign is seen only during clinical examination).
    - Exophthalmos (= protrusion of the eye globe forward due to inflammation and edema of the tissues in the orbit. The inflammation is caused by cytokines produced by fibroblasts in the orbit that respond to the autoantibodies.
Hypothyroidism (or myxedema)
- Primary hypothyroidism is caused by thyroid problems (common) whereas secondary hypothyroidism is caused by pituitary or hypothalamic problems (rare).
- Thyroid problems include:
  - Congenital deficiency of the enzymes involved in thyroid hormone synthesis
  - Severe iodine deficiency or excess. (Iodine excess inhibits thyroid function (Wolff-Chaikoff effect) by the following mechanisms: inhibition of iodination, inhibition of proteolysis of thyroglobulin and reduction of cAMP rise in response to TSH)
  - Tumors
  - Inflammation
  - Surgical removal
  - Autoantibodies that destroy the thyroid (Hashimoto's thyroiditis)
  - Antithyroid drugs (interfere with iodide trapping “perchlorate, nitrate and thiocynate” or block iodination and coupling “propylthiouracil and methimazole”)
- Features of hypothyroidism:
  - Low metabolism = decreased heat production = intolerance to cold
  - Hair changes (becomes coarse and sparse); loss of the outer eyebrow
  - Skin becomes dry and yellow (carotenemia)
  - Voice becomes characteristically husky and slow
  - CNS symptoms (sleepy, slow mentation and poor memory “myxedema madness”)
  - Bradycardia
  - Constipation
  - High cholesterol level in plasma

**Cretinism**
- Congenital hypothyroidism is caused by:
  - Maternal iodine or thyroid hormone deficiency
  - Maternal antithyroid antibodies that cross the placenta
  - Congenital absence of the thyroid gland
  - Congenital absence of enzymes involved in thyroid hormone synthesis
- In addition to the above features of hypothyroidism, cretinism is associated with: Mental retardation, short stature, large protruded tongue and umbilical hernia.

**Remember that:** early diagnosis and treatment of cretinism can prevent mental retardation.

**Fig 10.14: Congenital hypothyroidism (= Cretinism)**
**Goiter**

- Swelling of the thyroid gland caused by high TSH.
- High TSH (& therefore goiter) is caused by:
  - Iodine deficiency (endemic goiter)
  - Graves’ disease (due to the effect of long acting thyroid stimulating antibodies)
  - Anti-thyroid drugs (see above)
  - Goitrogens (chemical substances found in vegetables, converted in the intestine to an antithyroid agent that causes goiter “goitrin”)
  - Some causes of congenital hypothyroidism (peroxidase or de-iodinase deficiency)

**Fig 10.15: Endemic goiter**

Tests assessing thyroid function

1- Total & free T3 & T4

- Direct measurement of the total & free fractions of thyroid hormones is now available by radioimmunoassay. In the past, the thyroid function used to be assessed indirectly, by measurement of the basal metabolic rate.
2- TSH
- Measurement of TSH by radioimmunoassay differentiates between primary and secondary thyroid hormone abnormalities.
- Examples:
  - TSH is low in primary hyperthyroidism (due to the -ve feedback effect of T₃ on TSH).
  - TSH is high in primary hypothyroidism (due to loss of the –ve feedback mechanism).
  - TSH is low in secondary hypothyroidism. However, to differentiate between a pituitary and a hypothalamic cause, the response to an I.V. dose of TRH should be assessed. A good response (rise in TSH after I.V. TRH) indicates a hypothalamic cause of the hypothyroidism.

3- Radioactive iodine uptake
- A test dose of radioactive isotope of iodine (¹²³I) is given orally and then its uptake by the thyroid gland is measured by a gamma camera.
- The degree of uptake acts as an index of the thyroid function (high in hyperthyroidism and low in hypothyroidism).
- The use of radioactive iodine uptake as a diagnostic tool is now rare because of the availability of radioimmunoassay of the hormones. However, it is still used in treatment of some cases of hyperthyroidism and thyroid cancer (because the radioactive iodine, in large doses, destroys the thyroid cells).
THE ADRENAL GLAND

- The adrenal gland consists of two endocrine glands:

1- **Adrenal cortex:**
   - Essential for life.
   - Secretes the following steroid hormones synthesized from cholesterol:
     - Glucocorticoids (cortisol)
     - Mineralocorticoids (aldosterone)
     - Sex Hormones (androgens)

2- **Adrenal medulla:**
   - A sympathetic ganglion that lost its postganglionic axons and became modified into secretory cells.
   - Not essential for life but prepares the body for emergencies.
   - Secretes the catecholamines: (epinephrine, norepinephrine & dopamine).

**Fig 10.16: The adrenal gland**

**Anatomy of the adrenal gland**

**The adrenal cortex:**
- Cells of the adrenal cortex contain abundant lipid, mitochondria and smooth endoplasmic reticulum involved in steroid biosynthesis.
- The cortex is divided into 3 zones:
  - Zona glomerulosa (The outer zone. = 15% of the adrenal gland. Secretes aldosterone. Also responsible for formation of new cells to replace the lost ones, even from the other zones).
  - Zona fasciculata (The inner zone. = 50% of the gland. Secretes glucocorticoids).
  - Zona reticularis (The innermost zone. = 7% of the gland. Secretes sex hormones).

Remember that: corticosterone is secreted by the 3 zones, glucocorticoids are secreted by the two inner zones but mainly by zona fasciculate, sex hormones are also secreted by the two inner zones but mainly by zona reticularis; whereas secretion of aldosterone is confined to zona glomerulosa.
- The two inner zones (fasciculate and reticularis) respond to ACTH from the pituitary gland. They undergo hypertrophy in ACTH excess and atrophy in ACTH deficiency.
- In fetal life, the whole adrenal cortex is under pituitary control. It is involved in synthesis of androgens which are converted to estrogens in the placenta (the feto-placental unit). However, most of the fetal adrenal cells degenerate at birth.

The adrenal medulla:
- The adrenal medulla constitutes about 28% of the adrenal gland. It consists of densely innervated granulated cells; 90% of these are epinephrine-secreting cells and 10% are norepinephrine secreting cells (the dopamine secreting cells are unknown).

Biosynthesis of the adreno-cortical hormones
- The adrenocortical hormones are synthesized from cholesterol; so they contain the steroid nucleus (cyclopentanoperhydrophenanthrene nucleus).
- Cholesterol contains 27 carbons whereas the adrenocortical hormones contain 21 or 19 carbons (C\textsubscript{21} or C\textsubscript{19} steroids).
- Most of the C\textsubscript{19} steroids are 17-ketosteroids (contain keto group at position 17) and have androgenic activity.
- Most of the C\textsubscript{21} steroids are 17-hydroxycorticosteroids (contain hydroxyl group at position 17) and have mineralocorticoid &/or glucocorticoid activity.
- By the action of specific enzymes (most of which are members of the cytochrome P450 superfamily), cholesterol is converted first to pregnenolone and then to one of the adrenocortical hormones.

**Fig 10.17: Synthesis of adrenocortical hormones**
Important notes about adrenocortical hormone biosynthesis:
- Pregnenolone is formed in the mitochondria, androgens are formed in the smooth endoplasmic reticulum, and the last step in glucocorticoid formation occurs in the mitochondria.
- Androgens and glucocorticoids are formed in the cells of zona reticularis and zona fasciculata because these cells contain the enzymes 11β-Hydroxylase and 17α-Hydroxylase.
- These 2 enzymes are not present in zona glomerulosa; that is why it can not form cortisol and androgens. However, it contains an enzyme similar to 11β-Hydroxylase known as aldosterone synthase. This catalyzes formation of aldosterone.
- Zona fasciculata has higher 3β-Hydroxysteroid dehydrogenase activity than zona reticularis that is why it is more active in formation of glucocorticoids; on the other hand, zona reticularis has higher 17α-Hydroxylase activity that is why it is more active in formation of androgens.
- Congenital deficiency of these enzymes causes the adrenogenital syndrome in females:
  - 21β-Hydroxylase (common)
  - 11β-Hydroxylase (rare)
- The adrenogenital syndrome (one of the syndromes of congenital adrenal hyperplasia) is characterized by:
  - Decreased synthesis of cortisol.
  - High ACTH (this causes the adrenal hyperplasia).
  - Increased synthesis of androgens causing:
    - Virilization in females (= female pseudo-hermaphroditism)
    - Precocious pseudo-puberty in males
  - Hypotension (due to absent mineralocorticoids & Na⁺ loss in 21β-Hydroxylase deficiency; “salt losing type”).
Hypertension (due to the mineralocorticoid effects of 11-Deoxycortisol & 11-Deoxycorticosterone in 11β-Hydroxylase deficiency “hypertensive form”).

- Other syndromes of congenital adrenal hyperplasia may be caused by:
  - Absence of the protein that transports cholesterol to the mitochondria.
  - 3β-Hydroxysteroid dehydrogenase deficiency (= excess androgens).
  - 17α-Hydroxylase deficiency (= no androgens).

**Glucocorticoids**
- These are the adrenocortical hormones with predominant effects on glucose and protein metabolism.
- They include: cortisol (the dominant glucocorticoid in humans) and corticosterone (the dominant glucocorticoid in some animals).
- Synthetic steroids with high cortisol activity and with longer half-life:
  - Prednisolone (4 times cortisol activity and minimal aldosterone activity)
  - Dexamethasone (25 times cortisol activity and no aldosterone activity)
  - 9α fluorocortisol (10 times cortisol activity and appreciable aldosterone activity)

**CORTISOL**

**Characteristics**
- Cortisol is the most dominant glucocorticoid in humans.
- It is essential for life.
- Half life of cortisol= 60-90 min; with the liver as the main site of catabolism.
- Some of the metabolites (e.g. ketosteroids) are excreted in urine after hepatic conjugation.
- Most of the hormone is bound in the plasma to α globulin (transcortin or corticosteroid binding globulin “CBG”), plus minor binding to albumin.
- As in the case of thyroid hormone binding globulin, CBG level fluctuates during pregnancy.

**Control of cortisol**

- Feedback mechanism
- Circadian rhythm (high in the morning and low at night)
- The main stimulus: stress

**Fig 10.18: Control of cortisol**

**Effects of cortisol**

- **Metabolism of CHO:**
  - Cortisol causes hyperglycemia by anti-insulin action on the peripheral tissues and by increasing hepatic gluconeogenesis; however it causes glycogenesis in the liver by activating the enzyme glycogen synthase.
- **Metabolism of protein:**
  - Cortisol increases protein catabolism in skin & bone.
- **Metabolism of lipid:**
  - Cortisol increases mobilization of fat and stimulates formation of ketone bodies.

- **Metabolism of water:**
  - Cortisol increases the GFR and facilitates excretion of water load.
  - Patients with adrenal insufficiency may easily get into water intoxication.

- **Permissive effect for catecholamines and glucagon:**
  - At least small amount of cortisol is essential for the effects of glucagon (e.g. lipolysis) and the effects of catecholamines (e.g. vasoconstriction & bronchodilation).

- **Blood cells:**
  - Cortisol increases RBCs, platelets, neutrophils and monocytes. It decreases lymphocytes, basophils and eosinophils.

- **The nervous system:**
  - The effects of cortisol on the nervous system can be studied from the abnormal symptoms and signs that appear in patients with cortisol deficiency.
  - These include abnormal slowing of the EEG activity and personality changes (irritability apprehension and failure to concentrate).

- **Mineralocorticoid effect:**
  - Cortisol has a minor mineralocorticoid effect. It increases Na\(^+\) reabsorption & K\(^+\) secretion in the distal convoluted tubules and collecting ducts in the kidney.

- **Anti-inflammatory effect:**
  - Excess cortisol (e.g. when treating patients with high doses of prednisolone or hydrocortisone) decreases signs of inflammation (redness, hotness, pain and swelling); and inhibits the subsequent formation of fibrous tissue. This is achieved by inhibiting the enzyme
phospholipase A\textsubscript{2} thus preventing formation of the inflammatory mediators: prostaglandins and leukotrienes.
- Prevention of fibrous tissue formation is beneficial in patients with corneal ulcers. However, it may allow spread of bacteria in patients with active tuberculosis or pneumonia (unless antibiotics are administered at the same time).
  - **Anti-allergic effect**
    - Excess cortisol decreases allergic signs by inhibiting release of histamine by mast cells.
  - **Anti-immunity effect**
    - Excess cortisol decreases number of lymphocytes and release of lymphokines like IL-2 resulting in reduced proliferation of lymphocytes. It also decreases the size of lymphatic organs. These effects are needed in patients with transplanted organs to minimize the chance of rejection; that is why they are treated with high doses of prednisolone.
  - **Anti-stress effect**
    - Cortisol is essential for survival. It guards against stress; but the mechanism is unknown.
  - **Other effects:**
    - Cortisol accelerates surfactant production during fetal life. For this reason, prednisolone is administered to pregnant women suffering from contractions of premature labor.
    - Excess cortisol decreases growth hormone and TSH secretion.

**Abnormalities**

**Cortisol excess = Cushing's syndrome**
- It is caused by either: ACTH independent or ACTH dependent causes.
- ACTH independent causes (characterized by low ACTH) include:
  - Adrenal tumor secreting cortisol (primary Cushing’s).
- Prolonged use of drugs with cortisol activity (e.g. prednisolone in asthma).

- ACTH dependent causes (characterized by high ACTH) include:
  - Pituitary tumor secreting ACTH (secondary Cushing’s or Cushing’s disease).
  - Lung tumor secreting ACTH or CRH (ectopic Cushing’s).

- Features of Cushing’s syndrome include:
  - Thin skin and weak muscles (due to protein depletion) resulting in poor healing of wounds and easy bruising and ecchymoses.
  - Striae (appear in the skin of the abdomen because it is thin and stretched by the fat deposition).
  - Central obesity, moon face and thin limbs (due to redistribution of fat).
  - Buffalo hump (due to accumulation of fat at the upper trunk).
  - Plethora.
  - Hypertension (due to):
    - Salt and water retention by cortisol or deoxycorticosterone, which is also elevated
    - The permissive effect of cortisol on blood vessels
    - Increased secretion of angiotensinogen
  - Hypokalemia (contributes to muscle weakness).
  - Diabetes mellitus (hyperglycemia, hyperlipemia and ketosis).
  - Osteoporosis (loss of bone mass) and fractures.
  - Increased facial hair and acne (due to associated androgen secretion).
    - Remember that: facial hair in females is known as “hirsutism”.
  - CNS changes and personality changes (rapid EEG rhythm, increased appetite, insomnia, euphoria, or frank psychosis).
Fig 10.19: Cushing’s syndrome

Cortisol deficiency = Addison’s disease
- Primary adrenal insufficiency “Addison's disease” is caused by destruction of the adrenal cortex (by tuberculosis or autoantibodies).
- Secondary adrenal insufficiency is caused by pituitary disorders (decrease ACTH release).
- Tertiary adrenal insufficiency is caused by hypothalamic disorders (decrease CRH release).
- Adrenal insufficiency is characterized by:
  - Hyponatremia
  - Hypotension
  - Hyperkalemia
  - Hyperpigmentation (only in the primary type due to high ACTH)
  - Acidosis
  - Weight loss
  - Muscle weakness (due to hyperkalemia)
Small heart (because the low after load “the hypotension” decreases work of the heart).

Risk of death due:
- Addisonian crisis (caused by stress and characterized by circulatory collapse)
- Fasting (causes fatal hypoglycemia)
- Water intoxication (failure to excrete water).

MINERALOCORTICOIDS
- These are the adrenocortical hormones with predominant effects on Na$^+$ & K$^+$ excretion.
- They include:
  - Aldosterone (strong mineralocorticoid)
  - Deoxycorticosterone (has only 3% of aldosterone activity).

ALDOSTERONE

Characteristics
- The main mineralocorticoid; formed only in the zona glomerulosa of the adrenal cortex.
- Unlike cortisol, only small fraction is bound to plasma protein.
- Half life = 20 min; with the liver and kidney as the main sites of metabolism.

Control of aldosterone
- Normal regulation of aldosterone secretion is not under the control of the hypothalamo-pituitary axis.
- High ACTH can stimulate aldosterone secretion; whereas normal level of ACTH has no effect on zona glomerulosa of the adrenal cortex.
- The direct stimuli of aldosterone include:
1- Hyperkalemia
- Directly stimulates aldosterone release from the adrenal cortex (activates conversion of cholesterol to pregnenolone and conversion of corticosterone to aldosterone).

2- High level of ACTH
- The (ACTH) is released by the anterior pituitary gland to stimulate secretion of cortisol by the adrenal cortex. In high levels (levels higher than that which stimulate maximal cortisol secretion) ACTH can also stimulate aldosterone secretion.

3- The renin-angiotensin-aldosterone system
- In this system, renin enzyme, which is produced by the Juxta-glomerular apparatus in the kidney, converts the plasma protein “angiotensinogen” to “angiotensin I.” Then the angiotensin converting enzyme in the pulmonary circulation converts “angiotensin I” to “angiotensin II”. Angiotensin-II directly stimulates aldosterone secretion from the adrenal cortex (activates conversion of cholesterol to pregnenolone and conversion of corticosterone to aldosterone).

Remember that: The stimuli that activate the Juxta-glomerular apparatus to release renin are regarded as indirect stimuli of aldosterone secretion. These include:
- Hyponatremia
- Renal ischemia (caused by hypotension, standing, hypovolemia or renal artery stenosis)
- Sympathetic stimulation (associated with stressful stimuli like trauma, pain, surgery and hemorrhage; here cortisol secretion is also stimulated).
- ANP decreases aldosterone secretion by inhibiting renin secretion and decreasing the effects of angiotensin II on zona glomerulosa.
Effects of aldosterone
- Reabsorption of Na\(^+\) & secretion of K\(^+\) at the following sites: The DCT and CDs in the kidneys, the GIT (salivary ducts and colon) & the sweat glands.

Remember that: in the kidney, the reabsorption of Na\(^+\) is coupled to K\(^+\) secretion (or H\(^+\) secretion).

Abnormalities
Aldosterone excess
Primary hyperaldosteronism = Conn’s syndrome
- Caused by a tumor in the adrenal gland secreting aldosterone; here renin is inhibited and its level in plasma becomes very low.
- Characterized by:
  - High blood pressure (due to salt and water retention)
  - Low [K\(^+\)] (due to K\(^+\) secretion)
  - Alkalosis (due to hypokalemia and secretion of H\(^+\) in urine)
  - Muscle weakness (due to low K\(^+\))
  - Tetany (due to low Ca\(^{++}\) ions secondary to the alkalosis)
- Edema does not develop due to “aldosterone escape phenomenon” caused by ANP.
- Here ANP prevents salt and water retention above certain point (before development of edema) by antagonizing the effects of aldosterone and increasing excretion of sodium in urine (this causes polyuria).

Secondary hyperaldosteronism
- Unlike the primary type, secondary hyperaldosteronism is associated with high renin secretion and characterized by development of edema.
- It is associated with congestive heart failure, liver cirrhosis and nephrosis.
Aldosterone deficiency
- Hyporeninemic hypoaldosteronism occurs rarely due to impaired renin secretion by the diseased kidney whereas pseudo-hypoaldosteronism occurs due receptor defects.
- These disorders are characterized by salt loss, hypotension, hyperkalemia and acidosis.

QUESTIONS FOR SELF ASSESSMENT-5 (MCQS)

1. Hypothyroidism is characterized by:
   a. Increased heart rate
   b. Increased temperature
   c. Diarrhea
   d. Irritability
   e. Weight gain

2. The following is a feature of Graves’ disease:
   a. Drop of the upper eyelid
   b. High level of TSH
   c. Intolerance to cold
   d. High systolic blood pressure
   e. Constipation

3. Primary hyperaldosteronism (Conn’s syndrome) is characterized by:
   a. Oedema
   b. High plasma potassium
   c. Hyperglycemia
   d. High renin level in blood
   e. High plasma bicarbonate

4. Aldosterone is directly stimulated by:
   a. Hyponatremia
   b. Hyperkalemia
   c. Hyovolemia
   d. ADH
   e. Renin

5. Hyperglycemia and hypertension may occur in:
   a. Addison’s disease
   b. Diabetes mellitus
   c. Acromegaly
   d. Rickets
   e. Conn’s syndrome
6. **Hypothalamic TRH is released in response to:**
   a. Stress
   b. Neural signals
   c. Feedback from TSH
   d. Cold
   e. Sleep

7. **The physiological effects of cortisol include:**
   a. Lipogenesis
   b. Lymphocytosis
   c. Water retention
   d. Increased glucose utilization
   e. Gluconeogenesis

8. **Aldosterone exerts its effects on which of the following cells:**
   a. Parietal cells
   b. Podocytes
   c. Juxtaglomerular cells
   d. Intercalated cells
   e. Principal cells

9. **This hormone is synthesized in zona fasciculata of the adrenal cortex:**
   a. Aldosterone
   b. Cortisol
   c. Glucagon
   d. Adrenaline
   e. Androstenedione

10. **Hyperthyroidism is characterized by:**
    a. Hyperglycemia
    b. Bradycardia
    c. Fever with rigors
    d. Increased intestinal motility
    e. Mask face

11. **High dietary intake of sodium every day is expected to:**
    a. Increase plasma renin activity
    b. Lower rate of daily sodium excretion
    c. Decrease plasma ANP level
    d. Increase plasma vasopressin level
    e. Keep constant plasma aldosterone level

12. **Cushing's disease is characterized by:**
    a. Anemia
    b. Hypoglycemia
    c. Hypopigmentation
    d. Alkalosis
    e. Leucopenia

13. **The following effect is caused only by high level of plasma cortisol:**
    a. Feedback effect on ACTH
    b. Potentiates effects of norepinephrine on blood vessels
    c. Inhibition of inflammation
d. Gluconeogenesis
e. Increases GFR

14. Excessive secretion of one of these hormones is unlikely to increase normal rate of linear growth in children:
   a. Insulin
   b. Testosterone
   c. Growth hormone
   d. Thyroid hormones
   e. Vitamin D

15. In the following, a hormone and an abnormality are paired correctly:
   a. ADH & diabetes mellitus
   b. Prolactin & infertility
   c. Vitamin D & renal stones
   d. Aldosterone & Horner's syndrome
   e. Cortisol & Conn's syndrome

16. Aldosterone effects on target cells include all the following except:
   a. Insertion of ENaC (epithelial sodium channels) on cell membrane
   b. Activation of sodium-potassium pumps
   c. Binding to nuclear receptors
   d. Kaliuresis
   e. Has both rapid and long term effects

17. Aldosterone, but not cortisol, is increased during:
   a. Surgery
   b. Anxiety
   c. Hypovolemic shock
   d. Standing
   e. Physical trauma

18. Which of the following corticosteroids has the highest glucocorticoid activity and the lowest mineralocorticoid activity:
   a. Cortisol
   b. 9α-Fluorocortisol
   c. Prednisolone
   d. Dexamethasone
   e. Corticosterone

19. Steroid hormones are produced by which of the following glands:
   a. Adrenal cortex and pancreas
   b. Anterior Pituitary and thyroid
   c. Gonads and pineal gland
   d. Parathyroid glands and pancreas
   e. Gonads and adrenal cortex

20. Following slow intravenous infusion in humans, which of the following is increased by epinephrine but decreased by norepinephrine:
   a. Systolic blood pressure
   b. Total peripheral resistance
   c. Mean arterial pressure
   d. Blood glucose level
21. It is known that secretion of noreadrenaline is higher than adrenaline during rest; the reverse occurs during:
   a. Standing from sitting position
   b. Exercise (mild, moderate or severe)
   c. Hypoglycemia
   d. After surgery
   e. Pheochromocytoma

22. Hypokalemia is associated with:
   a. Insulin deficiency
   b. Aldosterone antagonists
   c. Use of diuretics
   d. Acidosis
   e. Addison's disease

23. Regarding thyroid hormones, which of the following is correct:
   a. They are soluble in water
   b. Secretion of TSH is regulated by level of T₃ in blood
   c. They are stored in intracellular rather than extracellular sites
   d. They increase metabolic activity of the brain
   e. The enzyme D3 thyroid deiodinase converts T₄ to T₃

24. The principal steroid hormone secreted by adrenal gland of the fetus is:
   a. Cortisol
   b. Dehydroepiandrosterone
   c. Progesterone
   d. Aldosterone
   e. Corticosterone

25. In myxedema, there is:
   a. Increased rate of metabolism
   b. Reduction of body weight
   c. Increased sweating
   d. Elevation of cholesterol level
   e. Pitting edema

26. Addison's disease is characterized by:
   a. Hypokalemia
   b. Hypernatremia
   c. Hypochloremia
   d. Hyperglycemia
   e. Hyperosmolarity

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THE PANCREAS

Structure
- The pancreas has both: an endocrine part (Islets of Langerhans = (2% of the pancreas)) & an exocrine part (with no ducts = (80% of the pancreas)).
- The islets of Langerhans are collections of cells scattered throughout the pancreas.
- They contain the following types of cells (according to morphology and staining properties):
  - Type A cells (or α): = 20% of all cells; secrete glucagon
  - Type B cells (or β): = 60-75% of all cells; secrete insulin
  - Type D cells (or δ): secrete somatostatin
  - Type F cells: secrete pancreatic poly peptide
- The B cells are located at the center of the islets surrounded by the other cells.
- All the hormones are polypeptides. They control glucose concentration in the blood.

INSULIN

Characteristics & synthesis
- Polypeptide hormone. Consists of 2 chains (A & B) connected by 2 disulfide bridges.
- It is synthesized in the rough endoplasmic reticulum of the beta cells (from mRNA synthesized by a gene on chromosome 11) and then packed into secretory granules in the Golgi apparatus as follows:
  - Preproinsulin (Straight molecule; contains signal peptide (of 23 amino acids), A chain (of 21 amino acids), B chain (of 30 amino acids) & C chain (of 31 amino acids)).
  - Proinsulin (Folded by the 2 disulfide bridges; contains A chain, B chain and C chain; the signal peptides is removed).
- Insulin (Folded by the 2 disulfide bridges; contains A chain and B chain; the C chain is detached but still remains in the secretory granules).
- The preproinsulin loses the signal peptide to give proinsulin. The proinsulin loses the C peptide to give insulin.
- The C peptide is released with insulin in the blood. Its presence in blood indicates endogenous release of insulin.
- Unlike the growth hormone, insulin is not species specific. There are minor differences between human insulin & insulin of other species (e.g. beef and pork insulin).
- This allows their use in humans for treatment of diabetes mellitus. However, the minor differences, although not sufficient to affect activity, are sufficient to induce antigenicity (i.e. antibody formation against the injected insulin).
- Human insulin produced in bacteria by recombinant DNA technology is now available to avoid antibody formation.
- Half life of insulin is about 5 minutes.

**Fig 10.20: Structure of insulin**
Control of insulin secretion
- Not by the hypothalamo-pituitary axis. It is stimulated by:
  - Glucose (see the mechanism described below).
  - Amino acids (leucine, arginine ...) and ketoacids.
  - GIT hormones including glucagon, gastrin, secretin, CCK...(which increase cAMP) and more important: GIP & glucagon like polypeptide “GLP-1” (which increase Ca++ influx through voltage gated channels).
  - Acetylcholine and parasympathetic stimulation (or stimulation of the Rt vagus). Acts on M4 receptors to increase ICF calcium for exocytosis.
  - Drugs (sulfonylureas, theophylline, β adrenergic agonists ...).

Mechanism of insulin release by glucose
- Glucose enters the beta cells via GLUT-2; then it is phosphorylated by glucokinase and converted to pyruvate in the cytoplasm
- Pyruvate enters the mitochondria to give ATP via the citric acid cycle
- ATP in the cytoplasm inhibits ATP-sensitive K+ channels
- This reduces K+ efflux and depolarizes the beta cells resulting in opening of voltage gated calcium channels
- Calcium enters beta cells and facilitate exocytosis of insulin granules
- On the other hand, some pyruvate in the citric acid cycle gives glutamate; glutamate also facilitates exocytosis of insulin granules.

Fig 10.21: Mechanism of insulin release
Insulin secretion is inhibited by:
- 2- Deoxyglucose.
- Somatostatin, catecholamines, galanin & insulin.
- Drugs (α adrenergic agonists, β adrenergic blockers, diazoxide, thiazide diuretics, phenytoin, alloxan …).
- Potassium depletion.
- Galanin (polypeptide released by some autonomic neurons; activates the ATP sensitive potassium channels to inhibit insulin release).

Remember that: The basal rate of insulin secretion is about 1 unit per hour; however, this increases to 5-10 units following a meal.
- Therefore the average insulin secretion per day is about 40 units.

**Effects of insulin**
- Insulin is a true anabolic and growth promoting hormone. It acts on cell membrane receptors. Its effects can be divided into rapid, intermediate and delayed effects:
  **Rapid effects (within seconds):**
  - Increases entry of the following inside insulin sensitive cells (e.g. muscle, fat, liver cells …):
    - Glucose
    - Amino acids
    - Potassium
  - Insulin increases glucose entry by increasing number of the glucose transporters 4 (GLUT-4) in the muscle and fat cells.
  - In the liver cells, which are permeable to glucose, insulin stimulates glucokinase; this decreases the free glucose intracellularly and therefore facilitates glucose entry inside the liver cells.
- The cells which do not need insulin to facilitate uptake of glucose are the cells of the:
  - Brain
  - Kidney
  - Intestine
  - Red blood cells

- Insulin increases potassium entry by unknown mechanism (may be by increasing the activity of the Na⁺-K⁺ ATPase pump).

**Intermediate effects (within minutes):**
- Increases synthesis & inhibits catabolism of glycogen, fat and protein.
- Inhibits gluconeogenesis.
- Activates lipoprotein lipase & inhibits hormone-sensitive lipase.

**Delayed effects (within hours):**
- Increases mRNAs for the enzymes involved in anabolism (= increases growth).

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**Remember that:** Insulin (with glucose infusion) is used clinically for rapid reduction of high plasma potassium.
- This is a life saving treatment in patients with hyperkalemia due to renal failure; waiting for dialysis. (They are given insulin with glucose infusion)

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**Insulin receptors**
- Insulin receptors are tetramer made up of two α and two β glycoprotein subunits; connected together by disulfide bridges.
- They are synthesized by a gene on chromosome 19; their molecular weight is about 340,000.
- The α subunits are located extracellularly whereas the β subunits span the cell membrane; with a tyrosine kinase activity in their intracellular portions.
- The mechanism of insulin action can be summarized in the following steps:
  - Insulin is attached to its binding site in the \( \alpha \) subunits
  - The tyrosine kinase activity in the \( \beta \) subunits is triggered producing autophosphorylation of the \( \beta \) subunits.
  - The autophosphorylation allows phosphorylation of some proteins and dephosphorylation of others.
  - The proteins mediate insulin effects.

### Abnormalities

- **Insulin excess: Hypoglycemia**
  - It may be caused by insulinoma, insulin injections or hypoglycemic drugs.
  - Insulin secretion is totally inhibited when glucose level in plasma is about 80 mg/dL (= normal level).
  - Further reduction of glucose stimulates the counter-regulatory hormones: glucagon, epinephrine, growth hormone and then cortisol (all these are hyperglycemic). Then symptoms of hypoglycemia start to develop with any further reduction in glucose level.
  - Symptoms in order of appearance, as glucose decreases, include:
    - Symptoms of autonomic discharge (sweating, palpitations, tremors & irritability).
    - Neuroglycopenic symptoms (hunger and confusion).
    - Lethargy & coma.
    - Convulsions
    - Permanent brain damage & death
  - Diabetic patients are usually aware of the symptoms of autonomic discharge (sweating, palpitations, tremors & irritability) as indications of hypoglycemia. However, some patients with long-term diabetes may develop hypoglycemic coma without having these symptoms.
Insulin deficiency: Diabetes Mellitus (DM).
- DM is a state of hyperglycemia and abnormal protein and fat metabolism resulting from absolute or relative insulin deficiency.

Diabetes mellitus is divided into 2 main types:
- IDDM: insulin dependent DM or type 1; appears early in life due to absolute insulin deficiency caused by autoimmune destruction of the beta cells. It is treated by insulin.
- NIDDM: Non insulin dependent DM or type 2; appears later in life, usually after the age of 40 years, due to relative insulin deficiency caused by insulin resistance (associated with obesity) and beta cell exhaustion. It is treated by oral hypoglycemic drugs.

- Both types (especially type 2 DM) usually occur in a genetically susceptible individuals.
- Other clinical types of D.M. include:
  - Secondary D.M. (secondary to acomegaly, pheochromocytoma, Cushing’s syndrome, chronic pancreatitis, pancreatectomy and drugs like diazoxide and thiazide diuretics).

The metabolic abnormalities in diabetes include:
- CHO: Hyperglycemia due to decreased entry of glucose in cells and increased output of glucose from the liver. Glucose output from the liver is high due to increased glycogenolysis and gluconeogenesis (resulting from not only the low insulin but also a high glucagon level in diabetes).
- Protein: Decreased entry of amino acids in cells; decreased synthesis of protein, increased their catablism and increased conversion of amino acids into glucose in the liver (negative nitrogen balance).
Fat: Increased level of free fatty acids, triglycerides and cholesterol in plasma due to:
  - Increased mobilization from adipose tissue (because the hormone-sensitive lipase is not inhibited by insulin)
  - Decreased deposition in adipose tissue (because the lipoprotein lipase is not activated by insulin)
  - Decreased lipogenesis with increased lipolysis in the liver (resulting in excessive acetyl-Co A production).
  - Decreased removal of VLDL and LDL from the circulation by the liver.

Ketosis: The excess acetyl-Co A is converted to ketone bodies (acetoacetic acid “which gives acetone” and beta-hydroxybutyric acid).
  - The ketone bodies are important source of energy in diabetes and also in the normal fasting state.
  - However, in diabetes they cause acidosis and consequently coma (= coma of diabetic keto-acidosis “DKA”).

Water and electrolytes: Dehydration and decreased total body Na⁺ & K⁺ occur due to polyuria and loss of Na⁺ & K⁺ in urine with the anions of ketone bodies.
  - Plasma Na⁺ is low when Na⁺ is lost in excess of water; however, plasma K⁺ is usually normal (because K⁺ moves out from cells in acidosis), except after treatment with insulin when K⁺ returns back to the cells.

Symptoms and signs of DM include:
  - Fatigue (due to low entry of glucose in muscle and depletion of its glycogen stores).
  - Polyuria (large urine volume due to loss of glucose in urine “osmotic diuresis”).
- Polydipsia (excessive thirst due to hypovolemia and hyperosmolarity caused by the polyuria).
- Hyperphagia (increased appetite due to decreased utilization of glucose by the cells of the ventromedial nuclei of the hypothalamus “satiety center”; thus allowing the appetite area to work without inhibition).
- Weight loss (due to loss of the energy substrate “glucose” in urine and its failure to enter the cells; the cells use protein and fat as alternative sources of energy).
- Kussmaul breathing (rapid deep respiration due to acidosis as in DKA).
- Coma (occurs due to many causes: diabetic keto-acidosis, non ketotic hyperosmolar coma, lactic acidosis and rarely brain edema).

Remember that: A diabetic patient may also present with hypoglycemic coma due to wrong higher dose of insulin or increased exercise with low food intake. This is usually fatal if not treated immediately.

**Investigations show:**
- Hyperglycemia (especially following meals due to decreased entry of glucose in cells and increased output of glucose from the liver).
- Glycosuria (when glucose concentration exceeds the renal threshold “180 mg/dL”).
- Ketosis & ketonuria (ketone bodies like acetone in plasma & urine; when D.M. is complicated by diabetic ketoacidosis (DKA)).
- Acidosis (low plasma pH due to the ketone bodies; when D.M. is complicated by diabetic ketoacidosis (DKA)).
- High Hb A1C (the glycated Hb is high; it is measured for follow up not for diagnosis).
- Diabetic curve in the oral glucose tolerance test “GTT”.
**Diagnosis of D.M. using the GTT:**

- Diagnosis is sometimes achieved by the oral glucose tolerance test.
- Here a standard dose of glucose (75 g) is administered orally. The concentration of glucose in venous blood is measured before administration of glucose “fasting” and then 0.5, 1.0, 1.5 and 2.0 hours after the dose (or just before the dose and then after 2.0 hours).
- A normal GTT curve is obtained when glucose in venous blood is:
  - Less than 110 mg/dL in the fasting state, before the dose (= less than 6.8 mmol/L).
  - Less than 180 mg/dL after 0.5-1.5 hours following the dose (= less than 10.0 mmol/L).
  - Less than 140 mg/dL after 2.0 hours (= less than 7.8 mmol/L).

- Abnormal glucose tolerance curves include
  - Diabetic curve: According to the latest WHO guidelines, a fasting glucose level of more than or equals 126 mg/dL (≥ 7.0 mmol/L) or a result of more than or equals 200 mg/dL after the 2.0 hours (≥ 11.1 mmol/L) indicates D.M.
  - Impaired GTT: Defined as two-hour glucose levels of 140 mg to 199 mg/dL (or 7.8 to 11.0 mmol/L). It may precede type II diabetes mellitus by many years & it is a known risk factor for cardiovascular ischemic problems.
  - Lag storage curve: Caused by partial gastrectomy & hyperthyroidism. The blood sugar rises rapidly from a normal fasting value to more than 180 mg/100 ml (due to the rapid absorption) but returns to the fasting value within 120 min & may overshoots to cause symptoms of hypoglycemia two hours after the test.
  - Curve of liver disease: This is a diabetic curve but the fasting plasma glucose level is low.
Complications expected in diabetic patients include:

- **Acute complications:**
  1. Diabetic ketoacidosis (DKA)
  2. Hyperosmolar non-ketotic coma

- **Long term complications:**
  1. Macro-vascular atherosclerosis (due to the high cholesterol; results in increased risk of stroke and ischemic heart disease “MI”).
  3. Peripheral neuropathy and autonomic neuropathy.
  4. Increased susceptibility to infections.

- For this reason, D.M. should be controlled tightly to avoid these complications.
Treatment of D.M.

Medical treatment includes:
- Insulin injections: for type 1 D.M.; given daily as a combination of short acting (e.g. regular insulin) and long acting insulin (e.g. lente insulin).
- Hypoglycemic drugs: for type 2 D.M.; these include:
  - Sulfonylureas (e.g. glibenclamide, glipizide …): These inhibit ATP sensitive K channels to stimulate insulin release.
  - Biguanides (e.g. metformin): This decreases glucose output by the liver by inhibiting gluconeogenesis.

Non-medical treatment includes:
- Diet control (high fiber diet, low in fat and refined sugars).
- Weight reduction (especially important in obese patients with the metabolic syndrome “syndrome X”). The increased adipose tissue in these patients is associated with high insulin resistance & weight loss decreases insulin resistance.
- Regular exercise (facilitates entry of glucose into the cells by stimulating insertion of GLUT-4 into their membranes).

Remember that: Features of “syndrome X” include: Obesity, insulin resistance (hyperinsulinemia), dyslipidemia (high triglycerides and low HDL) and atherosclerosis.

Fig 10.2 : Consequences of hypoglycemia:

<table>
<thead>
<tr>
<th>No.</th>
<th>ICF hypoglycemia results in:</th>
<th>ECF hyperglycemia results in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-</td>
<td>Increased catabolism of fat and protein</td>
<td>Glycosuria</td>
</tr>
<tr>
<td>2-</td>
<td>Ketone body formation</td>
<td>Osmotic diuresis = polyuria</td>
</tr>
<tr>
<td>3-</td>
<td>Hyperphagia</td>
<td>Dehydraion</td>
</tr>
<tr>
<td>4-</td>
<td>Depletion of glycogen stores</td>
<td>Polydipsia</td>
</tr>
<tr>
<td>5-</td>
<td>Weight loss</td>
<td>Increased Hb A\textsubscript{1C}</td>
</tr>
</tbody>
</table>

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GLUCAGON

Characteristics
- Polypeptide hormone of 29 amino acids in a single chain (molecular weight = 3485).
- Produced by A cells of the pancreas, L cells of the upper GIT and the brain.
- The preproglucagon at these sites gives glucagon plus other fragments; for example:
  o Glicentin (polypeptide with glucagon activity; released from upper GIT).
  o GLP-1 & 2 (glucagon like polypeptides; of these, GLP-1 is a potent stimulus for insulin release (more potent than GIP) & GLP-2 is a neurotransmitter. Both are produced in upper GIT and the brain).
  o Half life = 5–10 min.
  o Metabolism mainly in the liver; that is why its level is higher in patients with cirrhosis.

Effects of glucagon
- Glucagon is a hyperglycemis and a lipolytic hormone. It exerts the following effects:
  ▪ Glycogenolysis (in the liver but not in muscle).
  ▪ Gluconeogenesis.
  ▪ Lipolysis.
  ▪ Ketogenesis.
  ▪ Increased metabolic rate (= calorigenic effect). This is due to both hyperglycemia and increased hepatic deamination of amino acids.
  ▪ Positive inotropic effect on the heart (= increased contractility of the heart; but only when injected in large doses).
  ▪ Stimulates secretion of some hormones (growth hormone, insulin & somatostatin).
**Mechanism of action**
- Glucagon acts on cell membrane receptors, with cAMP as a second messenger; however, it also acts through Ca^{++} (note that both are activated through G-protein, see the introduction).
- cAMP, through protein kinase A, activates phosphorylase A (the enzyme responsible for release of glucose-1-phosphate from glycogen in the liver).

| Remember that | the enzyme “phosphorylase A” is not present in muscle cells, that is why glucagon cannot cause glycogenolysis in muscles. |

**Control of glucagon**
- Glucagon is stimulated by:
  - Amino acids (especially alanine, glycine, serine, cysteine & threonine).
  - GIT hormones (gastrin, CCK …).
  - Other hormones (cortisol, catecholamines …)
  - Sympathetic and stresses (emotions, exercise, infections …).
  - Parasympathetic (right vagus) and acetylcholine.
  - Drugs (β adrenergic agonists, theophilline …)
  - Fasting and starvation (glucagon increases and reaches a peak on the 3rd day (= day of maximum gluconeogenesis); then it declines).
- Glucagon is inhibited by:
  - Glucose
  - Free fatty acids
  - Ketones
  - Hormones (insulin, somatostatin, secretin …).
  - GABA
  - Drugs (phenytoin, α adrenergic agonists …).
Remember that: Insulin and glucagon have opposite effects; that is why when the concentration of one hormone rises in plasma, the other declines.
- For example the insulin-glucagon molar ratio is high in some situations (e.g. following a carbohydrate meal, a protein meal or glucose infusion); and low in others (e.g. during starvation “especially the 3rd day”).

**Abnormalities of glucagon**

**Glucagonoma:**
- Glycogen excess, caused by a pancreatic tumor secreting glucagon, results in hyperglycemia & other clinical manifestations due to glucagon excess.
- Its treatment includes administration of a somatostatin analogue (e.g. octreotide).

**SOMATOSTATIN**

**Characteristics & effects**
- Peptide hormone found in two forms (14 and 28 amino acids); produced by many sites in the body:
  - The brain: acting as a neurotransmitter.
  - The hypothalamus: acting as a growth hormone inhibitory hormone.
  - The GIT: acting as inhibitory hormone to other GIT hormones and to HCL secretion.
  - The pancreas: acting as inhibitory hormone to insulin, glucagon & pancreatic polypeptide.

Remember that: Hormones inhibited by somatostatin include insulin, glucagon, pancreatic polypeptide, growth hormone, thyroid stimulating hormone, VIP, GIP, secretin, CCK and gastrin.
Stimuli of somatostatin
- Include many stimuli of insulin (e.g. glucose, amino acids and CCK).

Abnormalities
- Pancreatic tumors secreting somatostatin result in hyperglycemia (Diabetes mellitus).

PANCREATIC POLYPEPTIDE
- Polypeptide hormone (36 amino acids). Similar in structure to:
  - Polypeptide YY (GI tract hormone).
  - Neuropeptide Y (found in the brain and autonomic nervous system).
- It is stimulated by parasympathetic, hypoglycemia, fasting, protein meal and exercise and it is inhibited by atropine, somatostatin and intravenous infusion of glucose.
- Pancreatic polypeptide slows the absorption of food in humans; however, its exact function is unknown.

Effects of exercise and hormones on CHO metabolism
- Exercise increases entry of glucose into skeletal muscle cells (by increasing GLUT-4 on cell membranes).
- Catecholamines cause an initial glycogenolysis followed by glycogen synthesis (initially they cause glycogenolysis in the liver but in the muscles glucose is converted to pyruvate and this is converted to lactate which diffuses to the circulation. When it reaches the liver, it is converted back to pyruvate and then to glycogen).
- Other effects of catecholamines (increase FFAs, decrease peripheral utilization of glucose and increase metabolic rate (increase lactate oxidation = calorigenic effect).
- Thyroid hormones increase intestinal absorption of glucose and potentiate the glycogenolytic effects of catecholamines. The hormones
also increase degradation of insulin. All these effects aggravate hyperglycemia in diabetics.

- Cortisol causes hyperglycemia and diabetes by antagonizing the peripheral effects of insulin (inhibits glucose phosphorylation), increases protein breakdown & increases gluconeogenesis (by glucagon permissive effect). It also increases glycogenesis and ketogenesis.

- Growth hormone causes hyperglycemia and diabetes by anti-insulin effects. It decreases uptake of glucose, increases mobilization of fat, increases ketogenesis and increases hepatic release of glucose. These effects are partially direct “due to GH” or indirect “due to IGF-1”.
REGULATION OF CALCIUM

INTRODUCTION

Calcium
Calcium in the body and its concentration in plasma
- Total body calcium in adults = 1100 grams (≈ 1kg). About 99% of this amount is found in bone whereas 1% is found in soft tissues & plasma. However, some calcium in bone is exchangeable with plasma.
- The level of calcium in plasma = 9-10.5 mg/dL or 2.1-2.6 mmol/L.
- About 53% (1.34 mmol/L) of plasma calcium is diffusible (i.e. ionized or complexed to citrate & bicarbonate) whereas 47% (1.16 mmol/L) is non-diffusible (i.e. bound to plasma proteins “albumin & globulin”).
- Calcium level in the plasma is affected by:
  - Total amount of proteins
  - Other electrolytes
  - pH (affects the ionized calcium not the total calcium in plasma)
- At low pH (acidosis), hydrogen ions are buffered by protein; therefore calcium binding to protein is decreased and the ionized calcium is increased. The opposite occurs at high pH (alkalosis).

Calcium in diet and its absorption
- Dietary sources of calcium include milk, milk products, other animal products & certain plants.
- Plants are not regarded as an important source of calcium since they contain high amounts of phosphate & oxalate which decrease calcium absorption.
- About 30-80% of ingested calcium is absorbed at the small intestine.
- Sites of absorption:
  - Duodenum (most efficient part)
  - Ileum (absorbs 60% of ingested calcium)
- Mechanisms of absorption:
  - Active transport (regulated by vitamin D)
  - Passive diffusion

- Factors that increase absorption:
  - Vitamin D
  - Protein diet

- Factors that decrease absorption:
  - Phosphate, oxalate
  - Caffeine
  - Fats (e.g. due to decreased bile salts)
  - High intestinal pH (e.g. due to gastrectomy)

**Calcium excretion**

- Calcium is excreted mainly in stool and some amount is excreted in urine.

- The filtered load of calcium in the kidney is about 450 mmol/day whereas the amount excreted is about 5 mmol/day indicating that 98-99% of filtered calcium is reabsorbed in the renal tubules.

- Reabsorption occurs in the PCT (reabsorbs about 60%), loop of Henle (ascending limb) and the DCT (here the amount reabsorbed is controlled by the parathyroid hormone).

**Functions of calcium**

- Formation of bone & teeth
- Contraction of muscles
- Conduction in nerves (facilitates exocytosis of neurotransmitters at the synapses)
- Intracellular second messenger
- Hemostasis (regarded as the clotting factor number 4). Many anticoagulants act by binding Ca^{++} (e.g. citrate, phosphate, EDTA …)
**Phosphate**

**Phosphate in the body & plasma**
- Total phosphate in adults is about 500-800 g; most of this amount (85-90%) is found in the skeleton.
- Concentration of phosphate in the plasma = 12 mg/dL.
- About two thirds of phosphate in plasma is organic phosphorus whereas one third is inorganic.
- Phosphorus is found in the following compounds:
  - ATP
  - cAMP
  - 2,3 DPG
  - Phosphoproteins
  - phospholipids

**Absorption of phosphate in the intestine**
- Phosphate is absorbed in the duodenum. Mechanisms of absorption:
  - Active transport (stimulated by vitamin D).
  - Simple diffusion

**Reabsorption of phosphate in the kidney**
- About 85-90% of filtered phosphate is reabsorbed actively; mainly in the PCT. PTH decreases reabsorption in the PCT.

**Bone**

**Structure of bone**
- Bone is a rigid structure that forms the skeleton. It is a type of connective tissue consisting of bone cells and a hard matrix surrounding the cells.
- The matrix consists of organic substances (collagen, especially type 1) and inorganic substances (salts of calcium and phosphate known as “hydroxyapatites”).
- The bone cells are many types; two of these types participate in calcium homeostasis:

- **Osteoblasts** (modified fibroblasts responsible for bone formation by laying down osteoid (contains collagen) and releasing alkaline phosphatase enzyme (involved in bone mineralization); resulting in transfer of calcium from the plasma to the bone matrix. These cells are activated by many hormones including vitamin D, growth hormone, thyroid hormones and sex hormones (estrogens & androgens).

- **Osteoclasts** (these cells are derived from monocytes. They are responsible for bone resorption. They break down collagen and release calcium from bone to the plasma). They are stimulated by PTH and also by vitamin D; and they are inhibited by calcitonin and certain drugs (e.g. bisphosphonates).

| Remember that: bone resorption (by osteoclasts) is followed by bone formation (by osteoblasts) in repeated cycles known as bone remodeling. These cycles continue throughout life. |

- There are two types of bone:

- **Compact bone** (= the outer layer of most bones; also known as cortical bone. It constitutes about 80% of the whole skeleton. Its cells receive their nutrition through Haversian canals (which contain blood vessels).

- **Spongy bone** (= the inner layer of bones; also known as trabecular bone. It constitutes about 20% of the whole skeleton but its surface area is larger than that of the compact bone. Its cells receive their nutrition by diffusion from the ECF).

**Bone growth**

- Most bones in the body are modeled in cartilage (during fetal life) which then undergoes ossification to form bone (= endochondral ossification).
Exceptions include the clavicles, mandibles and certain bones in the skull; these form bone directly (= intramembranous ossification).
- Linear bone growth (i.e. the increase in length) occurs during the growth period as long as the epiphyseal plate lays down new bone on the shaft side.
- The epiphyseal plate is the active cartilage that separates the end of a long bone “epiphysis” from the shaft “diaphysis”.
- Linear bone growth stops after puberty by ossification of the epiphyseal plate (= epiphyseal closure).
- This occurs due to estrogens (which are secreted by the ovaries in females or formed in the adipose tissue from androgens in males).
- The width of bones continues to grow throughout life in response to stress by muscles or weight. Remodeling also continues for renewal of bone and repair of fractures.
- Bone growth is affected by many hormones especially the growth hormone and IGF-1.

Functions of bone
- Functions of bone include:
  - Protection of vital organs (e.g. the brain, the spinal cord and the heart)
  - Movement and support (provides attachments for muscles and functions with the tendons, ligaments and joints to move the body)
  - Production of blood cells (hematopoiesis by the bone marrow)
  - Detoxification (stores some heavy metals to remove them from the blood)
  - Participation in hearing (can conduct sound waves “bone conduction”)
Diseases of bone

1- Osteoporosis
- Loss of bone matrix (or decreased bone mineral density); resulting in increased possibility of fractures.
- It develops when the rate of bone resorption exceeds the rate of formation; as in hyperparathyroidism, Cushing’s syndrome and postmenopausal period (decreased estrogen).

2- Osteopetrosis
- Excessive bone matrix (or increased bone mineral density); known as “marble bone disease”. Also results in increased fractures
- It is a rare inherited disorder characterized by defective osteoclasts; allowing the osteoblasts to lay down excessive amount of bone matrix.

3- Rickets and osteomalacia
- Rickets is softening and weakening of bones in children, leading to deformities and fractures. Deformities appear in many sites including the legs, ribs, wrists and skull.
- It is caused by severe and prolonged vitamin D deficiency or low Ca++ in diet; resulting in hypocalcemia and failure of bone mineralization.
- Osteomalacia is a similar condition in adults (= adult rickets).

4- Paget’s disease
- A chronic bone disorder characterized by bone deformities; described by James Paget.
- It results from excessive bone resorption due to increased osteoclastic activity.
- The osteoblastic activity is also increased as compensation; however, bone formation is disorganized, resulting in the deformities.
- It is treated by inhibition of osteoclastic activity using biphosphonates or calcitonin.
REGULATION OF CALCIUM

- Many hormones participate in calcium homeostasis; however, the most important are:
  - Parathyroid hormone (hypercalcemic; the most important, essential for life).
  - Vitamin D (hypercalcemic)
  - Calcitonin (hypocalcemic)

THE PARATHYROID HORMONE “PTH”

The parathyroid glands

- These are four small glands or more; each one is (3 x 6 x 2 mm), weighing about 20-50 mg.
- They lie in the posterior surface of the thyroid gland but their location may vary considerably; for example, they may be found in the chest.
- They are discovered by a Swedish medical student in 1880.
- They contain two types of cells:
  - Chief cells (or principal cells): The most abundant cells. They secrete PTH.
  - Oxyphil cells: Their function is unknown.

Fig 10.23: The parathyroid glands
Characteristics of the PTH
- PTH is a linear polypeptide (84 amino acids).
- Produced by chief cells in the parathyroid gland as prepro-parathyroid hormone (115 aa); this gives pro-parathyroid hormone (90 aa) and then parathyroid hormone (84 aa).
- The mature hormone is packed within the Golgi apparatus into secretory vesicles & secreted into the blood by exocytosis.
- Half life is about 10 min; fragmented in the liver & excreted by the kidney.

Control of the PTH
- It is not controlled by the hypothalamo-pituitary axis. It is increased by:
  - Hypocalcemia
  - Hypomagnesemia
  - Hyperphosphatemia (lowers plasma calcium and inhibits 1,25 (OH)2 D3).
  - Stimulation of β 2 receptors
- It is decreased by:
  - Hypercalcemia (-ve feedback)
  - Hypermagnesemia
  - Increased 1,25 dihydroxy-cholecalciferol

Mechanism of action
- PTH acts on cell membrane receptors bound to G-protein, with cAMP as the main second messenger.

Effects of PTH
- PTH is essential for regulation of calcium & phosphate level in plasma:
  - Increases calcium level (Hypercalcemic)
  - Decreases phosphate level (Hypophosphatemic)
- It acts on the bone and kidneys (directly) and on the intestine (indirectly) as follows:
o **Bone:**
  - Stimulates osteoclasts to increase bone resorption and release calcium

o **Kidney:**
  - Stimulates calcium reabsorption (in the DCTs & CDs)
  - Decreases phosphate reabsorption (in the PCTs)
  - Activates vitamin D (by activating the enzyme 1-α hydroxylase to add (OH) on carbon number 1)

o **Intestine:**
  - Increases calcium absorption indirectly (by activating vitamin D).

**Abnormalities**

- **Primary hyperparathyroidism**
  - Increased production of PTH due to:
    - Tumor in the parathyroid gland (either alone or multiple endocrine neoplasia "MEN")
    - A tumor in other site secreting PTH (e.g. lung tumor)
  - Patients develop hypercalcemia & hypophosphatemia.
  - Symptoms & signs do not appear early (asymptomatic); however, later patient may develop:
    - Bone manifestations (due to removal of calcium from bone):
      - Osteitis fibrosa cystica (subperiosteal resorption & bone cysts)
      - Osteoporosis
      - Fractures
    - Manifestations of hypercalcemia
      - Increased filtered load of calcium in the kidney & increased excretion of calcium & phosphate (hypercalciuria & hyperphosphaturia)
- Polyuria (osmotic diuresis)
- Renal stones (due to the hypercalciuria & hyperphosphaturia)
- Deposition of calcium in tissues (calcifications)
- Muscle weakness
- Impaired memory & mental confusion
- Coma

- **Secondary hyperparathyroidism**
  - Increased production of PTH due to chronic hypocalcemia (as in chronic renal failure, or rickets).
  - The condition is associated with hypertrophy of the parathyroid glands, and if the hypocalcemia persists for long time, the secondary hyperparathyroidism may be complicated by autonomus release of PTH causing **tertiary hyperparathyroidism** (with hypercalcemia).

- **Hypoparathyroidism**
  - Decreased production of PTH due to damage to the parathyroid glands by a tumor, auto-antibodies, or surgical removal.
  - Features:
    - Hypocalcemia
    - Convulsions
    - Neuro-muscular hyperexcitability (= tetany)

**TETANY**
= Neuromuscular hyper-excitability caused by hypocalcemia.
- Characterized by numbness or tingling sensation in the fingers, toes and lips, carpal or carpopedal spasm, muscle cramps, and risk of death due to laryngeal spasm.
It is explained as follows:

- The leak channels of sodium are guarded by calcium ions
- In hypocalcemia, sodium ions enter the muscle and nerve cells, thus elevating the resting membrane potential towards the threshold and making these cells more excitable “= latent tetany”.
- When the resting membrane potential reaches the threshold (in more severe hypocalcemia), the cells become excited and signs of tetany appear “= overt tetany”).

Therefore, two types of tetany can be described:

- Overt tetany
- Latent tetany

**Overt tetany**

- Signs of tetany (carpal spasm, muscle cramps and laryngeal spasm) appear because the resting membrane potential reaches the threshold.

**Latent tetany**

- Signs of tetany (e.g. carpal spasm & muscle cramps) do not appear because the resting membrane potential does not reach the threshold. However, the signs can be demonstrated by:
  - Chvostek’s sign (tapping the facial nerve causes contraction of facial muscles)
  - Trousseau’s sign (arresting blood flow to the forearm by sphygmomanometer causes carpal spasm)

**Fig 10.24: Carpal spasm in tetany**
- Causes of hypocalcemia that results in tetany include:
    - Thyroidectomy (the parathyroids are also removed; symptoms develop after 2 days or more).
    - Respiratory alkalosis (hyperventilation)
    - Metabolic alkalosis (vomiting, Cushing’s & Conn’s syndromes)

- **Pseudohypoparathyroidism**
  - Due to receptor disease
  - Characterized by the same signs & symptoms of hypoparathyroidism but with normal or elevated level of PTH

**PARATHYROID HORMONE RELATED PROTEIN “PTHRP”**
- Polypeptide (140 aa); partially similar to PTH.
- Acts on the same receptors of PTH (some of the receptors).
- It is produced loccly “local hormone” by different tissues in the body including: (Fetal cartilage, brain, breast, teeth, skin & smooth muscle).

**Actions:**
    - Growth & development of cartilage in the fetus
    - Inhibits excitotoxic damage to the developing neurons
    - Involved in calcium transport in placenta
    - Essential for teeth eruption
    - A cause of hypercalcemia in some malignancies

**SUMMARY TO THE CAUSES OF HYPERCALCEMIA**

- **Parathyroid hormone-related**
  - Primary hyperparathyroidism
  - Tertiary hyperparathyroidism

- **Vitamin D-related**
  - Vitamin D intoxication
- Granulomatous disease sarcoidosis, berylliosis, tuberculosis
- Hodgkin's lymphoma

**Malignancy**
- Humoral hypercalcemia of malignancy (mediated by PTHrP)
- Local osteolysis by secondaries from breast, skin or gonads (mediated by cytokines)

**Medications**
- Thiazide diuretics (usually mild), Lithium ...
- Milk-alkali syndrome (from calcium antacids)

**Other endocrine disorders**
- Hyperthyroidism
- Adrenal insufficiency
- Acromegaly
- Pheochromocytoma

**Others**
- Familial hypocalciuric hypercalcemia: mutated calcium-sensing receptor which mediate the −ve feedback effect of Ca^{++} on PTH
- Immobilization, with high bone turnover
- Paget's disease

**VITAMIN D**

**Characteristics, sources and activation**
- Vitamin D is a group of fat soluble vitamins that includes vitamin D_2_ (ergocalciferol) and vitamin D_3_ (cholecalciferol).
- The vitamins in this group and their metabolites are secosteroids (i.e. one of the rings in each steroid nucleus is open).
- Vitamin D_2_ is derived from plants and can substitute for Vitamin D_3_ in humans; however vitamin D_3_ is the major circulating form in the body.
- Vitamin D₃ “cholecalciferol” is synthesized in the skin by the action of sunlight on 7-dehydrocholesterol. It is also ingested with food.
- It is activated in the liver to form 25-hydroxycholecalciferol “25(OH) D₃” or “calcidiol” and then in the kidney (in the PCT cells) to form 1, 25-dihydroxycholecalciferol “1, 25 (OH)₂ D₃” or “calcitriol”; which is the active form. Activation in the kidney is catalyzed by the enzyme 1α hydroxylase. This enzyme is activated by PTH and other hormones (PTH, growth hormone, prolactin, human chorionic somatomammotropin and calcitonin).
- The active form “1, 25 (OH)₂ D₃” is also formed in the following sites: the placenta, the skin keratinocytes and the macrophages like the alveolar macrophages (this explains the hypercalcemia in patients with sarcoidosis).
- Vitamin D₃ is transported in plasma bound to the globulin: “vitamin D binding protein” & can be stored in the liver.

**Control**

- 1,25 (OH)₂ D₃ formation (the active form of vitamin D) is increased by:
  - Hypocalcemia
  - Hypophosphatemia
  - PTH, growth hormone, prolactin, human chorionic somatomammotropin “hCS” and calcitonin (all these hormones increase the activity of 1α-hydroxylase).
  - Estrogens (increase the total not the free form “by increasing the binding protein”).

- 1,25 (OH)₂ D₃ is inhibited by:
  - Hypercalcemia (here the kidneys form the inactive compound 24,25 (OH)₂ D₃)
  - Hyperphosphatemia
o 1,25 (OH)$_2$ D$_3$ (exerts -ve feedback on its own formation “i.e. it inhibits the enzyme 1α-hydroxylase”. It also exerts +ve feedback effect on the formation of 24,25 (OH)$_2$D$_3$ and an inhibitory effect on PTH production).

- Hyperparathyroidism (decreases the level of the hormone and causes osteoporosis).

- Many factors affect vitamin D formation; these include the geographical location, the season, the type of clothing and the color of the skin (melanin in the dark skin decreases penetration of sun light and reduces formation of vitamin D; that is why the whitish skin is more efficient in formation of vitamin D than the dark skin).

- Vitamin D supplementation is especially needed for: Infants, pregnant women, lactating women and old subjects.

**Effects of vitamin D**

- Regulation of calcium & phosphate level in plasma:
  - Increases calcium level (Hypercalcemic)
  - Increases phosphate level (Hyperphosphatemic)

- Sites of action:
  - Intestine: Increases calcium absorption and phosphate absorption.
  - Kidney: Increases calcium reabsorption and phosphate reabsorption.
  - Bone: Stimulates osteoblasts for bone calcification. Activation of the osteoblasts causes secondary activation of osteoblasts.

- In summary vitamin D increases absorption, reabsorption and bone formation (or calcification).

*Remember that:* Vitamin D acts on nuclear receptors. It increases transcription of some mRNAs and inhibits transcription of others.
Examples of mRNAs increased by vitamin D are those which form the calcium binding protein “calbindin D” which facilitates calcium absorption in the intestine.

Other effects of vitamin D “under investigation”: It stimulates differentiation of immune cells and skin keratinocytes and participates in growth regulation.

**Abnormalities**

- **Rickets:**
  - Occurs due to deficiency of vitamin D in children.
  - It is characterized by hypocalcemia and failure of bone mineralization resulting in weakness & bowing of bones (see above).
  - Rarely, rickets may not respond to treatment with vitamin D (= vitamin D resistant rickets). The possible causes include a gene defect involving the enzyme 1α-hydroxylase (type I) or a gene defect involving formation of vitamin D receptors (type II).
  - Note that type I responds to treatment with 1,25 (OH)₂ D₃ whereas type II does not.

- **Osteomalacia:**
  - Deficiency of vitamin D in adults. It si known as adult rickets. It is characterized by weak and easily fractured bones.

**Fig 10.25: Rickets**
CALCITONIN

Characteristics
- Polypeptide hormone (32 aa) that is produced by Clear (C) cells of the thyroid gland. Its half life is less than 10 minutes.

Control
- It is stimulated by: Hypercalcemia, GI hormones (gastrin, CCK, secretin, glucagon) and β adrenergic agonists

Actions
- Lower calcium & phosphate levels in the blood (hypocalcemic and hypophosphatemic)
- Inhibits bone resorption by inhibiting osteoclasts
- Increases calcium excretion in urine

**Remember that:** the physiological role of calcitonin is unknown. It may offer protection against postprandial hypercalcemia (i.e. short-term effect on calcium homeostasis; it has no long-term effect).
- It is used clinically for treatment of Paget’s disease (to inhibit the increased osteoclastic activity) and for treatment of severe hypercalcemia.

Abnormalities
Calcitonin excess: Occurs in medullary carcinoma of the thyroid. It is not associated with symptoms related to calcitonin.
Calcitonin deficiency: No reported syndrome.

**OTHER HORMONES AFFECTING CALCIUM HOMEOSTASIS:**

**Positive balance:**
- Growth hormone, androgens & IGF-1 (stimulate osteoblasts)
- Estrogen (inhibits osteoclasts and stimulates osteoblasts)

**Negative balance:**
- Glucocorticoids (inhibit osteoblasts)
- Thyroxine and vitamin A (stimulate osteoclasts)
**QUESTIONS FOR SELF ASSESSMENT-6 (MCQS)**

1- Physiological effects of glucagon include:
   - a. Glycogenesis in liver
   - b. Lipolysis in adipose tissue
   - c. Glycogenolysis in muscle
   - d. Inotropic effect in the heart
   - e. Stimulation of hunger in hypothalamus

2- In this photo, the endocrine abnormality is known as:
   - a. Gigantism
   - b. Acromegaly
   - c. Rickets
   - d. Diabetes mellitus
   - e. Cushing’s syndrome

3- The parathyroid hormone is stimulated by:
   - a. Low phosphate
   - b. High calcium
   - c. Low glucose
   - d. High chloride
   - e. Low magnesium

4- Calcitonin:
   - a. Is produced by chief cells of the parathyroid gland
   - b. Inhibits calcium mobilization from bone
   - c. Inactivates vitamin D in the kidney
   - d. Inhibits calcium absorption in the intestine
   - e. Excess causes hypocalcemia

5- Clinical features of diabetes mellitus include:
   - a. Oliguria
   - b. Hyperphagia
   - c. Insomnia
   - d. Hyperventilation
   - e. Weight gain

6- Physiological effects of parathyroid hormone include:
   - a. Reabsorption of phosphate
   - b. Deposition of calcium in tissues
   - c. Resorption of bone
   - d. Inhibition of vitamin D formation
   - e. Renal stone formation

7- Hypocalcaemia results in:
   - a. Increased membrane permeability to sodium
   - b. Enhanced transmitter release in the synapse
   - c. Decreased release of PTH
   - d. Increased stability in neurons
   - e. Increased formation of 24,25 D₃ by the kidney
8- All these hormones activate 1α-hydroxylase in the kidney EXCEPT:
   a. Growth hormone
   b. Prolactin
   c. 1,25 (OH)_{2} cholecalciferol
   d. Parathyroid hormone
   e. Calcitonin

9- Abnormal total plasma calcium concentration is a recognized feature in:
   a. Diabetes mellitus
   b. Hyperthyroidism
   c. Conn’s syndrome
   d. Hyperventilation
   e. Medullary carcinoma of the thyroid

10- Insulin production is best stimulated by:
   a. GLP-2
   b. Cholecystokinin
   c. Somatostatin
   d. Gastrin
   e. GIP

11- In the absence of insulin, patients may suffer from:
   a. Hypoglycemia
   b. Hypertension
   c. Hypercalcemia
   d. Metabolic acidosis
   e. Respiratory alkalosis

12- Regulation of plasma calcium in the short term depends on:
   a. Release or suppression of parathyroid hormone
   b. Secretion of calcitonin
   c. Activation of vitamin D3
   d. Renal reabsorption of calcium
   e. Activation of osteoblasts

13- One of the physiological roles of calcitonin is to:
   a. Stimulate bone growth in children
   b. Stimulate bone resorption in old age
   c. Safeguard against osteomalacia
   d. Prevent postprandial hypercalcaemia
   e. Recovery from hypocalcaemic tetany

14- Insulin:
   a. Decreases amino acid entry into cells
   b. Controls glucose absorption in the intestine
   c. Decreases lipoprotein lipase activity in plasma
   d. Increases glucose output from the liver
   e. Requires calcium for secretion from the beta cells

15- Hypoglycemia results in secretion of all of the following EXCEPT:
   a. Glucagon
   b. Somatostatin
   c. Adrenaline
d. Cortisol
e. Growth Hormone

16- This hormone increases calcium absorption:
   a. Calcitonin
   b. Calcitriol
   c. PTH
   d. Pancreatic Polypeptide
   e. Corticotropin Releasing Factor (CRF)

17- Insulin increases the entry of glucose into:
   a. All tissues
   b. Renal tubules
   c. The mucosa of the small intestine
   d. Most neurons of the cerebral cortex
   e. Skeletal muscle

18- Glucose increases plasma insulin by a process that involves:
   a. GLUT1
   b. GLUT2
   c. GLUT3
   d. SGLT1
   e. GLUT4

19- The parathyroid hormone:
   a. Is secreted by the thyroid para-follicular cells
   b. Decreases the renal excretion of phosphates
   c. If increased, it depresses the activity of the anterior pituitary
   d. Secretion is stimulated when blood calcium increases
   e. Mobilizes Ca++ mainly from the bone

20- Activation of hormone-sensitive lipase in adipocytes:
   a. Depends on insulin
   b. Is inhibited by cortisol
   c. Requires cAMP-dependent protein kinase
   d. Results in hydrolysis of cholesterol esters
   e. Increases monoglycerides and diglycerides in adipocytes

21- Prolonged fasting (more than 3 days) is associated with:
   a. Decreased lipolysis
   b. Increased excretion of nitrogen in urine
   c. Decreased gluconeogenesis
   d. Increased secretion of insulin
   e. Increased glucose utilization by the brain
CHAPTER (11)
HUMAN REPRODUCTION

INTRODUCTION
- The anatomical & physiological differences between males & females primarily are due to:
  - Presence or absence of the Y chromosome
  - Presence of either the testes (if Y chromosome is present) or the ovaries (if Y chromosome is absent)
- The testes produce androgens (sex hormones with masculinizing effects) whereas the ovaries produce estrogens (sex hormones with feminizing effects).
- The Y chromosome is essential for formation of the testes because it contains a gene that produces a DNA regulatory protein known as the “SRY” for “sex-determining region of the Y chromosome.” This protein acts as a transcription factor to initiate formation of the testes.

Fig 11.1: Male and female chromosomes

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomes</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td></td>
<td>6 7 8 9 10</td>
<td>6 7 8 9 10</td>
</tr>
<tr>
<td></td>
<td>11 12 13 14 15</td>
<td>11 12 13 14 15</td>
</tr>
<tr>
<td></td>
<td>16 17 18 19 20</td>
<td>16 17 18 19 20</td>
</tr>
<tr>
<td></td>
<td>21 22 X Y</td>
<td>21 22 X X</td>
</tr>
<tr>
<td>Total count Autosomes</td>
<td>23 pairs (= 46 chromosomes)</td>
<td>23 pairs (= 46 chromosomes)</td>
</tr>
<tr>
<td>Sex chr... Note</td>
<td>22 pairs (= 44 chromosomes)</td>
<td>22 pairs (= 44 chromosomes)</td>
</tr>
<tr>
<td></td>
<td>One pair (= XY)</td>
<td>One pair (XX)</td>
</tr>
<tr>
<td></td>
<td>Y chr. is smaller than X</td>
<td>One X chr. is inactive</td>
</tr>
</tbody>
</table>
Remember that: Each ovum produced by female gametogenesis contains 22 chromosomes + X chromosome; whereas each sperm produced by male gametogenesis contains 22 chromosomes + either X or Y chromosome.
- A genetic male (44, XY) results when a sperm containing Y chromosome fertilizes an ovum containing X chromosome.
- A genetic female (44, XX) results when a sperm containing X chromosome fertilizes an ovum containing X chromosome.
- Only one of the X chromosomes in females is active; the inactive one appears as the “Barr body” within the nuclei of female cells or as a “drumstick” in some of their polymorphonuclear leukocytes.

- The embryo in the 7th week of pregnancy has both:
  - The male genital duct (Wolffian duct)
  - The female genital duct (Mullerian duct)
- In the presence of Y chromosome the testes develop. They release:
  1- Testosterone to increase development of the Wolffian duct into epididymis & vas deferens. Testosterone is also converted to dihydrotestosterone, which forms the external genitalia in males.
  2- Mullerian inhibitory substance (MIS) to cause regression of the Mullerian duct.
- In the absence of the Y chromosome the testes do not develop. The ovaries are developed and the Mullerian duct persists. It gives the uterus & the uterine tubes.

**Fig 11.2: Drumstick chromosome**
Abnormalities of sexual differentiation
- These are caused by two main types of abnormalities:
  Chromosomal abnormalities & hormonal abnormalities

Chromosomal abnormalities:
- Occur due to non-disjunction (or failure of separation) of the sex chromosomes during gametogenesis.
- This results in formation of abnormal gametes with 24 & 22 chromosomes rather than 23.
  - Examples for abnormal sperm patterns: (22,XY) and (22,O)
  - Examples for abnormal ovum patterns (22,XX) and (22,O)
- Fertilization that involves an abnormal sperm and/or an abnormal ovum may cause one of the following syndromes:

Turner syndrome
- Also known as “ovarian agenesis” because the ovaries are not developed (streaks). It occurs due to non-disjunction. E.g. when an abnormal sperm (22,O) fertilizes a normal ovum (22,X); the developing subject is a female with 45 chromosomes (44,XO).
- Features of Turner’s syndrome include:
  - Female genitalia with absent ovaries
  - Failure of maturation at puberty (no ovaries = no hormones= no features of puberty)
  - Primary amenorrhea
  - Short stature
  - Broad chest
  - Poor breast development with wide separation of the nipples
  - Webbing of the neck
  - Cubitus valgus (turned-out elbows or increased carrying angle)
  - Congenital anomalies (e.g. coarctation of the aorta)
Klinefelter's syndrome
- Also known as “seminiferous tubule dysgenesis”.
- It occurs due to non-disjunction, for example when an abnormal sperm (22,XY) fertilizes a normal ovum (22,X).
- The developing subject is a male with 47 chromosomes (44,XXY); i.e. with additional X.
- Features of Klinefelter’s syndrome include:
  - Male genitalia with small testicles
  - Azospermia (low sperm count in semen) due to dysgenesis of seminiferous tubules (= reduced fertility “sterility”)
  - Tall stature
  - Gynecomastia
  - Higher incidence of mental retardation

True hermaphroditism
- It also occurs due to non-disjunction.
- The developing subject is a true hermaphrodite with XX / XY mosaicism.
- True hermaphrodite subject has both ovaries & testes

**Fig 11.3: Chromosomal abnormalities of sexual differentiation**
Remember that: The incidence of non-disjunction is increased as the maternal age of the mother increases.

- Non-disjunction also occurs in chromosomes other than the sex chromosomes as in chromosome 21. Here each cell contains three rather than two copies of chromosome 21 (i.e. trisomy 21).
- Patients with trisomy 21 suffer from "Down syndrome" (characterized by mental retardation and certain physical features: flat nasal bridge, low set ears, protruding tongue, single palmar crease and a short neck).
- In addition to non-disjunction, chromosomal abnormalities may involve transposition of some parts of a chromosome to another chromosome (e.g. transposition of the short arm of chromosome Y to the X chromosome of the father). Since the short arm of Y chromosome contains the gene that produces the SRY, which forms the testis; the developing embryo who takes the X from the father and an other X from the mother is a male.

**Fig 11.4: Chromosomal abnormalities**
**Hormonal abnormalities**
- Hormones (usually androgens) result in two types of abnormal sexual differentiation:
  - Female pseudohermaphroditism
  - Male pseudohermaphroditism

**Female pseudohermaphroditism**
- Genetic female (44,XX) but with external genitalia of males (and internal genitalia of females).
- Due to exposure of the female embryo to androgens in intrauterine life (during the 8th to 13th week of gestation).
- Sources of androgens:
  - Mother taking androgens (e.g. athletes)
  - Congenital adrenal hyperplasia

**Male pseudohermaphroditism**
- Genetic males (44,XY) but with external & internal genitalia of females.
- Occurs due to a defect in the testes during development, resulting in failure to secrete androgens & MIS (therefore both the external and the internal genitalia are of females).

**Other causes of Male pseudohermaphroditism:**
- Testicular feminization syndrome
  - This is one of the forms of male pseudohermaphroditism due to “complete androgen resistance” caused by receptor defect.
  - Androgens and MIS are secreted normally; however, because of the receptor defect, androgens fail to form internal or external genitalia of males.
  - On the other hand, the MIS acts normally to prevent formation of female internal genitalia. Therefore in this patient there is female external genitalia but the vagina ends blindly because there is no internal genitalia.
- 5 alpha reductase deficiency
- The enzyme that converts testosterone to dihydrotestosterone (see below).
- 17 alpha hydroxylase deficiency
- See the adrenal gland.

**PUBERTY**

**Definition**
- The period when the endocrine & gametogenic functions of the gonads have first developed to attain reproductive capacity.

**Onset**
- Onset of puberty varies according to genetic and environmental factors.
- It is at the age range of (9-13 y) in females and (11-15 y) in males.

**Mechanism of Onset**
- Although the pituitaries of children contain gonadotrophins and their hypothalami contain GnRHs; their release is inhibited by unkown neural mechanism.
- What initiates the release of these hormones and starts puberty is still unknown. However, it is thought to be some sort of CNS maturation.
- The CNS maturation initiates release of GnRH in a **pulsatile pattern** from the hypothalamus.
- This results in release of gonadotrophins (FSH & LH) from the pituitary gland.
- The gonadotrophins control functions of the gonads and release of the sex hormones (testosterone in males; estrogen and progesterone in females).
- The sex hormones result in appearance of the characteristic features of puberty.
- The hormone **leptin** (the satiety-producing hormone produced by fat cells) probably plays a role in control of puberty. That is why some young females with loss of weight fail to menstruate unless they gain weight.

**Features of puberty**

- Growth spurt.
- Development of secondary sex characters.
- Enlargement of reproductive organs.
- Attainment of reproductive capacity.

  - Note the following features in females:
    - **Thelarche:** Development of the breast (an early feature of puberty in females).
    - **Menarche:** The first menstrual period.
    - **Pubarche:** Development of axillary and pubic hair. Also occurs in males; however, the pattern of hair distribution at the pubic area differs between males and females.
    - **Adrenarche:** Increased secretion of adrenal androgens (occurs in both sexes).

**The secondary sex characters**

*In males:*

- Enlargement of internal genitalia (testes, ducts and glands; the glands start secretion).
- Enlargement of external genitalia (penis and scrotum).
- Deep voice (due to enlargement of the larynx & thickening of the vocal cords).
- Growth of hair in the:
  - Face: beard & moustache; with receding of hairline on the scalp.
  - Pubic area: in a triangular pattern, with its apex facing up.
  - Other areas: axilla, chest, anus & other hair in the body.
- Emotional changes (more active, aggressive and interested in the opposite sex).
- Conformational changes (enlargement of muscles and broadening of shoulders).
- Secretion of sebaceous glands increases and thickens; predisposing to acne.

**In females:**
- Enlargement of the internal genitalia (uterus and vagina).
- Enlargement of the external genitalia (labia majora, labia minora and clitoris).
- Enlargement of the breasts.
- The voice remains high pitched (no enlargement of the larynx).
- Deposition of subcutaneous fat (especially in the breasts and buttocks).
- Development of pubic and axillary hair:
  - Due to adrenal androgens in both sexes (adrenarche)
  - The female pattern of hair distribution at the pubic area is also triangular, with its apex facing down (i.e. flat-topped pattern).
- Emotional changes & conformational changes (broad hips with narrow shoulders).

**Abnormalities of puberty**

**Precocious puberty:**
- Early development of secondary sex characters, due to early release of sex hormones (androgens in males & estrogens in females). The early release of sex hormones may or may not be associated with gonadotrophin release.
  - When the gonadotrophins are also released, the child becomes capable of gametogenesis.
Therefore the precocious puberty is described as true precocious puberty.

When the gonadotrophins are not released, the child is not capable of gametogenesis. Therefore, the precocious puberty is described as pseudo-puberty.

Causes of true precocious puberty:
- Constitutional (no apparent cause)
- Lesions in the posterior hypothalamus (tumor or infection)
- Congenital abnormality

Causes of precocious pseudo-puberty:
- Congenital adrenal hyperplasia (in males)
- Adrenal tumors secreting androgens or estrogens
- Testicular tumors secreting androgens
- Ovarian tumors secreting estrogens

Note: There is no single age that reliably separates normal from abnormal. However, precocious puberty is clinically important because:
- It results in early closure of epiphyseal plates in bones (= short stature).
- It may indicate presence of a tumor in the adrenals or gonads.

Delayed puberty
Can be considered if features of puberty fail to develop by the age of 17 in females or 20 in males. The delay occurs due to failure of gonadotrophin or sex hormone secretion.

Causes of delayed puberty include:
- Pituitary disorder (e.g. panhypopituitarism)
- Chromosomal abnormality (e.g. Turner syndrome)
- Gonadal problems
- Unknown causes
THE MALE REPRODUCTIVE SYSTEM

STRUCTURE

- The male reproductive system consists of the following organs:

The testes

- The testes hang outside the abdominal cavity of the male & lie within the scrotum.

- Each testis is composed of:
  - Seminiferous tubules containing Germ cells (to produce sperms) & Sertoli cells (to do many functions, see below).
  - Interstitial cells “or Leydig cells” (to release testosterone).

- The testes begin their development in the abdominal cavity but descend into the scrotal sacs later during pregnancy.

- This is required because the internal body temperature is too high for sperm production.

Fig 11.5: The testes

The duct system:

Epididymis: The narrow, tightly coiled tube that connects the testes to the vas deferens on each side. It stores sperms produced by the testes until the time of ejaculation. These sperms are immature and not motile. They
become able to swim during their transit through the epididymis; however, final maturation to acquire the ability for fertilization occurs within the female genital tract (= Capacitation).

**Vas deferens:** The muscular duct that connects the epididymis on each side to the ejaculatory ducts. Each tube is about 30 centimeters long. It is part of the spermatic cord. It moves sperms by peristalsis.

**Ejaculatory ducts:** Two ducts, each one is 2 cm in length; formed by the union of the seminal vesicle with the vas deferens. It evacuates semen into the urethra.

**Urethra:** The narrow tube that connects the urinary bladder to the outside of the body. In addition to its excretory function, it has a reproductive function; it transports semen to the outside.

- **Associated glands:**

  **Seminal vesicles:** Two glands, each one is about 5 cm long; found postero-inferior to the urinary bladder and above the prostate. They secrete about 70% of the seminal fluid. Their secretion contains proteins, enzymes, fructose, mucus and prostaglandins. Fructose provides nutritional energy for the sperms within the female genital tract. Its secretion starts at puberty.

  **Prostate:** The exocrine gland that surrounds the urethra just below the urinary bladder. It secretes about 10-30% of the seminal fluid. Its secretion contains prostate specific antigen (PSA), acid phosphatase and zinc. The secretion is slightly alkaline to neutralize acidity in the female genital tract. The PSA hydrolyses inhibitors of sperm motility in semen. Small amount of PSA escapes into the plasma in normal conditions. High plasma level of PSA is an important indicator of prostatic cancer.

  **Cowper's glands:** Also known as “the bulbourethral glands.” Two small exocrine glands, homologous to Bartholin's glands in females. Their ducts
open into the urethra at the base of the penis. They produce a clear, viscous fluid known as (pre-ejaculate). This fluid helps to flush the urethra from any residual urine & to lubricate it for passage of sperms.

**The penis**
The penis is the copulatory organ of the males. It has a long shaft and enlarged tip called the glans penis. It is made up of three columns of erectile tissue: two corpora cavernosum (responsible for erection) and one corpus spongiosum (contains the urethra).

**Fig 11.6: The male reproductive organs**

*Functions of Sertoli cells:*
- Sertoli cells are large, complex glycogen-containing cells. They line the walls of the seminiferous tubules in the testes. They perform many functions, for example:
  - Formation of blood testes barrier "BTB"
    - Formed by fusion of adjacent Sertoli cells by tight junctions near the basal lamina of seminiferous tubules.
- The blood testes barrier prevents passage of large molecules from the interstitium of the testes to the lumen of Seminiferous tubules, where sperms are formed (i.e. protective function).
- Certain substances as testosterone (which is essential for spermatogenesis) crosses this barrier easily.

- **Physical support of germ cells**
  - The survival of germ cells requires direct contact with Sertoli cells.

- **Maintenance of fluid composition in the lumen of seminiferous tubules**
  - The fluid in the lumen of seminiferous tubules differs from that of plasma; it contains less protein & glucose but more androgens, estrogens, K+, inositol & glutamate.

- **Release of Mullerian inhibitory substance "MIS"**
  - The MIS causes regression of Mullerian duct in the male fetus.

- **Release of androgen binding protein**
  - This protein is released by Sertoli cells in response to FSH.
  - It binds testosterone within the lumen of seminiferous tubule to lower its concentration. Therefore, testosterone continues to diffuse passively from the interstitium to the lumen of the tubules.

- **Release of inhibin**
  - A peptide hormone secreted by the gonads in both males and females.
  - In both sexes, it causes inhibition of FSH (as a negative feedback mechanism).

- **Conversion of androgens to estrogens**
  - The enzyme aromatase is found within Sertoli cells.
  - It converts androgens into estrogens.
  - Estrogens in males are also formed from androgens in the adipose tissue.
**Spermatogenesis**

**Definition:**
- Spermatogenesis is the process of sperm production.
- It starts at puberty and continues throughout the life of males.

**Stages:**
- Germ cells or spermatogonia (46 chromosomes) divide to give primary spermatocytes (46 chromosomes) by mitotic division.
- Primary spermatocytes (46 chromosomes) divide to give secondary spermatocytes (23 chromosomes) and then spermatids (23 chromosomes) by the two steps of meiotic division.
- Finally, spermatids are transformed into spermatozoa (23 chromosomes).

**Important points:**
- The process takes 74 days.
- It needs temperature lower than the body (about 32 °C).
- This low temperature is achieved by:
  - Location of the testes outside of the abdominal cavity.
  - The countercurrent system between spermatic arteries and veins at the pampiniform plexus. (By the exchange between the supplying arteries and the draining veins, this system not only maintains low temperature at the scrotum but also maintains high concentration of testosterone within the testes).
- One spermatogonium gives about 512 spermatids.
- At first sperms are not fully motile.
- Motility increases with passage through the epididymis (this involves activation of a protein in the tails of sperms "CatSper" that allows Ca^{++} influx).
Role of hormones in control of spermatogenesis:

- **Testosterone (androgens):** Needed for the last step only (conversion of spermatids to spermatozoa). Previous steps are independent of androgens.

- **FSH:** Acts on Sertoli cells to release androgen binding protein (and inhibin). The androgen binding protein is needed to bind testosterone & maintain it in high concentration within the seminiferous tubules. Inhibin exerts a negative feedback effect on the pituitary to inhibit FSH.

- **LH:** Acts on Leydig cells to release testosterone. Testosterone exerts a negative feedback effect on the pituitary to inhibit LH.
**Semen**
- Fluid ejaculated by the male. Its volume is about 2.5 to 3.5 ml. It contains sperms & secretions of the associated glands (seminal vesicles, prostate & Cowper's glands). Count of sperms: 100 million/ml. Sperm count of less than 20 million/ml indicates infertility.
- The rete testes (at the hilar part of the testes) contain concentrated sperms. Damage or failure of concentration at this part produces diluted semen and results in infertility.

**Fig 11.9: Structure of human spermatozoon**

**Erection**
- Erection is the increase in size and turgor of the penis.
- It occurs when the two erectile columns in the penis (the corpora cavernosa) become engorged with venous blood. In addition, the third erectile column (the corpus spongiosum), which contains the urethra, also becomes slightly engorged with blood, but to a lesser extent.
- It is stimulated by erotic psychic stimuli or direct tactile stimulation of the genitalia.
- Efferent impulses pass through the parasympathetic fibers in the pelvic splanchnic nerves to dilate the arterioles of the penis.
- When the erectile tissue fills with blood, the draining veins are compressed, this keeps blood within the penis causing its enlargement and increasing its turgor (= erection).
- The neurotransmitters released by the neurons in the pelvic splanchnic nerves include acetylcholine, vasoactive intestinal polypeptide “VIP” and nitric oxide “NO”.
- “NO” plays a major role in erection; it acts intracellularly to activate the enzyme guanylyl cyclase. This triggers production of cGMP (a potent vasodilator) from GTP.
- cGMP is broken down by phosphodiesterases. For this reason, the phosphodiesterase inhibitor, Sildenafil (or Viagra) is used for treatment of erectile dysfunction (impotence) by preventing breakdown of cGMP.

**Ejaculation**
- Ejaculation is the ejecting of semen from the urethra, and is usually accompanied by orgasm (sexual climax).
- It usually results from sexual stimulation, but it may occur spontaneously during sleep.
- It occurs as a spinal reflex that involves two phases: emission and ejaculation proper.
- The emission phase is under control of the sympathetic nervous system (integrated in the lumbar segments and mediated through the hypogastric nerves); whereas the ejaculatory phase is under control of somatic nervous system (integrated in he lower abdominal and upper sacral segments and mediated through the pudendal nerve).
- During emission, the vas deferens and the seminal vesicles contract to propel semen from the epididymis to the urethra.
- During ejaculation proper, the semen is ejected through the urethra with rhythmic contractions.
- These rhythmic contractions are part of the male orgasm. They are generated by the bulbocavernosus muscle.
**Testosterone**  
**Characteristics**  
- Steroid hormone (C₁₉) with masculinizing effects.  
- Synthesized from cholesterol by Leydig cells in the testes.  
- Also synthesized from androgens secreted by the adrenal cortex (androstenedione and dehydroepiandrosterone).  
- Activated to dihydrotestosterone (by the enzyme 5α reductase).  
- In the female, small amount of testosterone is secreted from the ovary and the adrenal gland.  
**Control**  
- Testosterone secretion starts in the male fetus before birth (to stimulate formation of the male genital organs), then the secretion increases during the neonatal period for unknown reason and then stops until puberty.  
- At and following puberty, the control of secretion is through the hypothalamo-pituitary axis.  
- The hypothalamus releases GnRH to the pituitary, which releases LH. Then LH acts on Leydig cells in the testes to release testosterone.  
- Testosterone, to control its plasma level, exerts a negative feedback effect on LH.  
- In old men, secretion of testosterone never stops; however, its plasma level decreases.  
- On the other hand, the plasma level of estrogens (formed from androgens) increases in old men.  
**Transport in plasma**  
- Most of testosterone in plasma (98%) is bound to:  
  - Gonadal steroid-binding globulin "GBG": β globulin, binds 65% of testosterone  
  - Albumin: binds 33% of testosterone
Metabolism
- Products of testosterone metabolism in the liver and peripheral tissues:
  - 17-Ketosteroids (e.g. androsterone, excreted in urine)
  - Estrogen
Note: About two thirds of 17-ketosteroids in urine are metabolic products of adreno-cortical hormones.

Effects of testosterone
- Formation of male genitalia (the internal genitalia is formed directly by testosterone whereas the external genitalia is formed by its active form "dihydrotestosterone").
- Spermatogenesis (assisted by FSH).
- Development of the secondary sex characters.
- Anabolic action (protein synthesis) = increases growth.
- Retention of water and electrolytes (secondary to increased growth).
- Negative feedback effect on LH at the anterior pituitary gland (it has no effect on FSH except in very high level).

**Important note:** Testosterone injections inhibits (rather than stimulates) spermatogenesis. This is because systemic testosterone is not enough for spermatogenesis, whereas it is enough for inhibiting LH secretion by the pituitary. This explains the importance of the countercurrent mechanism that keeps high testosterone level within the testes.

Remember about dihydrotestosterone
- It is formed from testosterone by the action of 5-α reductase in the scalp, genital skin and the prostate.
- It binds to the same intracellular receptors of testosterone before binding DNA in the nucleus; however, its receptor-hormone complex is more stable than that of testosterone. That is why it is more active than testosterone although its plasma level is only 10% of that of testosterone).
- It is responsible for formation and enlargement of external genitalia, enlargement of the prostate, and growth of facial hair, formation of acne and receding of hairline on the scalp.

Remember that: 5-α reductase inhibitors (e.g. finasteride) are widely used to treat benign prostatic hypertrophy; which is a common cause of urine retention in old men.

Abnormalities

Deficiency of 5 α reductase enzyme

- = Deficiency of dihydrotestosterone.
- This results in absence of male external genitalia; the patient is regarded as female (= male pseudohermaphroditism).
- However, at puberty, due to high production of testosterone, the patient develops male configuration and libido, facial hair and increased size of clitoris.
- Then investigations confirm that he is a male.

Other abnormalities related to the male reproductive system

Cryptorchidism "un-descended testes"

- The testes descend during fetal life from the abdominal cavity to its normal position in the scrotum due to MIS and other factors.
- Un-descended testes at birth require treatment (by gonadotrophins or better by surgery); because of:
  - The higher incidence of malignancy
  - The irreversible damage to the testes at puberty due to the high temperature within the abdomen.

Male hypogonadism

- Develops either due to testicular disease or pituitary/hypothalamic disorder. Accordingly, the plasma level of gonadotropins is either:
- Increased (in testicular disease) causing hypogonadotropic hypogonadism
- Decreased (pituitary/hypothalamic disorder) causing hypogonadotropic hypogonadism

- Other important point is the development of the secondary sex characters in these patients; this depends on the date of abnormality; e.g:
  - Congenital or childhood abnormality:
    - Results in absence of male secondary sex characters. Patients have the following features:
      - Tall stature (due to delayed closure of epiphyseal plates in bones).
      - Female features (eunuchoidism): narrow shoulders, small muscles, small genitalia, high pitched voice, female contours and pattern of pubic hair.
      - Example: Kallmann's syndrome (= hypogonadotropic hypogonadism due to an inherited hypothalamic abnormality. It is characterized by congenital anosmia, low GnRH and therefore low FSH, LH and sex hormones; resulting in delayed puerty and infertility).

Remember that:
Public and axillary hairs are due to the androgens from the adrenal cortex.

Abnormality after puberty:
- Results in regression of the secondary sex characters. However, the voice (which is due to enlargement of the larynx) remains deep.
THE FEMALE REPRODUCTIVE SYSTEM

STRUCTURE
- The female reproductive system consists of the following organs:

Ovaries
- The ovaries are two oval shaped female reproductive organs located in the lateral wall of the pelvis. Each one measures approximately (3 x 1.5 x 1.5) cm.
- They contain the primordial follicles (also known as ovarian follicles); each follicle contains an immature ovum “oocyte” and surrounded by two types of cells (granulosa cells and thecal cells).
- The total count of these follicles decreases (due to degeneration) from about 7 millions in the fetus to 2 millions at birth; however, one million of these are normal, they start their first meiotic division and enter stage of arrest in prophase. Of these, less than 300,000 follicles survive until puberty.
- Following puberty (& until menopause) the ovarian follicles continue to decrease in number because each month a few of them start to grow in response to FSH and then become atretic except one follicle that reaches maturation.
- The total count of follicles that reach maturation within the reproductive life of a female that never gets pregnant is about 500 follicles ("12 follicles per year" times "40 years").

- The mature ovarian follicle:
  - Also known as Graafian follicle
  - The ovum (in stage of primary oocyte) becomes surrounded by the zona pellucida (a mucopolysaccharide layer) and some granulosa cells (these form the cumulus oophorus following ovulation).
- The granulosa cells form several layers around the follicle and contains fluid that fills the follicle (the antrum) and pushes the ovum to one side.
- The theca cells become differentiated into two layers: Theca interna (well vascularized) & theca externa (less vascularized)
- The primary oocyte completes its first meiotic division giving secondary oocyte & first polar body (this occurs just before ovulation).
- The mature follicle is now ready for ovulation (usually 9 hours following LH peak).

**Fig 11.10: The mature ovarian follicle**

![Diagram of the mature ovarian follicle]

**Uterine tubes**
- Also known as the “Fallopian tubes” or the “oviducts”.
- These are two tubes, attached to either side of the upper end of the uterus, and each one is about 7-14 cm long, terminating near the ovary.
- There are four regions of the fallopian tube from the ovary to the uterus: Infudibulum (contains the fimbria), ampulla (the site of fertilization), isthmus & intramural oviduct (inside the uterine wall).
### Uterus
- The uterus (or womb) is the major female reproductive organ.
- Its lower end (the cervix) opens into the vagina.
- Its upper part is connected on both sides to the Fallopian tubes.
- The uterus is the site that accepts the fertilized ovum and allows its implantation.
- It provides nutrition for the developing embryo and fetus through the placenta.
- The layers that form the wall of the uterus are as follows:
  - The endometrium (the layer that lines the uterine cavity from inside)
  - The myometrium (the smooth muscle that forms the wall of the uterus)
  - The perimetrium
  - The peritonium

### Cervix
- The cervix (the uterine neck) is the lower, narrow portion of the uterus, which provides passage between the uterine cavity and the vaginal cavity.
- It is about 4 cm long, with 2 cm projecting into the upper vaginal cavity.
- The cervical opening into the vagina is called the external os.

### Vagina
- In humans, the vagina is about 9 cm long on average (with the anterior wall slightly shorter than the posterior one).
- It is located in front of the rectum and behind the bladder.
- In most virgins, the external opening to the vagina is partially closed by a thin fold of tissue known as the hymen.

### External genitalia (or vulva)
- The parts of the female reproductive system, which lie external to the vagina. They include the labia majora, mons pubis, labia minora, clitoris, and glands within the vestibule (lesser and greater vestibular glands).
The clitoris is an erectile organ that responds to sexual stimulation (similar to the male penis).

The two lesser vestibular glands (also known as Skene's glands, periurethral glands and paraurethral glands) are equivalent to the male prostate in both histology and secretion (they produce clear fluid similar to that produced by the male prostate during sexual stimulation).

The two greater vestibular glands (also known as the Bartholin's glands) are located near the opening of the vagina. They secrete mucus to provide lubrication (equivalent to Cowper's glands in males).

**Fig 11.1: The female reproductive organs**

THE MENSTRUAL CYCLE
- Cyclic changes in the female that occur in the:
  - Ovaries (= ovarian cycle)
  - Uterus (= uterine cycle)
  - Other organs (e.g. cervix, vagina and breasts)
- These changes start to occur following puberty and cease at the age of menopause (between 45 & 55 years old). They can be regarded as periodic preparations for fertilization and pregnancy.
- The average duration of each cycle is about 28 days, but it varies between 20 & 35 days.
THE OVARIAN CYCLE
- The ovarian cycle is controlled by the hypothalamo-pituitary axis.
- It is related to the other cycles (in the uterus, cervix and vagina) by the hormones produced from the ovaries.
- The ovarian cycle is divided into three phases:
  - Follicular phase (or preovulatory phase)
  - Ovulatory phase
  - Luteal phase (or postovulatory phase)

The follicular phase
- Each month following puberty, a few follicles start to grow in response to FSH. Most of them become atretic & only one reaches maturation.
- In the mature follicle (= Graafian follicle) the ovum (the primary oocyte) completes its first meiotic division just before ovulation giving secondary oocyte & first polar body. The secondary oocyte completes the second meiotic division with fertilization.
- The granulosa cells in the follicles form estrogens and some progesterone (they are the primary source of estrogen in the follicular fluid).
- Theca interna cells also form estrogens (they are the primary source of estrogen in the circulation) and supply the granulosa cells with androgens to convert it into progesterone.
- Estrogens exert negative feedback effect on both FSH & LH.
- However, towards the midcycle, this –ve feedback effect is converted into +ve feedback effect (due to unknown cause).

The ovulatory phase
- Usually occurs 14 days prior to the last day of the cycle; for example, at day 14 (mid-cycle) if the cycle is 28 days or at day 16 if the cycle is 30
days (note that the first day of the cycle is the first day of menstrual bleeding).

- During the follicular phase, estrogens exert –ve feedback effect on both FSH & LH.
- Towards the day of ovulation (the mid-cycle), the rising estrogen exerts +ve feedback on both FSH & LH resulting in mid-cyclic peak of FSH & LH.
- This is followed by rupture of the follicle & shedding of the ova (ovulation) into the abdominal cavity (usually 9 hours following the LH peak).
- The ova is picked up by the fimbria of the uterine tube and transported towards the uterus.
- Blood fills the ruptured follicle forming "the corpus hemorrhagicum" and may escape into the abdominal cavity causing lower abdominal pain due to irritation of the peritoneum (= an indicator of ovulation).
- Unlike FSH peak, the peak of LH at the mid-cycle is essential for ovulation.

Fig 11.12: Hormonal changes during the ovarian cycle
The luteal phase
- LH acts on the ruptured follicle following ovulation, resulting in appearance of yellowish cells rich in lipids known as "the luteal cells"; here the follicle is called "the corpus luteum".
- The luteal cells secrete both estrogens & progesterone.
- Estrogens and progesterone exert –ve feedback effect on FSH and LH to reduce their concentrations.
- If there is no pregnancy, the corpus luteum degenerates (usually 4 days before the end of the cycle) forming "the corpus albicans". Accordingly, estrogens & progesterone decline whereas FSH & LH rise to start new cycle (i.e. to stimulate growth of new group of follicles).
- If there is pregnancy, the embryo secretes human chorionic gonadotropin "hCG", see below.
- This maintains the corpus luteum and therefore maintains estrogen & progesterone secretion (i.e. no new ovarian cycle, usually until after delivery).

Fig 11.13: The ovarian cycle
THE UTERINE CYCLE

- Involves changes in the endometrium that are divided into 3 phases:
  - Proliferative phase
  - Secretory phase
  - Menstrual phase

The proliferative phase
- Starts after menstruation and continues to the time of ovulation (e.g. from day 5 to day 14). It depends on the action of estrogens, which causes proliferation of the endometrium.
- In the endometrium, the stromal cells and the blood supply are increased due to estrogen (the thickness is increased 10 times, from 0.5mm to 5mm).

The secretory phase
- Starts from ovulation to menstruation (e.g. from day 14 to the end of the cycle "day 28").
- Depends on the action of progesterone.
- Under the effect of progesterone, the glands in the endometrium become tortuous and start to secrete mucus, sugar, amino acids and glycogen.
- Arteries in the superficial two thirds of the endometrium (stratum functionale), is supplied by long, coiled spiral arteries whereas arteries in the deep third of the endometrium (stratum basale) are short and straight.
- The length of this phase is constant (about 14 days). It ends if there is no pregnancy, but continues if there is pregnancy (because the level of progesterone is not decreased).

The menstrual phase
- Shedding out of the superficial two thirds of the endometrium (stratum functionale) with bleeding (during the first 3 to 5 days of the cycle) occurs due to endometrial necrosis as follows:
- Degeneration of the corpus luteum
- Reduction estrogen and progesterone level in plasma
- Thinning of the endometrium (due to loss of the hormonal support)
- The endometrial arteries become more tortuous
- Appearance of foci of necrosis in the endometrium
- Release of lysosomal enzymes from the necrotic cells
- The enzymes stimulate formation of prostaglandins form cellular phospholipids
- Narrowing of endometrial arteries due to the locally released prostaglandins
- Extensive endometrial necrosis and shedding of endometrium with bleeding.

- The lost menstrual blood is generally arterial blood; its volume is about 30 mL but loss of higher volumes (up to 80 mL) is normal.
- It does not clot because it contains fibrinolytic substances (fibrinolysin).
- It also contains cellular debris and prostaglandins.

**Fig 11.14: The uterine cycle**
CYCLIC CHANGES IN OTHER ORGANS
- Occur due to the effect of ovarian hormones (see below).
- Examples include changes in the cervix, vagina & the breasts.

Changes in the Cervix
- The cyclic changes appear in mucus, not the epithelium, as follows:
  - During the proliferative phase (due to the effect of estrogens):
  - Mucus in the cervix is thin, alkaline and has high elasticity (can be stretched into a long thread); these changes facilitates transport of sperms.
  - During the secretory phase (due to the effect of progesterone):
    - Mucus in the cervix becomes thick & difficult to penetrate.

Changes in the vagina
- The cyclic changes are less obvious; they appear in the epithelium & mucus as follows:
  - During the proliferative phase (due to the effect of estrogens):
    - The epithelium becomes cornified.
  - During the secretory phase (due to the effect of progesterone):
    - The epithelium becomes infiltrated with WBCs and covered by thick mucus.

Changes in the Breasts
- The cyclic changes appear in the ducts and alveoli of breast tissue as follows:
  - During the proliferative phase (due to the effect of estrogens):
    - There is proliferation of the ductular system of the breast.
  - During the secretory phase (due to the effect of progesterone):
    - There is growth of the lobules & alveolar system of the breast, resulting in breast swelling; that is why some females feel tenderness in the breast during the last week of the cycle.
Indicators of ovulation
- As mentioned above, ovulation usually occurs 14 days prior the end of each cycle. Sometimes the cycle is completed without ovulation (= anovular cycle); here the bleeding at the end of the cycle occurs because estrogens continue to cause endometrial proliferation until some areas break down to initiate bleeding; usually before completing 28 days.
- Anovular cycles normally occur for about one year after menarche and before menopause. However, it may occur in abnormal conditions resulting in infertility.
- There are certain features that indicate occurrence of ovulation, these indicators include:
  - Rise of body temperature (due to the thermogenic effect of progesterone)
  - LH peak (or surge)
  - Secretory phase in the endometrium
  - Lower abdominal pain at the time of ovulation

OVARIAN HORMONES
- Hormones secreted by the ovary include:
  - Estrogens
  - Progesterone
  - Relaxin
  - Inhibin

Estrogens
Characteristics
- Steroid hormones (C\textsubscript{18}) with feminizing effects. Their types include:
  - 17 \( \beta \) estradiol: most active
  - Estriol: the least active
  - Estrone
- Produced from androgens in females by:
  - Granulosa cells
  - Theca interna cells
  - Corpus luteum
  - Placenta
  - Fat tissue (from androstenedione and testosterone by the action of aromatase).

- Produced from androgens in males by:
  - Fat tissue (the main site of synthesis; from androgens by the action of aromatase).
  - Sertoli cells & Leydig cells in the testes (form small amount of estrogens)

Transport in plasma
- Most of estrogens (98%) is bound to plasma proteins.
- About 60% is bound to albumin and 38% is bound to the β globulin that transports testosterone (GBG).

Metabolism
- Site of metabolism: the liver.
- The metabolites are conjugated and excreted in urine.

Control
- Through the hypothalamo-pituitary axis.
- The hypothalamus releases GnRH (at and following puberty).
- The pituitary releases LH & FSH.
- LH acts on theca interna cells to stimulate synthesis of androgens (androstenedione) from cholesterol; some of this is converted to estradiol and another part diffuses to granulosa cells.
- The granulosa cells, stimulated by both FSH & LH, convert the androgen coming from theca interna into estradiol.
- Estradiol formed by theca interna cells enters the circulation whereas that formed by granulosa cells enters the follicular fluid.
- During each menstrual cycle, estradiol level in plasma peaks just before ovulation and during the mid-luteal phase. It declines to its lowest values after menopause.

**Estrogen effects**

- **Growth:**
  - Increases growth (has anabolic effect)

- **Bone:**
  - Inhibits osteoclasts (that is why old women develop osteoporosis after menopause)
  - Closes epiphysis (that is why females, who have earlier onset of puberty, develop epiphyseal closure at early ages and become shorter than men).

- **Secondary sex characters at puberty:**
  - See above (puberty)

- **Ovary:**
  - Responsible for the follicular phase of the ovarian cycle

- **Uterus:**
  - Responsible for the proliferative phase of the uterine cycle
  - Increases the bulk of uterine muscle & its blood flow
  - Increases motility of uterine tubes
  - Facilitates the effect of oxytocin on the uterus (makes it more excitable)

- **Cervix & vagina:**
  - Makes the cervical mucus more thin
  - Makes the vaginal epithelium cornified
• Breast:
  o Increases growth of ductular tissue in the breast (responsible for breast enlargement at puberty).

• The gonadotropins "FSH & LH":
  o Has negative feedback effect on both FSH & LH.
  o That is why contraceptive pills containing estrogen & progesterone are used to inhibit FSH & LH and therefore prevent pregnancy.
  o Just before ovulation, it has positive feedback effect on both LH & FSH.

• Sexual arousal:
  o Increases "libido" in humans and "estrous behavior" in animals (the estrous cycle occurs in the animals that do not menstruate.
  o Here the sexual interest of a female animal is aroused at the time of ovulation).

• Formation of some plasma proteins by the liver:
  o Estrogens increase hepatic production of:
    ▪ TBG (thyroid binding globulins)
    ▪ Angiotensinogens
    ▪ Clotting factors (when administered orally to reach the liver through the portal circulation; that is why estrogen therapy causes thrombosis).

• Other effects:
  o Salt and water retention
  o Vasodilatation (by increasing NO production)
  o Decreases cholesterol level in plasma
    (= cardio-protective effect)
**Progesterone**

**Characteristics**
- Steroid hormone (C\textsubscript{21}).
- Produced by:
  - Corpus luteum
  - Placenta
  - Granulosa cells (from pregnenolone from theca interna cells)
- Since it is formed during steroid biosynthesis in the adrenal cortex and the testes, small amount is released by these glands into the circulation.

**Transport in plasma**
- Most of progesterone (98%) is bound to plasma proteins.
- About 80% is bound to albumin and 18% is bound to corticosteroid binding globulin.

**Metabolism**
- Site of metabolism: the liver.
- The metabolites are conjugated and excreted in urine.

**Control**
- The hypothalamo-pituitary axis (through the effect of LH on the corpus luteum).

**Progesterone effects:**
- Uterus:
  - Responsible for the secretory phase in the uterus.
  - Inhibits action of oxytocin on the uterus (decreases excitability, anti-estrogen effect).
- Cervix and vagina:
  - Makes mucus in the cervix and vagina more thick.
- Breasts:
  - Increases growth of lobules and alveolar tissue in the breast.
Thermogenic effect:
- Increases the metabolic rate and therefore the temperature of the body at ovulation, following ovulation and contributes to the rise during pregnancy.

Respiration:
- Stimulates the respiratory center (causes hyperventilation during pregnancy).
- This explains the low plasma PCO₂ during pregnancy & the luteal phase.

LH:
- Has negative feedback effect on LH.
- Potentiates the inhibitory effect of estrogens on FSH.

Natriuresis:
- In large doses, it inhibits the action of aldosterone.

**Relaxin**
- Polypeptide hormone.
- Produced by:
  - Corpus luteum
  - Placenta
  - Uterus
  - Mammary glands
  - Prostate in men

**Relaxin effects**
- Facilitates delivery (relaxes the pelvic joints and dilates the cervix).
- Inhibits uterine contractions.
- Contributes to development of the mammary glands.
- In men: maintains sperm motility and facilitates fertilization.
**Inhibin**
- Inhibin is a peptide hormone secreted by the gonads in both males and females (Sertoli cells in the testes of males and granulosa cells in the ovaries of females). It is also secreted by the placenta and other organs.
- It consists of an α and β subunits linked by disulfide bonds.
- Two forms of inhibin exist in humans (A & B), differ in their β subunits, but their alpha subunits are identical.
- In both females and males, inhibin inhibits FSH production.
- Measurement of inhibin A in the blood of pregnant women is used as screening test for Down syndrome (high result indicates Down syndrome).

**Activin**
- Activin is a peptide hormone that is partially similar to inhibin but exerts an opposite effect (stimulates FSH secretion).
- It contains two β subunit that are identical to either or both β subunits (A or B) of inhibin, allowing for the formation of three forms of activin: A, AB, and B.
- It is also produced by the gonads, placenta and other organs in the body.

**Terms used to describe menstrual abnormalities:**

**Primary amenorrhea:**
- Absence of menstrual bleeding (bleeding never occurred).
- Example: chromosomal abnormalities "Turner syndrome."

**Secondary amenorrhea:**
- Absence of menstrual bleeding after being started normally for some time.
- Example: Pregnancy, emotional stress, systemic diseases & abnormalities of the hypothalamus, pituitary or the ovaries.
Dysmenorrhea:
= Painful menstruation; caused by accumulation of prostaglandins in the uterus.
Hypomenorrhea:
= Scanty menstrual bleeding.
Menorrhagia:
= Excessive menstrual bleeding.
Metrorrhagia:
= Bleeding from the uterus between periods

FERTILIZATION, IMPLANTATION & PREGNANCY
FERTILIZATION
- The sperms take 0.5-1 hour to reach the ovum (in stage of 2ary oocyte) at the uterine tube.
- The ovum remains viable for about 3 days; however, it is fertilizable for shorter period. On the other hand, sperms are viable for about 3 days (sometimes up to 5 days).
- That is why the possibility of fertilization is highest with coitus at or one to two days before ovulation.
- Fertilization occurs at the outer portion of the uterine tubes "the ampulla".
- Before fertilization, sperms complete their maturation at the isthmus of the uterine tubes "capacitation".
- About 50-100 sperms reach the ovum; however, one of these fertilizes the ovum as follows:
  - Chemoattraction of the sperm to the ovum (by chemicals released by the ovum)
  - Adherence to the zona pellucida (by the sperm protein fertilin)
- Penetration of the zona pellucida & acrosomal reaction (release of enzymes in the acrosome to facilitate penetration through the zona pellucida).
- Adherence of the sperm head to the cell membrane of the ovum and release of its nucleus into the cytoplasm of the ovum.

- After fertilization, the fertilized ovum (blastocyst) takes about 3 days to reach the uterus.

**IMPLANTATION**
- When the blastocyst reaches the uterus, it becomes surrounded by two types of trophoblasts:
  - Syncytiotrophoblast
    - Multinucleated mass with no cell boundaries
    - Erodes the endometrium to allow embedding of the blastocyst "implantation"
    - Release the hormones hCG & hCS (see below)
  - Cytorophoblasts
    - The inner layer of the trophoblasts (towards the embryo).
    - Serve to anchor the embryonic placenta (chorion) to maternal endometrium.

- The usual site of implantation is the dorsal wall of the uterus; however, there are abnormal sites of implantation. These include: The uterine tube, other sites within the uterus and rarely the abdomen (extra-uterine pregnancy).

**Human chrionic gonadotropin “hCG”**
- The hormone hCG is a glycoprotein, similar in structure to TSH, LH & FSH (all these hormones are glycoproteins consisting of two subunits:
alpha and β; they have the same α subunit but the β is different; it is the β subunit that determines the activity of each of these hormone).

- hCG is released by the syncytiotrophoblast to maintain the corpus luteum (luteinizing & luteotropic); therefore the corpus luteum continues its release of estrogens, progesterone and relaxin to maintain pregnancy.
- After 6 weeks, the placenta takes over the release of estrogen, progesterone and relaxin; however, the corpus luteum remains functioning to the end of pregnancy.
- hCG appears in blood after 6 days of implantation; and in urine after 14 days of implantation.
- Its detection indicates pregnancy (= the basis of pregnancy test). However, it is also detected in patients suffering from some GIT cancers (= regarded as a tumor marker).

**Human chorionic somatomammotropin "hCS"**
- The hormone hCS is a protein, similar in structure to GH and prolactin.
- It is produced by the syncytiotrophblasts.
- It is found mainly in maternal blood (not fetal blood).
- Its effects include:
  - Promotion of growth (instead of GH which is not increased during pregnancy).
  - Stimulation of milk production (lactogenic); for this reason, it is used to be called human placental lactogen "hPL".
  - Reduction of glucose utilization by the mother (to spare it for the use of the fetus).
  - Lipolysis (to provide the mother with FFAs as another source of energy).
  - Retention of electrolytes (nitrogen, potassium, calcium …).
Functions of the placenta

- Transfer function
  - The placenta transfers oxygen, carbon dioxide, glucose, minerals & IgG antibodies.

- Filtration of toxic substances
  - The placenta filters out toxic substances and prevent their passage into fetal blood; however, certain chemicals and viruses cross the placenta and cause fetal damage.

- Endocrine function
  - The placenta synthesizes the following hormones: hCG, hCS, progesterone, estrogen (oestriol) relaxin, inhibin and others (GnRH, CRH, endorphins, MSH, leptin, prolactin …).

Remember that: Estrogen (oestriol), is formed from androgens produced by fetal liver and adrenal gland; on the other hand, cholesterol metabolites formed in the placenta are converted to cortisol in the adrenal gland of the fetus; this is known as "the feto-placental unit".

MATERNAL RESPONSES TO PREGNANCY

- Physiological and anatomical changes develop in many organs during the course of pregnancy. These changes are due to:
  - The metabolic demands of the fetus
  - Hormones of pregnancy (particularly progesterone and estrogen)
  - The mechanical pressure from the expanding uterus

Changes in body fluids and electrolytes

- There is marked retention of fluids and electrolytes due to:
  - Growth of tissues
  - Hormones of pregnancy (estrogen)
  - Activation of the renin-angiotensin-aldosterone system
Changes in the blood
- The blood volume increases progressively from the 6-8 weeks of gestation to reach a maximum at approximately 32-34 weeks. The increase is due to:
  - Increased plasma volume (by 40-50%)
  - Increased red blood cell mass (by 20-30%)
- The increase in plasma volume is relatively greater than the increase in red blood cell mass; this causes hemodilution (reduction in the concentration of hemoglobin, PCV and red blood cell count).
- For this reason, anemia of pregnancy is diagnosed when hemoglobin concentration becomes lower than 12 g/dL.
- This is usually prevented by adequate nutrition and by taking iron and folic acid supplementation.
- Other changes in the blood:
  - Leukocytes are variable during gestation, but usually normal
  - Platelets are increased
  - Clotting factors are increased

Note: The blood loss during delivery is compensated by the blood released by the contracting uterus.

Changes in the cardiovascular system
- Stroke volume: increased (up to 35%)
- Heart rate: increased (up to 15%)
- Cardiac output: increased (more than 8 L/min at term and even higher in the immediate postpartum period)
- Peripheral resistance: decreased due to skin vasodilatation for heat loss
- Systolic blood pressure: increased due to increased cardiac output
- Diastolic blood pressure: decreased due to decreased peripheral resistance
- Pulse pressure: increased due to increased systolic and decreased diastolic blood pressure

Note: From mid-pregnancy, when a pregnant lady lies supine, the enlarged uterus compresses the abdominal veins. This compression causes:
  o Reduction in venous return followed by reduction in the cardiac output
  o Distension of veins & lower limb edema (in some women)

**Changes in the respiratory system**
- Respiratory mucosa: swelling of mucosa and engorgement of capillaries due to hormonal changes and increased blood flow
- Lung volumes and capacities: reduced by the upward displacement of the diaphragm which is caused by the enlarged uterus.
- Minute ventilation: increased progressively to reach about 50% above normal levels around the second trimester. This increase is due to:
  o Increased tidal volume (up to 40%)
  o Increased respiratory rate (up to 15%, i.e. 2-3 breaths/minute)
- Remember that hyperventilation decreases alveolar and arterial PCO2 and progesterone is partly responsible for this hyperventilation.

**Changes in the gastro-intestinal system**
- The stomach & intestine: are displaced by the growing uterus.
- Reflux esophagitis: due to increased intragastric pressure caused by mechanical effect of the uterus and relaxation of the lower esophageal sphincter.

**Changes in the renal system**
- Renal blood flow: increased progressively (by up to 50-60% at term) due to increased blood volume and cardiac output.
- GFR: increased progressively (by up to 50-60% at term) due to increased renal blood flow.
- Blood urea and serum creatinine: decreased by up to 40%.
- Glucosuria: loss of glucose in urine may occur because:
  - During pregnancy the renal threshold for glucose is lower (<180 mg/dL)
  - The high GFR causes filtration of high amount of glucose that may overwhelm the ability of the renal tubules to reabsorb glucose.
- Loss of amino acids and water-soluble vitamins in urine because of the high GFR.
- Plasma osmolarity: decreased due to the hemodilution.

**Changes in metabolism**

- Carbohydrate metabolism:
  - Characterized by increased glucose utilization during early weeks of pregnancy followed by decreased utilization in the second half of pregnancy.
  - The early higher utilization is associated with higher response of insulin to glucose whereas the later lower utilization is associated with higher insulin level with resistance to insulin effects. This develops due to the hormones hCS, cortisol and glucagon.
- Protein metabolism: Anabolism due to the placental hormones. The net gain of protein throughout pregnancy is about 1 kg.
- Fat metabolism: Anabolism in the early stages of pregnancy (to store energy). The mother stores about 4 kg of fat in the subcutaneous tissue by the end of pregnancy.

- Note: Total weight gain during pregnancy should be about 11 to 15 kg in normal women, with normal body mass index (in form of protein, fat, body fluids, electrolytes and additional tissues “breast, placenta and fetal tissues”).
- Inadequate weight gain during pregnancy is associated with fetal abnormalities (e.g. intrauterine growth retardation and low birth weight).
QUESTIONS FOR SELF ASSESSMENT-7 (MCQS)

1- LH is:
   a. A protein
   b. Not present in males
   c. Inhibits ovulation
   d. Increased in females after menopause
   e. Not needed for spermatogenesis

2- Turner syndrome is characterized by:
   a. Gynecomastia
   b. Male genitalia
   c. Absent ovaries
   d. Tall stature
   e. Mental retardation

3- Most of the seminal fluid is provided by:
   a. Prostate
   b. Seminal vesicles
   c. Cowper’s glands
   d. Epididymis
   e. Ejaculatory ducts

4- Which of the following hormones is expected to rise following ovulation:
   a. LH
   b. FSH
   c. Estrogen
   d. Progesterone
   e. hCG

5- During pregnancy, the corpus luteum:
   a. Is known as the corpus albicans
   b. Is controlled by the placenta
   c. Is essential for maintenance of pregnancy
   d. Degenerates during the second trimester
   e. Responds to both FSH and LH

6- Normal spermatogenesis requires the following cells:
   a. Sertoli cells, Germ cells and acidophils of the pituitary
   b. Leydig cells, Germ cells and Chromophobes of the pituitary
   c. Sertoli cells, Leydig cells and Basophils of the pituitary
   d. Germ cells, Leydig cells and stem cells of the bone marrow
   e. Cutaneous cells, Sertoli cells and neural cells in the hypothalamus

7- The corpus luteum of pregnancy:
   a. Is under control of LH
   b. Is formed only from theca interna cells
   c. Produces progesterone but not estrogen
   d. Degenerate as soon as the fertilized ovum is implanted
   e. Requires human chorionic gonadotrophin
8- Normal spermatogenesis requires:
   a. A peak of LH
   b. FSH and testosterone
   c. A temperature equal to body temperature
   d. Low potassium in seminal fluid
   e. 120 days for development of sperms

9- During the menstrual cycle, progesterone is responsible for:
   a. Proliferative phase in the uterus
   b. Thick mucus in the cervix
   c. Ovulation
   d. LH peak during mid-cycle
   e. Ductular growth in the breast

10-Ovulation:
   a. Normally occurs 14 days following uterine bleeding
   b. Immediately occurs following LH surge
   c. Is usually associated with a central abdominal pain
   d. Is due to rupture of the corpus luteum
   e. Leads to a rise in the body temperature

11- Home-use Kits for determining a woman’s pregnancy depends on detection of this hormone in her blood or urine:
   a. FSH
   b. Progesterone
   c. Estradiol
   d. hCG
   e. LH

12- Concerning spermatogenesis, which of the following is correct:
   a. Sperm production is cyclic
   b. Continuous release of GnRH is essential for spermatogenesis
   c. Sertoli cells are needed for mitotic and meiotic activity of germ cells
   d. FSH acts on Leydig cells to stimulate release of testosterone
   e. LH acts on Sertoli cells to stimulate release androgen binding protein

13-During 2nd and 3rd trimester of pregnancy, the primary source of estrogen and progesterone is the:
   a. Corpus luteum
   b. Granulosa and theca cells in ovaries
   c. Placenta
   d. Adrenal cortex
   e. Pituitary gland

14- Which of the following statements about estrogen is not true:
   a. Interacts with intracellular protein receptors
   b. Increases synthesis of thyroid binding protein
   c. Decreases uterine contractions
   d. Decreases FSH secretion
   e. Is released from the testes

15- Testosterone is not:
   a. Produced during intra-uterine life
b. An anabolic hormone

c. Mostly protein bound

d. Inhibited directly by inhibin

e. Inhibitory to LH

16- In a normal menstrual cycle:

a. High estrogen maintains the corpus luteum
b. Progesterone is highest during early days of menstrual cycle
c. LH peak is preceded by estrogen peak
d. Ovulation depends on FSH surge
e. The life span of corpus luteum determines duration of the cycle

17- Which of the followings is NOT secreted by Sertoli cells:

a. Androgen binding protein
b. Testosterone
c. Mullerian inhibitory substance
d. Inhibin
e. Estrogens

18- Concerning spermatogenesis:

a. Testosterone is not essential
b. The secondary spermatocyte contains 23 chromosomes
c. FSH has no role
d. The process takes 74 hours
e. Involves division of Sertoli cells to form sperms

19- Progesterone:

a. Acts on cell membrane receptors
b. Stimulates the respiratory centre to increase respiration
c. Acts directly on the hypothalamus to activate the temperature centre
d. Promotes proliferative changes in the endometrium
e. Stimulates development of ducts in the breast

20- Human chorionic somatomammotropin (hCS):

a. Is a steroid hormone
b. Prevents glucose utilization by the fetus
c. Causes lipolysis
d. Is secreted by the granulosa cells
e. Is detected by pregnancy test to diagnose pregnancy

21- Maternal responses to pregnancy do not include:

a. Increased GFR
b. Increased volume of plasma
c. Increased cardiac output
d. Increased lung volumes and capacities
e. Decreased erythropoiesis

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CHAPTER (12)
THE SENSORY SYSTEM

STRUCTURE & FUNCTION

- The sensory system is the part of the nervous system responsible for detection, transmission, and processing of sensory information about events occurring at the internal and the external environments.
- It consists of: Receptors, Afferents, Tracts & Sensory cortex.

Fig 12.1: The sensory system

- The sensory information obtained after arrival of action potentials to the brain include:
  - Type of sensation (= modality)
  - Site of stimulation (= locality)
  - Strength of stimulation (= intensity)
  - Duration of stimulation
- Generally, a sensation carried by a somatic afferent neuron is known as a somatic sensation whereas a sensation carried by an autonomic afferent neuron is known as a visceral sensation.
- The autonomic afferent neurons carry information that does not reach consciousness. Examples include information about lung inflation, blood pressure, blood pH, and ECF volume.
- Some somatic afferent neurons also carry information that does not reach consciousness. These include information about muscle length from the muscle spindle and muscle tension from the Golgi tendon organ (see the motor system).

**A- SENSORY RECEPTORS**
- Sensory receptors are specialized structures found at the peripheral ends of afferent neurons.
- They respond to sufficient stimulation by generating action potentials that are transmitted through afferent neurons towards the brain.
- The stimuli that activate the sensory receptors include various forms of energy (mechanical, chemical …); therefore, receptors act as transducers that convert energy into action potentials.

**Classifications of receptors**

**Traditional classification:**
1. Special senses (Receptors for hearing, vision, smell, taste, rotational and linear acceleration)
2. Cutaneous senses (Receptors in the skin for touch-pressure, cold, warmth and pain).
3. Visceral senses (Receptors in the internal structures)

**According to the site of event:**
1. Teleceptors (Detect distant events, e.g. visual receptors)
2. Exteroceptors (Detect events at the immediate external environment, e.g. touch receptors)
3. Interoceptors (Detect events at the internal environment, e.g. chemoreceptors)
4. Proprioceptors (Detect changes in position of the body. Found at joints, tendons and ligaments)

According to the type of stimulus (energy):

- Mechanoreceptors (Stimulated by mechanical energy, e.g. touch and pressure receptors)
- Thermoreceptors (Stimulated by thermal energy, e.g. warm and cold receptors)
- Nociceptors (These are pain receptors, stimulated by any form of energy that causes tissue damage)
- Chemoreceptors (Stimulated by chemical changes in body fluids e.g hypoxia, hypercapnia and acidosis)
- Baroreceptors (Stimulated by elevation of blood pressure)

According to the structure of the receptor:

1. Free nerve endings
   - E.g. pain and temperature receptors
   - Some of the receptors for other modalities of sensation may be free nerve endings

2. Encapsulated
   - E.g. Pacinian corpuscles for touch and Meissner’s corpuscles for vibration

   **Remember that:** Pacinian corpuscles are specialized for touch but not for pressure, which is sustained touch; this is because they adapt rapidly and dissipate pressure

3. Expanded tip
   - Slowly adapting receptors. E.g. Merkel’s discs and Ruffini endings

4. Sense organs
   - When the receptors combine with non-neural cells, they form sense organs. E.g. organ of Corti for hearing & otolithic organ for posture
According to the degree of adaptation:
- Receptors can be rapidly adapting, slowly adapting, or non-adapting (see properties of receptors).

**Fig 12.2: Types of sensory receptors**

| Sense organ | Pacinian corpuscle | Merkel discs | Free nerve endings |

**Properties of receptors**
- Receptors are characterized by three characteristics: Adequate stimulus, excitability and adaptation.

1. **Adequate Stimulus**
- Each type of receptor is most sensitive to a specific form of energy called its adequate stimulus. For example:
  - Adequate stimulus for touch receptors = Mechanical energy
  - Adequate stimulus for temperature receptors = Thermal energy
  - Adequate stimulus for visual receptors = Electromagnetic energy
- Note:
  - Adequate stimulus for pain is not specific because any form of energy can cause pain if it causes tissue damage.
  - Other types of receptors may respond to stimuli other than their adequate stimuli, but in a much higher threshold.
2- Excitability of receptors
- Stimulation of the receptor results in Receptor potential (or Generator potential).
- This may occur due to either:
  o Sodium influx
  o Calcium influx
  o Inhibition of the Na⁺/K⁺ pump
- Unlike action potentials, receptor potentials are:
  o Localized (not propagated along axons of neurons as action potentials).
  o Graded (increase or decrease in amplitude depending on strength of stimuli; i.e. their excitability is not all or none as in action potentials).
  o Can be summated (can be added together to reach sufficient magnitude and cause action potential).

3- Adaptation of receptors
- Results from sustained stimulation of receptors with constant strength.
- This causes decrease in the frequency of action potential generated at some receptors, especially the encapsulated receptors (e.g. Pacinian corpuscles).
- Adaptation can be explained as follows:
  The capsule that surrounds the terminal part of the axon undergoes some alterations in its shape due to the sustained stimulation; this decreases pressure exerted by that capsule on the axon and therefore decreases frequency of firing.
- Accordingly, receptors can be classified as:
  o Rapidly adapting or phasic receptors: e.g. touch receptors (Pacinian corpuscles)
Slowly adapting receptors or tonic receptors: e.g. proprioceptors (Ruffini endings)

Intermediately adapting receptors: e.g. temperature receptors (free nerve endings)

Non-adapting receptors: e.g. pain receptors (free nerve endings)

B- AFFERENTS

- The afferent neurons (sensory neurons) carry nerve impulses from the receptors or sense organs towards the central nervous system.

- There are two types of afferent neurons:

  - **Somatic afferent neurons**
    - Conduct impulses from receptors in the skin, skeletal muscles, tendons, joints, and parietal layers of the pleura and the peritoneum.
    - They enter the spinal cord through the dorsal roots & their cell bodies are located in the dorsal root ganglia.

  - **Visceral “or autonomic” afferent neurons**
    - Conduct impulses from smooth and cardiac muscles and from baroreceptors, chemoreceptors, volume receptors, and taste buds.
    - They enter the spinal cord through the dorsal roots & their cell bodies are located in the dorsal root ganglia or the equivalent ganglia for the cranial nerves VII, IX & X.
    - When they reach the brain stem, they make connections with the nucleus of tractus solitarius (NTS) which integrate all visceral information. However, visceral pain ascends in the spinothalamic tract like somatic pain to reach the sensory cortex.

- Afferent neurons, according to their degree of myelination, can be:

  - **Thick myelinated (Type A)**
    - Rapidly conducting neurons
Further divided into:
- A alpha (its conduction velocity = 70-120 m/s)
- A beta (its conduction velocity = 30-70 m/s)
- A gamma (its conduction velocity = 15-30 m/s)
- A delta (its conduction velocity = 12-30 m/s)
  - Thin myelinated (Type B)
    - Less rapidly conducting neurons
    - Its conduction velocity = 3-15 m/s
  - Non myelinated (Type C)
    - Slowly conducting neurons
    - Its conduction velocity = 0.5 -2 m/s

| - Generally, specialized receptors (for proprioception & touch) send their impulses via type Aβ fibers whereas free nerve endings (for pain and visceral sensation) send their impulses via type A delta or C fibers. |

**C- SENSORY TRACTS**
- These are two types of ascending pathways in the white matter of the spinal cord:
  - Dorsal column tract (DCT) or (Lemniscal tract)
  - Spinothalamic tract (STT) or (Anterolateral tract)

1- **Dorsal column tract (DCT) or (Lemniscal tract)**
- Carries: Fine touch & pressure, vibration, position sense & two point discrimination.
- Afferents are type A beta fibers.

2- **Spinothalamic tract (STT) or (Anterolateral tract)**
- Carries: Crude touch, temperature (hot and cold), pain, sexual sensation and itching sensation.
- Afferents are type A delta or C fibers.
Pathways:
- Each tract consists of 3 orders of neurons as follows:

- **The dorsal column tract:**
  - 1\(^{st}\) order neurons:
    - Cell bodies in dorsal root ganglia.
    - Axons pass from the receptors to the spinal cord. Then they ascend in the dorsal white matter of the spinal cord (dorsal column) until they reach the medulla where they synapse with second order neurons.
  - Second order neurons:
    - Cell bodies in the Gracile and Cuneate nuclei in the medulla.
    - Axons cross to the opposite side and ascend in the medial lemniscus until they reach the specific nuclei of the thalamus (the ventro-posterior nuclei of the thalamus “VPNT”) where they synapse with third order neurons.
  - Third order neurons:
    - Cell bodies in the thalamus (VPNT). Axons ascend in the sensory radiation to reach the sensory cortex (in the post-central gyrus).

- **The spinothalamic tract:**
  - 1\(^{st}\) order neurons:
    - Cell bodies in dorsal root ganglia.
    - Axons pass from the receptors to the spinal cord. Then they enter the gray matter in the posterior horn of the spinal cord where they synapse with second order neurons.
  - Second order neurons:
    - Cell bodies in the posterior horn.
    - Axons cross to the opposite side in front to the central canal of the spinal cord and ascend in the white matter until they reach the specific nuclei of the thalamus (the VPNT).
- **Third order neurons:**
  - Cell bodies in the thalamus (VPNT). Axons ascend in the sensory radiation to reach the sensory cortex (in the post-central gyrus).

Note: In the STT, axons of second order neurons cross to the opposite side in front of the central canal of the spinal cord. That is why these neurons are damaged in Syringomyelia whereas neurons of the DCT remain intact.
- Sensory signs of Syringomyelia include loss of pain and temperature sensations, but intact touch, vibration and position sensations. This characteristic sign is known as “dissociated sensory loss”). Whereas damage to motor neurons in syringomyelia results in paralysis or paresis.

**Fig 12.3: The sensory tracts**

```
DORSAL COLUMN TRACT (DCT)

1st order neuron
(axons ascend in the dorsal column tract)

Thalamus

2nd order neuron
(axons cross & ascend in the medial lemniscus)

Graefe or Cuneate nucleus

Medulla

Dorsal root ganglion

From the receptors

Spinal cord

Sensory cortex

3rd order neuron
(axons pass in the sensory radiation to the sensory cortex)

STT

1st order neuron
(axons synapse in the dorsal horn)

Dorsal root ganglion

From the receptors

Spinal cord

2nd order neuron
(axons cross & ascend in the spinothalamic tract)

Sensory cortex

3rd order neuron
(axons pass in the sensory radiation to the sensory cortex)
```
Note
- The gray matter of the spinal cord that forms the posterior horn is subdivided into 6 laminae (from I to VI). Other laminae include lamina VII that lies in the intermediate zone, lamina VIII that lies in the anterior horn (for interneurons), lamina IX lies in the anterior horn (for alpha and gamma motor neurons) and lamina X for neurons surrounding the central canal.
- Synapses of the first order neurons (of the spinothalamic tract with the second order neurons at these laminae are distributed as follows:
  - Type C afferents (carrying pain & temperature), synapse at laminae I & II
  - Type Aδ afferents (carrying pain & cold), synapse at laminae I & IV
  - Type Aδ afferents (carrying mechanoreceptor sensation) synapse at III & IV
  - Type Aβ afferents (carrying mechanoreceptor sensation) at laminae III, IV, V & VI

Remember that mechanoreceptor sensation is mainly carried through Aβ afferents; however, type Aδ & C afferents (mainly for pain and temperature) carry some mechanoreceptor sensation.

Fig 12.4: Laminae of the gray matter in the spinal cord
- Within the spinothalamic tract (antero-lateral tract), touch fibers mainly ascend in the anterior part whereas pain fibers mainly ascend in the lateral part.
- Within the spinothalamic tract, fibers carrying sensation from the lower parts of the body (lower limbs and buttocks) are pushed laterally by the fibers which enter the spinal cord at higher segments, as they cross the midline and ascend. In other words, fibers of the spinothalamic can be classified (from lateral to medial) as sacral, lumbar, thoracic, and cervical fibers. For this reason, extramedullary tumors (tumors arising outside the spinal cord) compress the spinal cord from outside and present with loss of pain and temperature sensation in the buttocks and lower limbs whereas intrameduulary tumors (tumors arising from inside the spinal cord) present with sensory loss at a higher level.
- Fibers of the dorsal column tract are similarly distributed, but with the sacral fibers medially and the upper fibers laterally.

**Fig 12.5: Distribution of fibers within the sensory tracts**

- Posterior column tract
- Lateral STT (pain & temperature)
- Ventral STT (touch & pressure)

\[
\begin{align*}
S & = \text{Sacral fibers} \\
L & = \text{Lumbar fibers} \\
T & = \text{Thoracic fibers} \\
C & = \text{Cervical fibers}
\end{align*}
\]
D- SENSORY CORTEX
- The site that receives sensory tracts. There are two sensory areas:
  o Area I or primary sensory area (in the postcentral gyrus).
  o Area II or secondary sensory area (in the wall of Sylvian fissure).

**Fig 12.6: The sensory cortex**

- Function of the sensory cortex: Perception and discrimination between modalities, localities, intensities, and durations of different sensations.
- All parts of the body are well represented in the postcentral gyrus, with legs at the top and head at the bottom of the gyrus.
- The size of representation of each part is proportional to the number of its receptors (therefore the cortical areas for the lips, tongue and hands are very large, compared with the cortical areas for the trunk and the back).
- The right postcentral gyrus contains a map for the left half of the body and vice versa.
- Representation at area II is not as detailed as in area I.
Coding of sensory information
- All types of sensation reach the brain in form of action potentials. In spite of that, the brain can discriminate four features for each sensation:
  - Type of sensation (modality)
  - Site of sensation (locality)
  - Strength of sensation (intensity)
  - Duration of sensation
- The information processing in the brain that results in discrimination of the above four features is known as “coding of sensory information.”
- How can the brain discriminate each feature is explained as follows:

1- Modality (= doctrine of specific nerve energies)
- Each modality of sensation generally has specific adequate stimulus, specific receptor, specific afferent, specific sensory tract, and specific sensory area in the cerebral cortex to be activated. In other words, the sensory pathway for each modality (from the receptor to the cortex) is different from the pathways of other modalities.
- When action potentials of one sensory pathway reach the cerebral cortex, the sensation perceived is that to which the receptor is specialized for; even if the stimulation is applied along the pathway, not directly on the receptor. This principle is known as doctrine of specific nerve energies.

2- Locality (= law of projection)
- To discriminate between different localities of various stimuli, the brain projects the coming impulses of each stimulus to the site of the receptor; even if the stimulation is applied along the pathway, not directly on the receptor. This is known as the law of projection.
- The law of projection explains the phenomenon of “phantom limb” in which a subject with an amputated limb feels pain at the absent limb; for example at the big toe of an amputated foot. This occurs due to
stimulation or spontaneous firing of nerve fibers (previously coming from the big toe) at the site of amputation. To localize the coming impulses, the brain projects them to the site of the receptors (i.e. the absent big toe).

3- **Intensity**
- The brain discriminates between different intensities of stimulation (whether weak, moderate or strong) by variation in the number of receptors stimulated and frequencies of action potentials generated.
- When these are increased or decreased, the brain interprets that as an increase or decrease in the intensity of stimulation.

4- **Duration**
- The brain discriminates the duration of stimulation by determining the period from the onset of receptor activation to the end of activation (i.e. from the time of energy gain in the receptor to the time of energy loss).
SENSORY MODALITIES

PAIN

Definition
- Defined as unpleasant sensation produced by stimuli that cause tissue damage.
- It is associated with both emotional and physical reactions.
- The physical reaction that accompanies pain is regarded as a protective reflex (e.g. the withdrawal reflex; to get a way from the painful stimulus).

Quality of pain
- Pricking pain:
  - Also known as fast or first pain. It occurs immediately following stimulation, well localized and transmitted through type A (delta) fibers.
- Burning pain:
  - Also known as slow or second pain. It develops slowly, not well localized and transmitted through type C fibers.

Pain receptors
- These are free nerve endings (found in almost all tissues in the body).
- Their adequate stimulus is not specific (any form of energy can cause pain if it causes tissue damage).
- Tissue damage releases pain-producing substance (PPS or P factor). This substance stimulates pain receptors to cause pain.
- The nature of PPS is unknown. However, it could be a substance released from the damaged tissues like K+ ions.

Afferents
- Type A (delta):
  o For fast pain (conduction velocity = 12-30 m/s)
  o Terminate on laminae I & V
  o Release the neurotransmitter glutamate
- Type C:
  - For slow pain (conduction velocity = 0.5-2 m/s)
  - Usually found on the lateral part of the dorsal roots
  - Terminate on laminae I & II
  - Release the neurotransmitter substance P

Note: The dorsal horn, especially substantia gelatinosa, which is formed by lamina II & part of lamina III, is regarded as a gate for pain.

Tract
- Spinothalamic tract (mainly the lateral part)

Sensory cortex
- Pain activates the contra-lateral primary (S1) & the secondary (S2) sensory areas in the cerebral cortex. It also activates other areas in the brain like the cingulate gyrus, frontal lobe, insula, and cerebellum (Note that frontal lobotomy abolishes the emotional reaction to pain).
- The sensory cortex can discriminate intensity and locality of pain; it also mediates the emotional reaction to pain. However, the modality of pain is discriminated at a lower level (at or even below the thalamus; that is why thalamotomy is used sometimes to treat severe pain).

Types of pain
- According to the site of receptors, pain can be classified into 3 types: cutaneous, deep somatic and visceral pain.

- **Cutaneous pain**
  - Receptors are found in the skin
  - Has two types:
    - Fast (accurately localized, transmitted through Aδ fibers)
    - Slow (not well localized, transmitted through C fibers)
  - Not referred and not associated with autonomic stimulation (sweating, vomiting, tachycardia) or contraction of nearby muscles
- **Deep somatic pain**
  - Receptors are found deep in muscles, joints, bones
  - Generally has one type (slow), this is because it is usually transmitted by type C fibers (little Aδ fibers).
  - Not well localized and can be referred
  - Associated with autonomic stimulation (sweating, vomiting, tachycardia)
  - Associated with contraction of nearby muscles

- **Visceral pain**
  - Receptors are found in the viscera (small in number)
  - Generally has one type (slow), this is because it is usually transmitted by type C fibers (little Aδ fibers).
  - Poorly localized
  - Can be referred
  - Associated with autonomic disturbances (sweating, vomiting, tachycardia)
  - Associated with spasm of overlying skeletal muscles, making the abdominal wall rigid. This protects the viscera from external trauma; for this reason, it is known as “guarding.” It is an important clinical sign in cases of “acute abdomen”.

**Note**
- Ischemic pain in muscles is a classical deep somatic pain.
- Here the pain occurs due to tissue damage caused by inadequate blood supply during exercise and disappears upon rest.
- The low blood supply is caused by partial arterial obstruction (as in atherosclerosis).
- Examples include angina pectoris (due to myocardial ischemia) & intermittent claudication (pain in leg muscles due to ischemia).
- Exercise induces pain because the pain producing substance accumulates (due to tissue damage). However, during rest, the PPS is washed out and pain disappears.
- When the obstruction is complete (as in myocardial infarction) pain appears during rest and persists until the tissues become non-viable (infarcted).

**Referred pain**
- Pain is felt in another area, not the diseased structure (usually the skin of the same dermatome “or embryonic segment” from which the diseased structure was developed).
- It is a feature of deep somatic and visceral pain.
- Occurs according to the dermatomal rule (pain is referred to the skin supplied by the same dorsal root that supplies the organ).

**Common examples:**
- Pain originating from the heart= is felt on the skin of inner aspect of left arm
- Pain originating from the appendix= is felt around the umbilicus
- Pain originating from the diaphragm= is felt on the tip of the shoulder
- Pain originating from the teeth= is felt on the head
- Pain originating in the kidneys and ureters= is felt in the testicles

**Mechanism of referred pain:**
- Referred pain can be explained by Convergence & Facilitation theories

**Convergence theory:**
- Afferents from a diseased viscus and from skin of the same dermatome converge on the same spinothalmic second order neuron. The brain, which is used to receive impulses from the skin and not from the viscus, localizes pain sensation from the viscus to the skin.
Facilitation theory:
- Pain fibers from the skin are always carrying impulses that are normally not enough to stimulate the second order neuron & cause pain.
- Impulses arising from a diseased viscus are carried through afferents that give collaterals to the same second order neuron that comes from the skin; provided that the skin and the viscus were originated from the same dermatome.
- Through the collaterals, impulses from the viscus facilitate stimulation of the second order neuron; this gives sensation of pain in the skin and not the viscus.

Fig 12.7: Mechanisms of referred pain

Central inhibition of pain
- The following mechanisms explain how the perception of pain may be inhibited within the central nervous system:
  - The gate control theory
  - The opiate system of the brain

The gate control theory
- The substantia gelatinosa is a gate for pain.
- It opens with pain impulses coming through type C fibers (the 1st order neuron of spinothalamic tract) and closes with touch impulses coming
through collaterals from type Aβ fibers (the first order neuron of dorsal column tract).

- Rubbing at or around the painful area in the skin stimulates touch receptors in that area; this causes closure of the gate (through the Aβ fibers) and therefore inhibits pain sensation.

**The opiate system of the brain**

- Morphine, a medication derived from opium, is a highly potent analgesic drug. It acts on certain receptors within the central nervous system.
- These receptors also respond to morphine-like peptides synthesized within the body to relieve pain.
- The synthesis of these morphine-like peptides is highly increased during stress. They are known as opioids and they include:
  - Encephalins (found in the hypothalamus, periaqueductal gray matter, thalamus, limbic system and spinal cord)
  - Endorphins (produced by the hypothalamus & the pituitary gland from the large precursor molecule “pro-opio-melanocortin” which also gives ACTH)
- The opioid receptors are synthesized within the dorsal root ganglia. Then they migrate peripherally and centrally to be located at the following sites:
  - Peripheral tissues (when inflammation occurs at these tissues, the opioid receptors respond to opioid peptides released by immune cells to relieve pain)
  - The dorsal horn (this is the site of the gate, here the opioid receptors respond to opioids to cause presynaptic inhibition of type C fibers, this inhibits release of substance P and therefore closes the gate)
  - Limbic System (receptors at these sites respond to opioids to give a sense of well-being)
- Periaqueductal area within the midbrain (the receptors at this site respond to encephalins to activate descending tracts that release serotonin to mediate closure of the gate).

- The above mechanisms can explain the following observations:
  - Rubbing around injury decreases pain:
    - Because rubbing closes the gate by generating touch impulses that are transmitted through Aβ fibers
  - Ignorance of pain during emotional stress as in games and battles:
    - Because stress increases production of opioids, which act centrally to inhibit pain sensation
  - Analgesia induced by acupuncture:
    - Because acupuncture induces release of opioids (when the site of analgesia is far from the site of acupuncture)
    - Because acupuncture generates touch impulses to close the gate (when the site of analgesia is near to the site of acupuncture)

**Fig 12.8: Central inhibition of pain (the gate theory)**
TOUCH
Receptors
- Receptors for touch and pressure (which is maintained touch) are specialized, rapidly adapting receptors (e.g. Pacinian corpuscles). However, some free nerve endings also act as receptors for touch.
- Known as mechanoreceptors because they are stimulated by mechanical energy.
Afferents
- Type Aβ fibers; however, some Aδ & C fibers transmit touch sensation from the free nerve endings.
Tracts
- The two sensory tracts are involved in transmission of the two types touch sensation:
  - Fine touch (well localized, low threshold touch) through the dorsal column tract
  - Crude touch (poorly localized, high threshold touch) through the spino-thalamic tract
Cortex
- The contra lateral sensory cortex (the primary & secondary sensory areas).

TEMPERATURE
Receptors
- Free nerve endings.
- Cold receptors are more numerous than heat receptors (by 4 to 10 times).
- Known as thermoreceptors because they respond to thermal energy.
- Their stimulation is determined by the temperature of the subcutaneous tissue.
- Cold receptors respond to 10-38 °C whereas heat receptors respond to 30-45 °C.

Afferents
- Type Aδ & C fibers for cold sensation, and type C for heat sensation.

Tracts
- Spino-thalamic tract (mainly the lateral division).

Cortex
- The contra lateral sensory cortex (the primary & secondary sensory areas) and the ipsilateral insular cortex.

PROPRIOCEPTION

Receptors
- Slowly adapting receptors, found in and around the joints (tendons and ligaments).

Afferents
- Type Aβ fibers.

Tracts
- The dorsal column tract.

Cortex
- The contra lateral sensory cortex (the primary & secondary sensory areas).
- Many fibers go to the cerebellum to give information about position of the body. Together with the touch sensation and impulses from muscle spindles and Golgi tendon organs, proprioception gives conscious image about position of the body in space.
- Damage to the dorsal column tract results in sensory ataxia. However, ataxia appears when the patient closes his eyes because this eliminates the compensation of position image created by the visual sensation (= the basis of Romberg’s sign).
**TWO POINT DISCRIMINATION**
- The ability to discriminate between two stimuli applied simultaneously into two different points, close to each other, is known as two-point discrimination.
- It depends on intact touch sensation (transmitted through the dorsal column tract) and intact sensory cortex.
- The minimal distance required to discriminate between two points is larger at the back than at the tip of the fingers. This is related to the higher density of receptors at the tip of the fingers.

**STEREOGNOSIS**
- The ability to identify objects by handling, with the eyes closed (e.g. keys, coins, papers ...).
- It depends on intact touch sensation (transmitted through the dorsal column tract). However, the sensory cortex plays a major role in the identification.
- Failure to identify objects by handling "astereognosis" is an early sign of parietal lobe lesions.
### QUESTIONS FOR SELF ASSESSMENT-8 (MCQS)

1. The receptor potential is:
   - a. Propagated
   - b. All or none
   - c. Perceived as a light sensation
   - d. Related to intensity of stimulation
   - e. Only generated in encapsulated receptors

2. Concerning pain sensation:
   - a. It is transmitted through the dorsal column tract
   - b. Receptors are encapsulated nerve endings
   - c. Slow pain is transmitted in C fibres
   - d. Modality discrimination occurs at the sensory cortex
   - e. Localization occurs at the level of the thalamus

3. The dorsal column tract carries:
   - a. Crude touch
   - b. Pain
   - c. Vibration sense
   - d. Temperature sensation
   - e. Itching sensation

4. Localization of a touch sensation is a function of:
   - a. Adequate stimulus
   - b. Encapsulated receptors
   - c. Sensory cortex
   - d. Thalamus
   - e. Spinal cord laminae IV & V

5. Visceral pain is characterized by all the following except:
   - a. Its receptors are free nerve endings
   - b. Its localization is a function of the cerebral cortex
   - c. It is associated with autonomic activation
   - d. It is associated with contraction of nearby muscles “guarding sign”
   - e. It is referred to another visceral structure, not the diseased one

6. The intensity of a stimulus is determined by:
   - a. Type of receptor
   - b. Type of nerve fibre
   - c. Type of sensory tract
   - d. Frequency of action potential
   - e. Personality of subjects

7. Regarding adaptation of receptors:
   - a. Depends on type of adequate stimulus applied
   - b. Occurs at the same rate in different receptors
   - c. Is due to release of inhibitory neurotransmitters
   - d. Is due to inactivation of ion channels
   - e. Never occurs in free nerve endings
8. Sensory ataxia:
   a. Results from damage to spinothalamic tract
   b. Is associated with negative Romberg’s sign
   c. Is characterized by loss of proprioceptive sensation
   d. Is a cause of drunken man gait
   e. Causes coma when a patient closes his eyes

9. Which of the following receptors are “phasic”:
   a. Touch receptors
   b. Pain receptors
   c. Temperature receptors
   d. Chemoreceptors
   e. Proprioceptors

10. Hemisection of the right side of the spinal cord results in:
    a. Loss of pain on the right side
    b. Loss of temperature sense on the same side
    c. Loss of vibration sense on the opposite side
    d. Intact touch on the same side
    e. Loss of position sense on the right side

11. Which of the following neurons has the highest conduction velocity:
    a. Type A delta
    b. Type B
    c. Type Ib
    d. Type A alpha
    e. Type III

12. The first pain:
    a. Receptors are Pacinian corpuscles
    b. Is carried by type C fibres
    c. Is transmitted in the lateral part of the spinothalamic tract
    d. Is usually visceral
    e. Is a burning sensation

13. Concerning the deep somatic pain, which of the following is not true:
    a. Is associated with sweating and vomiting
    b. Is associated with contraction of nearby skeletal muscles
    c. Is well localized
    d. Is carried through type C afferents neurons
    e. Can be referred

14. Which of the following receptors is non-adaptive:
    a. Touch receptor
    b. Vibration receptors
    c. Pain receptor
    d. The muscle spindle
    e. Pressure receptors

15. Which of the following statements about sensory modalities is not true:
    a. Pain receptors are naked nerve endings
    b. Slowly adaptive receptors are protective
    c. Teleceptors convey information about distant events
d. Pain is inhibited by stimulation of paraventricular area in the brain stem
e. First order neurons carrying vibration sense cross to opposite side in the spinal cord

16. Pacinian corpuscles:
   a. Are only present in the skin
   b. Are slowly adaptive
   c. Their afferents synapse with second order neurons in the medulla oblongata
d. Are stimulated by all types of energy
e. Their afferents synapse with second order neurons in substantia gelatinosa

17. Concerning temperature sensation, which of the following is not true:
   a. Receptors are free nerve endings
   b. Cold spots in the skin are 4-10 times higher than warm spots
c. Afferents for cold receptors are type A delta and C fibres
d. Pathway is the ventral spinothalamic tract
e. Afferents for warm receptors are type C fibres only

18. Concerning position sense, which of the following is not true:
   a. Depends on impulses coming from receptors in and around joints
   b. Receptors are probably Pacinian corpuscles
c. Receptors are known as muscle spindles
d. A large proportion goes to the cerebellum
e. Lesions results in sensory ataxia

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CHAPTER (13)
THE SPECIAL SENSES

VISION

THE EYES

- The eyes are complex sense organs specialized for vision.
- Each eye consists of the following structures:

1- The sclera
   - The outer opaque protective layer of the eye.
   - Contains collagen and elastic fibers (usually whitish in color).
   - It maintains the shape of the globe and provides insertions for the extraocular muscles.

Fig 13.1: Structure of the eye
2- **The cornea**
- The transparent anterior part of the sclera.
- Allows light rays to enter the eye.
- Together with the lens, it refracts light to be focused on the retina (its contribution to light refraction in the eye is higher than that of the lens).
- It has no blood supply. It gets oxygen directly from the air; that is why contact lenses reduce oxygen supply to the cornea.

3- **The choroid**
- It is part of the uveal tract which forms the middle layer of the eye.
- The uveal tract lies between the retina and the sclera. It is formed by the choroid, ciliary body, iris and the area located near the attachment of the iris and sclera (called pars plana).
- Contains blood vessels that supply the eyeball structures.
- Contains darkly colored melanin pigments to prevent reflections of light within the eye.

4- **The retina**
- The inner layer which lines the posterior two thirds of the choroid.
- Contains the visual receptors (rods and cons) that respond to light.
- The output from the retina (in form of action potentials) passes through the optic nerve and other structures of the visual pathway to give perception of light.
- Characterized by presence of an area that lacks visual receptors called the optic disc (or the blind spot). It lies 3 mm medial to and slightly above the posterior pole of the eye. It is the area where the optic nerve leaves the eye and the blood vessels enter it.
- Temporal to the optic disc there is another area known as the macula.
- At the center of the macula is the fovea centralis; the area with the highest visual acuity (contains cons only).
5- The ciliary body
- The anterior part of the choroid.
- Consists of the ciliary muscle which adjusts the convexity of the lens and the ciliary processes which are the inward folding of the choroid layers.
- It participates in accommodation (see below), produces the aqueous humor and maintains the lens zonules.

6- The lens
- The transparent biconvex structure that refracts light rays to the retina.
- The ciliary muscle increases or decreases its convexity to focus the eye on objects at different distances from it (= accommodation).

7- The suspensory ligament (zonule)
- The ligament that holds the lens in its position.
- It is attached to the ciliary body.

8- The iris
- The pigmented part of the eye.
- It contains two types of muscle that adjust the diameter of the pupil to control the amount of light reaching the retina.
- The muscles are:
  - Dilator pupillae: contains radial muscle fibers that cause pupillary dilatation in response to sympathetic stimulation.
  - Sphinctor pupillae: contains concentric muscle fibers that cause pupillary constriction in response to parasympathetic stimulation.

9- **Vitreous humor**
- The clear gelatinous material that fills the space between the lens and the retina. Consists of water, salts, sugars and collagen fibers.
- It provides structural support to the eyeball and allows passage of light rays to the retina.

10- **Aqueous humor**
- The clear liquid that fills the space between the lens and the cornea.
- Provides nutrients to the avascular parts of the eye (the lens and cornea) and eliminates their waste products.
- Its pressure maintains the normal convexity of the cornea.
- Produced by diffusion and active transport from plasma in the ciliary body and reabsorbed into a venous system “the canal of Schlemm” (which is found in the anterior chamber at the junction between the iris and the cornea). Increased production of the aqueous humor or decreased drainage through the canal leads to increased intraocular pressure (normal range 10-20 mmHg). This is especially serious in patients with glaucoma. Here, the high intraocular pressure aggravates the damage to the optic nerve causing severe visual loss and eventually complete blindness.
- For this reason, the intraocular pressure should be lowered in these patients by β blockers or carbonic anhydrase inhibitors (both decrease aqueous humor production) or by cholinergic agonists (increase aqueous humor drainage).
The retinal cells
- In addition to the rods and cons, the retina consists of many types of neuronal cells arranged in 10 layers. These neuronal cells include: Bipolar cells, ganglion cells, horizontal cells and amacrine cells.
- Light rays pass through these cells before reaching the rods and cones which are found at the back of the eye, next to the choroid. The rods and cones converge on bipolar cells and these converge on ganglion cells.
- The axons of the ganglion cells form optic nerve. The horizontal cells make connections between the rods and cones to form the outer plexiform layer. The amacrine cells make connections between the ganglion cells to form the inner plexiform layer.
- The rods are about 120 millions in each eye; they are specialized for dark vision whereas the cones are about 6 millions in each eye; they are specialized for day vision & color vision.

Fig 13.3: The retinal cells

The visual pathway
- Light rays are refracted by the cornea and lens to be focused on the retina. This results in generation of action potentials in the rods and cones.
- Action potentials are transmitted through the visual pathway to the cerebral cortex to give the sensation of vision.
The visual pathway consists of the following structures:

- **Optic nerve**: (Each nerve carries both nasal fibers (from the medial side of each eye) and temporal fibers (from the lateral side of each eye).
- **Optic chiasma**: (here the two optic nerves meet and pass to the optic tract. The nasal fibers in each optic nerve cross to the other side whereas the temporal fibers pass uncrossed on the same side).
- **Optic tract**: (each optic tract carries temporal fibers from the same side and nasal fibers from the other side).
- **Lateral geniculate body**: (a relay station in the thalamus).
- **Optic radiation**: (where the visual fibers travel through the deep white matter of the cortex “as the geniculocalcine tract” towards the occipital lobe).
- **The primary visual cortex in the occipital lobe**: (= area 17, at the sides of the calcarine fissure).

**Fig 13.4: The visual pathway**
**Interruption of the visual pathway (= Visual field defects)**

- The visual field is the total area in which objects can be seen while the eye is focused on a central point. It is divided into nasal and temporal fields.
- Because of the spherical shape of the eye globe:
  - Optic nerve fibers originating from the nasal half of the retina look to the temporal field of vision.
  - Optic nerve fibers originating from the temporal half of the retina look to the nasal field of vision.
  - Optic nerve fibers originating from the upper half of the retina look to the lower field of vision.
  - Optic nerve fibers originating from the lower half of the retina look to the upper field of vision.

**Fig 13.5: The retina & the visual field**

- Lesions occurring at different locations of the visual pathway cause different forms of visual field defects.
- The defects are either uniocular or binocular.
- Uniocular field defects are caused by lesions at the optic nerve. Here the defects occur at the same eye.
- Binocular field defects are caused by lesions at or behind the optic chiasma. Here the defects occur in both eyes.
- Examples of visual field defects (A-E) can be studied from this figure:

**Fig 13.6: The visual field defects**

- **Optic nerve lesions (A):**
  - Cause complete unilateral blindness on the same side.

- Partial optic nerve damage may cause scotomas (areas of reduced vision):
- **Optic chiasma lesions (B):**
  - Cause bitemporal hemianopia (i.e. heteronymous hemianopia).

- **Optic tract lesions (C):**
  - Cause homonymous hemianopia.

- **Optic radiation lesions (D):**
  - Cause homonymous quadrantopia.

- **Occipital lobe lesions (E):**
  - Causes cortical blindness. (Note the macular sparing!).
The light reflex
This reflex occurs directly and indirectly.
- Direct light reflex:
- When light is shone on an eye, its pupil constricts
- Indirect (Consensual) light reflex
- When light is shone on an eye, the pupil of the other eye constricts

Fig 13.7: The light reflex

The pathway of the light reflex:
- The first order neuron passes through:
  - Optic nerve
  - Optic chiasma
  - Optic tract
  - Superior colliculus and then pretectal nucleus in the midbrain
- The second order neuron:
  - From the pretectal nucleus to oculomotor nerve nucleus “Edinger Westphal nucleus” (on both sides)
- The third order neuron:
  - Oculomotor nerves (on both sides) to the ciliary ganglion (on both sides)
- The fourth order neuron:
  - From the ciliary ganglion to the ciliary body.

Note: The pathway on the same side mediates the direct light reflex whereas that on the other side mediates the consentual light reflex.
The near response
- Light rays are refracted by the cornea and lens to be focused on the retina.
- On looking to a distant object (more than 6 meters):
  - light rays are coming in parallel.
  - ciliary muscle is relaxed & the lens is flat.
  - the rays are brought to a focus on the retina.
- On looking to a near object (closer than 6 meters):
  - light rays are diverging.
  - they will be focused behind the retina. However, this is prevented by the near response.
  - the near response consists of:
    1. Increased convexity of the lens (accommodation)
    2. Convergence of the visual axis
    3. Pupillary constriction

The near point
- The nearest point to the eye where an object can be clearly seen.
- Here, the lens is convex to the maximum.
- By increasing age, the lens loses elasticity and its convexity is decreased.
- Therefore the near point (where one can see clearly) is increased with age as follows:
  - From 9 cm at 10 years
  - to 18 cm at 40 years
  - to 100 cm at 70 years
- That is why old people use convex lens for reading.
Abnormalities involving the light reflex & the near response

Argyll Robertson pupil
- Loss of the light reflex with intact near response (i.e. intact accommodation).
- Caused by syphilis.
- Both pupils are affected but to a symmetrical degree.

Holmes-Adie (myotonic) pupil
- Loss of the light reflex with sluggish accommodation.
- Usually unilateral and more common in women.
- Occurs due to defect in the postganglionic neurons from the ciliary ganglion to the sphincter pupillae and the ciliary muscle.
- Benign condition (does not need treatment).

Horner’s syndrome
- Occurs due to loss of sympathetic supply to the face because of cervical sympathectomy.
- Characterized by many signs in the face including constriction of the eye pupil (meiosis) on the affected side.

Errors of refraction

1- Hypermetropia (farsightedness):
- Occurs when the eye ball is shorter than normal. Therefore the light rays are focused behind the retina.
- For this reason patients can see distant objects better than near ones.
- To see near objects, excessive accommodation is needed. This causes hypertrophy of ciliary muscles, headache and may predispose to squint.
- The condition is corrected by convex lenses.

2- Myopia (near sightedness):
- Occurs when the eye ball is longer than normal.
- Therefore the light rays are focused in front of the retina.
- For this reason patients can see near objects better than distant ones.
- The condition is corrected by biconcave lenses.

**Fig 13.8: Errors of refraction**

3- **Astigmatism**
- Occurs when the curvature of the cornea is irregular.
- Therefore light rays are focused at different locations; producing blurred image.
- Patients are characteristically unable to localize the point where a horizontal and a vertical line cross.
- The condition is corrected by cylindrical lenses.

4- **Presbyopia**
- Occurs when the lens elasticity is decreased (e.g. by advancing age) resulting in loss of accommodation.
- Subjects become unable to read without wearing glasses with convex lenses.

*The core of medical physiology (vol 2) ed 2*
The visual receptors & the photosensitive pigments
- The following figure summarizes the structure of the visual receptors (the rods and cones).

**Fig 13.9: The visual receptors**

- The photosensitive pigments are found in the outer segments of the rods and cones. They consist of 2 proteins:
  - Retinene$_1$ (the aldehyde of vitamin A, so it is called retinal)
  - Opsin

**In rods:**
- The pigment is called rhodopsin
- Rhodopsin consists of retinene$_1$ and opsin (opsin is also called scotopsin).
- In the dark, light changes the shape of retinene$_1$ in rhodopsin
- This changes the configuration of the opsin
- This initiates reactions resulting in action potential transmitted by the optic nerve. The reactions can be summarized as follows:
  - Light
  - Structural change in retinene$_1$
  - Conformational change in opsin
- Activation of transducin (a G protein coupled with rhodopsin)
- Activation of the enzyme phosphodiesterase
- Decreased intracellular cGMP (converted to 5’-GMP)
- Closure of sodium channels (because they are maintained open by cGMP)
- Hyperpolarization
- Decreased release of the transmitter (which is released continuously from the synaptic terminals of the rods)
- Electrical responses in the bipolar cells due to reduction in transmitter release
- Action potentials in the ganglion cells
- Conduction through the visual pathway

**In cones:**
- There are 3 different types of retinene₁ & opsin (in 3 different types of cones).
- Their responses to light are similar to that of rhodopsin.
- Each cone pigment is most sensitive to one of the 3 primary colors: (red, green & blue).
- The input from one type of cone gives a sensation of one of the primary colors.
- When the input is added to that from the other cones in the pathway to the cortex, it gives the sensation of the other colors.
- The sensation of any color is determined by the frequency of impulses in each of the 3 types of cones (Young-Helmholtz theory).

**Recovery following transduction:**
- After the change in shape of retinene₁ in rhodopsin, it separates from the opsin and undergoes reduction by the enzyme alcohol dehydrogenase in the presence of NADH to form vitamin A₁. This vitamin reacts with opsin to
form rhodopsin again. However, direct regeneration of rhodopsin also occurs.
- Generation of cGMP following transduction occurs due to reduction of calcium concentration in the photoreceptors because of the light. The low calcium inhibits the phosphodiesterase (which decreases cGMP) and activates guanylyl cyclase (which increases cGMP). Then the high cGMP opens the sodium channels.

Tests for vision

- Fundoscopy (ophthalmoscopy)
  - For examination of the retina (macula, optic disc and blood vessels).
  - The ophthalmoscope is used for this examination.
  - Fundoscopy is important in conditions like glaucoma, diabetes and hypertension.
  - It is especially important to do fundoscopy before doing lumbar puncture in a patient suspected to have high intracranial pressure.
  - Here detection of papilledema with the ophthalmoscope (swelling of the optic disc) indicates intracranial hypertension & therefore lumbar puncture is contraindicated.

- Visual Acuity
  - This is the degree to which the details and contours of objects are perceived. The “Snellen’s charts” are used for this examination.
  - The charts include letters that are located at a distance of 6 m (20 ft) from patients who are asked to read the smallest line that can be clearly seen; then the results are expressed as a fraction (e.g. 6/6 if the acuity is normal or 6/36 if it is low).
  - A value of 6/36 indicates that acuity of the patient from 6 meters is similar to that of a normal subject from 36 meters.
Color vision
- The “Ishihara charts” are used for this examination.
- These charts are polychromatic plates containing figures printed with special colors so as not to be seen by patients with color blindness.
- Color blindness is inherited as X-linked recessive (this is because two of the cone pigments are encoded by genes on chromosome X).
- For this reason it is more common in males than females (Note: females are carriers whereas males are victims).

Fig 13.10: Instruments used in eye examination

Visual field
- As mentioned above, the visual field is the total area in which objects can be seen while the eye is focused on a central point (see the visual field defects). It can be tested with the following methods:
  - Confrontation method
    - The doctor sits infront of the patient.
    - He compares his own peripheral visual filed with that of the patient.
Fig 13.11: Confrontation method

- Perimetry
  - The systematic evaluation of the visual field using dedicated machinery.
  - Examples include:
    - Goldmann kinetic perimetry (here a trained examiner maps the visual field).
    - Automated perimetry (here a computer program maps the visual field according to patient’s responses to flashing light).

Fig 13.12: Automated perimetry

- Other tests:
  - Slit lamp examination (= examination of the anterior eye structures with the slit lamp machine).
  - Tonometry (= Measurement of intra-ocular pressure with a tonometer).
HEARING

- Hearing is the ability to detect sound. It is a function of the ear.
- The ear converts sound waves into nerve impulses that are perceived by the brain. It is divided into 3 parts: external ear, middle ear, & internal ear.

The External ear

- Consists of:
  - Auricle (ear pinna)
  - External auditory meatus (ear canal)
  - Tympanic membrane (ear drum)

- Directs sound waves to pass through the external auditory meatus and strike on the tympanic membrane.

Fig 13.13: The ear

The Middle ear

- Air filled cavity within the temporal bone.
- Opens into the pharynx through the Eustachian tube (auditory tube).
- This tube equalizes the air pressure between the two sides of the tympanic membrane.
- The middle ear contains 3 ossicles and 2 muscles.
- The three ossicles are: Malleus, incus, and stapes.
- Vibrations of the tympanic membrane move the malleus, which is fused with the tympanic membrane, the malleus moves the incus and this moves the stapes (all these ossicles are attached to each other). The stapes knocks on the oval window, which is part of the inner ear (part of the cochlea). This generates pressure waves in the cochlear fluid (see below).
- The 2 muscles are:
  - Tensor tympani muscle (increases tension of the tympanic membrane)
  - Stapedius muscle (separates the stapes from the oval window)
- These muscles prevent transmission of very loud sound to the inner ear & therefore protect the inner ear from damage by the very loud sound.

**The inner ear**
- The inner ear (or the labyrinth) is series of channels in the petrous part of the temporal bone (= bony labyrinth) duplicated by membranous structures (= membranous labyrinth).
- Between the bony and membranous labyrinth there is fluid called perilymph whereas inside the membranous labyrinth there is fluid called endolymph.
- The perilymph is similar to the extracellular fluid (rich in sodium) whereas the endolymph is similar to intracellular fluid (rich in potassium).
- Structures that form the labyrinth are six structures:
  - One organ for hearing: cochlea
  - Five organs for equilibrium: three semicircular canals plus utricle and saccule (the utricle and the saccule are known collectively as the vestibule).
- Receptors in all these structures are hair cells stimulated by movement of the endolymph.
The cochlea
- Coiled tube, 35 mm long (makes less than 3 turns). Divided into 3 chambers by the Basilar membrane & the Reissner's membrane.
- The three chambers are Scala vestibule, scala media, & scala tympani.
- Both scala vestibuli and scala tympani contain perilymph and communicate with each other through the helicotrema (small opening at the apex of the cochlea); whereas scala media contains endolymph and does not communicate with the other chambers.
- Scala vestibuli ends on the oval window, which is attached to the stapes; whereas the scala tympani ends on the round window (both windows bulge into the middle ear).

Fig 13.14: The middle and inner ears

- When the stapes knocks on the oval window, it generates pressure waves in the perilymph of both scala vestibuli and and scala tympani. The waves are transmitted to the endolymph through the thin, Reissner's membrane.
- Hair cells are found in the basilar membrane, they are the auditory receptors. Together with phalangeal cells, they form the organ of Corti (the sense organ of hearing).
- The organ of Corti extends throughout the length of the basilar membrane. It is formed by 4 rows of hair cells, three rows lateral to the rods of Corti (outer hair cells) and one row medial to the rods of Corti (inner hair cells).
- The rods of Corti are pillar like cells that support a tough membrane pierced by the processes of hair cells (the reticular lamina). In addition, the outer hair cells are covered by a thin, elastic membrane known as the tectorial membrane.

**Fig 13.15: The organ of Corti**

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**Mechanism of hearing**

- Sound waves are directed by the ear pinna to strike on the tympanic membrane.
- Vibrations of the tympanic membrane result in movement of the ossicles in the middle ear (malleus, incus, and stapes).
- The stapes knocks on the oval window.
- This generates pressure waves in the perilymph of the scala vestibuli and scala tympani. Waves in the perilymph generate waves in the endolymph of scala media.
- The endolymph moves the tectorial membrane; this stimulates the hair cells in the organ of Corti (by causing potassium influx).
- The resulting action potentials are transmitted through the cochlear division of the vestibulo-cochlear nerve (the 8th cranial nerve) to the dorsal and ventral cochlear nuclei in the medulla, then to the medial geniculate body in the thalamus.
- They eventually reach the auditory cortex at the temporal lobe (in the Sylvian fissure) to give the sensation of hearing.

**Mechanism of hair cell stimulation**
- Hair cells are found in all structures of the inner ear (cochlea, utricle, saccule, and semicircular canals).
- In each of these structures, they combine with sustentacular cells to form the following sense organs:
  - Organ of Corti in cochlea for hearing
  - Otolithic organ in utricle for equilibrium (detects linear movement in the horizontal plane)
  - Otolithic organ in saccule for equilibrium (detects linear movement in the vertical plane)
  - Crista ampullaris in each of the three semicircular canals for equilibrium (detects rotational movement)
- Hair cells have two types of hair processes projecting from their apical membranes:
  - Stereocelia:
    - Motile cilia, found in all types of hair cells
    - Increase progressively in height towards the other type (the kinocilium)
  - Kinocilium:
    - One immotile, large cilium
    - Found in all structures of the inner ear except the cochlea
- The processes of hair cells are bathed into the endolymph (which is rich in potassium ions) whereas their bases are bathed into perilymph.
- Pressure waves in the endolymph pushes the shorter stereocilia towards the kinocilium (or towards the highest stereocilium as in the cochlea); this causes opening of mechanically gated cation channels, allowing potassium, and calcium influx.
- The generated action potential stimulates release of a neurotransmitter (most probably glutamine) from the bases of hair cells. This generates afferent impulses in either the cochlear or the vestibular division of the vestibule-cochlear nerve.

**Fig 13.16: Mechanism of hair cell stimulation**

![Mechanism of hair cell stimulation](image)

**Intensities & frequencies of sound waves**
- Sound waves travel through air at a speed of about 344 m/s, at 20 c° at sea level; the speed becomes higher with temperature, altitude, and water.
- They differ in their amplitudes and frequencies.
- Generally, the frequency of a sound determines its pitch and its amplitude determines its loudness (note that frequency also affects loudness and other factors may contribute to both pitch and loudness).
- The frequency (or pitch) of sound is expressed in Hz (cycles per second).
- The frequencies audible to humans range from 20 to 20,000 Hz. However, the best audible frequencies (or pitches) lie in the range 1000 to 4000 Hz (note that the voice pitch of humans during conversation is about 120 Hz for males and 250 Hz for females).
- Amplitude of sound (or its intensity) is expressed in decibels (dB).
- Number of dB = 10 log x intensity of sound/intensity of standard sound.
- Because this is a log scale, when the number of dB = zero, the intensity of sound is equal to the intensity of standard sound (which is the sound that is just audible to average humans).
- Sound intensity of 140 dB is damaging to the hair cells in the cochlea.

“Why do we have two ears?”... “For sound localization!”
- When sound waves reach the two ears on both sides of the head, there are differences in:
  - Time of arrival (less time on the side closer to the source of the sound)
  - Intensity of sound (louder sound on the side closer to the source of the sound)
- These two factors enable the brain to determine the source of sound (sound localization).
- Because the ear pinna is turned slightly forward, sounds coming from in front or behind the ears differ in their quality. This difference in quality is used for localization.

**DEAFNESS**
- Deafness is loss of hearing. It is two types:
  - Conductive deafness
  - Nerve deafness
Causes of conductive deafness
- Occlusion of the external ear by foreign body or wax
- Otitis media (causes thickening or perforation of the tympanic membrane)
- Otosclerosis

Causes of nerve deafness
- Acoustic neuroma
- Drugs (aminoglycosides like streptomycin and gentamycin)
- Advanced age (due to gradual loss of hair cells and neurons)
- Genetic causes (e.g. Pendred's syndrome which is characterized by deafness and goiter)

Tests for hearing
- The following tests are used to diagnose deafness and to differentiate between its two types (conductive and nerve deafness).

Weber's test
- Done by placing base of vibrating tuning fork on vertex of the skull to allow bone conduction
- Normal subjects hear equally on both sides (= negative test)
- Patients with conductive deafness hear better on the affected side (due to loss of the masking effect of the environment)
- Patients with nerve deafness hear better on the normal side

Rinne's test
- Done by placing base of vibrating tuning fork on mastoid process behind the ear (for bone conduction) until the sound disappears, then its apex is placed in air next to the ear (for air conduction)
- Normal subjects hear vibrations in air after the bone conduction is over (i.e. air conduction is better than bone conduction)- (= negative test)
- Patients with conductive deafness hear bone conduction but not air conduction
- Patients with complete nerve deafness do not hear any sound whether conducted by air or bone; however, those with partial nerve damage hear vibrations in air after the bone conduction is over

**Audiometry**
- An audiometer is used to measure the degree of hearing loss
- The device presents tones with different intensities and frequencies to a subject through earphones; the subject responds when he hears a sound
- Audible frequency is plotted against intensity on a graph paper as a percentage of normal hearing

**THE SEMICIRCULAR CANALS**
- Found on each side of the head.
- Lie perpendicular to each other.
- Oriented in 3 planes
- Each has dilated end (ampulla) containing hair cells that form a receptor organ known as crista ampullaris.
- The endolymph inside the semicircular canals moves in rotational movements. This stimulates the hair cells in crista ampullaris.
- Action potentials are transmitted through the vestibular division of the 8th cranial nerve to the vestibular nuclei in the medulla and the vestibulonodular lobe in the cerebellum.
- From the vestibular nuclei (superior & medial nuclei), fibers project to the nuclei of the cranial nerves III, IV & VI (which control eye movements) and then to the somatosensory cortex, through the thalamus.
UTRICLE AND SACCULE
- Concerned with linear movement in the:
  - Horizontal plane (utricle)
  - Vertical plane (saccule)
- Hair cells inside them form receptor organs known as the otolithic organs or maculas (formed by hair cells + sustentacular cells + otolithic membrane in which CaCO3 crystals are embedded).
- Action potentials are transmitted through the vestibular division of the 8th cranial nerve to the vestibular nucleus in the medulla and the vestibulonodular lobe in the cerebellum.
- From the vestibular nucleus (lateral or Deiters’ nucleus), some fibers project to the spinal cord through the vestibulospinal tract. Other fibers project to the reticular formation and the somatosensory cortex, through the thalamus.

SMELL & TASTE
THE SENSE OF SMELL (OLFACTION)
- Depends on chemoreceptors found in the mucosa of the superior portion of the nasal cavity.
- Some air reaches this poorly ventilated area with each respiratory cycle.
- The amount of air reaching the olfactory mucosa is greatly increased with sniffing, which is usually performed when an odor attracts attention.
- Molecules can be detected once dissolved in the mucus layer.

Pathway
- Chemoreceptors
  - Found in the olfactory mucus membrane
  - Rapidly adapting receptors
- Olfactory nerve
  - Its neurons pierce the cribriform plate of the ethmoid bone

- Olfactory bulb
  - The neurons pass from the olfactory bulb to the cerebral cortex
  - Smell is the only modality of sensation that does not pass through the thalamus

- Olfactory cortex
  - Smell area is located in the orbitofrontal gyri of the frontal lobe
  - It is part of the limbic system; however, some fibers pass to other parts of the limbic system (e.g. the amygdala) to mediate the emotional reaction to smell. Other fibers pass to areas concerned with olfactory memories.

**Note**
- Humans can recognize more than 10,000 different odors (because there are large number of different odor receptors, large number of olfactory neurons, special organization of different cells within the olfactory bulb, and different receiving areas in the olfactory cortex).
- The ability to discriminate different intensities of an odor is poor; a concentration change of about 30% is needed before a difference in intensity can be perceived.
- Females (in all ages) are slightly superior to males in odor identification.

**Fig 13.17: Olfactory pathway**
**Smell disorders**

**Anosmia & hyposmia**

- Anosmia is loss of smell whereas hyposmia is reduced ability to smell
- **Causes:**
  - Upper respiratory tract infections (common cold)
  - Head injury (with fracture base of the skull)
  - Kallmann’s syndrome (hypothalamic hypogonadism with anosmia)
  - Advancing age

**Hyperosmia**

- Hyperosmia is heightened sense of smell
- **Causes** pregnancy and psychological disorders (e.g. hysteria)

**Dysosmia**

- Distortion of smell (i.e. odors smell different)
- **Causes** include sinusitis, mouth infections, depression and viral hepatitis

**TASTE SENSATION**

- Depends on chemoreceptors in taste buds.
- The taste buds are scattered in the tongue, epiglottis, palate, and pharynx.
- The taste buds are the sense organ for taste (each taste bud consists of four types of cells; one of these types acts as cheoreceptor for taste).
- The chemoreceptive cells in each taste bud have microvilli on their apical surfaces; the microvilli project into the taste pore, an opening in the upper surface of the taste bud.
- The cells are exposed to chemicals through this taste pore.
**Fig 13.18: The taste bud**

Tate pathway

- Afferent neurons from taste buds (1\textsuperscript{st} order neurons):
  - Chorda tympani branch of the facial nerve (from the anterior two thirds of the tongue)
  - Glossopharyngeal nerve (from the posterior third of the tongue)
  - Vagus nerve (from the pharynx)
- Nucleus of tractus solitarius in the medulla (cell bodies of 2\textsuperscript{nd} order neurons): Axons ascend in the medial lemniscus to the thalamus
- The ventral posteromedial nucleus of the thalamus (cell bodies of 3\textsuperscript{rd} order neurons): Axons pass in the sensory radiation to the postcentral gyrus and insular cortex

**Taste modalities**

- Taste is usually described as:
  - Sweet (stimulated by sugars)
  - Salt (stimulated by sodium chloride)
  - Sour or acid (stimulated by protons “hydrogen ions”)
  - Bitter (stimulated by poisons and some drugs like quinine)
  - Umami (A pleasant taste stimulated by mono-sodium glutamate, added recently to taste modalities. Sauces with umami and salty tastes are very popular for cooking, such as tomato sauces and ketchup).
**Areas of taste on the tongue**
- Taste buds in the tongue are found in the fungiform papillae (mainly near the tip of the tongue) and the vallate papillae (mainly at the back of the tongue); but not the filiform papillae (on the dorsum of the tongue).
- The five modalities of taste are sensed from all areas of taste sensation in the tongue. The common misperception that each taste modality is confined to special area in the tongue “taste map” is obsolete.

**Important notes**
- The receptors for sour and salty taste are ion channels whereas the receptors for sweet, bitter, and umami are coupled to G-protein.
- The ability to discriminate different intensities of a taste sensation is poor; a concentration change of about 30% is needed before a difference in intensity can be perceived.
- Flavor of food is produced by the combination of taste, smell, touch and temperature.

**Taste disorders**

**Ageusia & hypoguesia**
- Aguesia is total loss of taste whereas hypoguesia is reduced taste sensitivity
- Causes:
  - Drugs like penicillamine & captopril (cause transient aguesia)
  - Local inflammation
  - Deficiency of vitamin B3 (Niacin) or zinc
  - Advancing age
  - Damage to the afferent nurons (e.g. Bell’s palsy)
**QUESTIONS FOR SELF ASSESSMENT-9 (MCQS)**

1. **Conductive deafness is caused by:**
   - a. Cochlear damage
   - b. Foreign body in the auditory tube
   - c. Otosclerosis
   - d. Streptomycin
   - e. Acoustic neuroma

2. **The sense organ for hearing is known as:**
   - a. Macula
   - b. Cochlea
   - c. Crista ampularis
   - d. Organ of corti
   - e. Otolithic organ

3. **Weber test in a patient with conductive deafness:**
   - a. Gives results similar to nerve deafness
   - b. Shows better hearing on the affected side
   - c. Shows better hearing on the normal side
   - d. Shows equal hearing on both sides
   - e. None of the above is correct

4. **Concerning vision, which of the following is not true:**
   - a. Refraction of light is larger at the cornea than at the lens
   - b. Myopia is corrected with biconcave lenses
   - c. Rods are responsible for color vision
   - d. Color blindness is found in males more than females
   - e. The fovea centralis does not contain rods

5. **Heteronymous hemianopia is caused by damage to:**
   - a. Optic nerve
   - b. Optic tract
   - c. Optic chiasma
   - d. Optic radiation
   - e. Cerebral cortex

6. **Concerning tests for hearing, which of the following is correct:**
   - a. In normal subjects, bone conduction is better than air conduction
   - b. Using Weber test, conductive deafness is diagnosed when hearing is better on the normal side
   - c. Audiometry is useful in deaf children
   - d. In audiometry frequency of sounds are expressed in decibels
   - e. In partial nerve deafness air conduction is better than bone conduction

7. **Homonymous hemianopia is caused by damage to the:**
   - a. Optic nerve
   - b. Optic tract
c. Optic chiasma
d. Optic radiation
e. Angular gyrus

8. The sense organ for linear acceleration is known as:
   a. Organ of Corti
   b. Crista ampularis
c. Otolithic organ
d. Calcium carbonate crystals
e. Hair cells

9. Which of the following statements is correct:
   a. Semicircular canals are concerned with hearing
   b. Negative Runne’s test indicates nerve deafness
c. Wax in the external auditory canal is a recognized cause of nerve deafness
d. Acoustic neuroma presents with nerve deafness, ataxia and vertigo
e. Taste sensation from anterior two thirds of the tongue are carried in trigeminal nerve

10. Which of the following is a recognized cause of both hyperosmia and hypergeusia:
    a. Kallmann syndrome
    b. Vitamin A deficiency
c. Pregnancy
d. Addison’s disease
e. Frontal lobe tumor

11. Vertigo occurs due to damage to:
    a. Cerebellum
    b. Mid brain
c. Vestibular system
d. Cerebral cortex
e. Thalamus

12. The sense organ for rotational acceleration is known as:
    a. Organ of Corti
    b. Crista ampularis
c. Otolithic organ
d. Calcium carbonate crystals
e. Hair cells

13. When the light rays are focused behind the retina, the subject is:
    a. Hypermetropic
    b. Myopic
c. Presbyopic
d. Immetropic
e. Normal
14. Which of the following structures gives the eye its characteristic color:
   a. Cornea
   b. Lens
   c. Iris
   d. Retina
   e. Sclera

15. In a patient with hypermetropia:
   a. The eye ball is larger than usual
   b. Light rays are focused in front of the retina
   c. Near objects can be seen better than distant objects
   d. Visual acuity is usually 6/6
   e. Vision is improved with convex lenses

16. Concerning the intraocular pressure, which of the following is not true:
   a. It is normally between 10 and 20 mmHg
   b. It increases with age
   c. High pressure is a risk factor for glaucoma
   d. High pressure can be lowered by taking acetazolamide
   e. High pressure causes cataract

17. The tympanic membrane:
   a. Reduces frequency of sound waves reaching the ear
   b. Bulges inwards when the auditory tube is blocked
   c. Separates the middle ear from the inner ear
   d. Is directly attached to the stapes
   e. Cannot transmit sound waves if it is perforated

18. All the following statements about visual adaptation of a subject entering a dark room are correct except:
   a. Adaptation to poor light takes about 20 minutes
   b. The major cause of adaptation is regeneration of bleached receptor pigments
   c. Adaptation involves the cones before involving the rods
   d. Adaptation is better for peripheral (rods) than central vision (cones)
   e. The threshold light intensity starts to rise

12.  b  13. a  14. c  15. e  16. e  17. b  18. e
## CHAPTER (14)

### THE MOTOR SYSTEM

- The motor system comprises all the following systems: pyramidal system, the extrapyramidal system, the vestibular system and the cerebellum.
- These systems control posture, reflexes, muscle tone and voluntary movement of muscles.
- Their pathways originate in the brain or brainstem and descend down the spinal cord to control spinal motor neurons.
- The spinal motor neurons originate in the anterior horns of the spinal cord; they send their axons via the ventral spinal roots and spinal nerves to control motor activities of skeletal muscles. They also form the final common pathway for the spinal reflexes, which are integrated at the spinal cord.

### THE SPINAL CORD & REFLEXES

#### Anatomy of the spinal cord

- The spinal cord is the part of the nervous system that is protected and enclosed by the bony vertebral column.
- The adult human spinal cord is about 45 cm in males and 42 cm in females; extending from the medulla oblongata to the conus medullaris at the vertebral level of “L1-2” where it ends in a fibrous extension known as the filum terminale.
- The outer region of the spinal cord is a white matter consisting of the ascending and descending neural tracts. This surrounds a “butterfly” or “H” shaped central region of gray matter consisting of the cell bodies of sensory and motor neurons.
- The cell bodies of the sensory neurons are found in the posterior horns of the gray matter whereas the cell bodies of motor neurons are found in the anterior horns.

- At the center of the gray matter is the central canal which is an extension of the brain ventricles. It contains cerebrospinal fluid (CSF).

**Fig 14.1: The spinal cord**

![Diagram of the spinal cord]

**Fig 14.2: The gray and the white matters of the spinal cord**

![Diagram of the gray and white matters of the spinal cord]
- Like the brain, the spinal cord is covered by the three meninges:
  - Dura mater “outer layer”, Arachnoid mater “middle layer” & Pia mater “inner layer”
- The arachnoid mater is separated from the pia mater by the “subarachnoid space” which also contains cerebrospinal fluid.
- The cerebrospinal fluid is a clear, isotonic fluid produced from blood by the choroid plexus in the lateral and fourth ventricles in the brain, it flows from the lateral ventricles to the third ventricle through the interventricular foramina “foramen of Monro”, then to the fourth ventricle through the cerebral aqueduct and then to the subarachnoid space through the foramina of Luschka and foramen of Magendie; from there it is reabsorbed back to the venous blood (in the cerebral venous sinuses) by the arachnoid villi.

- **Functions of the CSF:**
  - Mechanical protection of the brain “Cushion effect”
  - Distribution of some neuroendocrine factors
  - Homeostasis & metabolism of the brain
  - Prevention of brain ischemia (absorption of the fluid decreases intracranial pressure & allows blood to flow through the vessels).

**Table 14.1: Characteristics of the CSF**

<table>
<thead>
<tr>
<th>Character</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>150 ml</td>
</tr>
<tr>
<td>Daily production</td>
<td>550 ml/day</td>
</tr>
<tr>
<td>Protein</td>
<td>15 to 40 mg/dL; or 0.3% of plasma protein concentration</td>
</tr>
<tr>
<td>Cells</td>
<td>0-5 mono-nucleaar cells</td>
</tr>
<tr>
<td>Glucose</td>
<td>50-80 (two-thirds of blood glucose)</td>
</tr>
<tr>
<td>Pressure</td>
<td>70 - 180 mmH₂O</td>
</tr>
</tbody>
</table>
The spinal cord consists of segments. Each segment has a pair of spinal nerves. Each spinal nerve is formed of:

- A dorsal root (contains sensory axons of neurons located in the dorsal root ganglion)
- A ventral root (contains motor axons of neurons located at the anterior horn)

The spinal nerves that originate from these segments are divided into four groups:

- Cervical (8 spinal nerves, from C₁ to C₇)
- Thoracic (12 spinal nerves, from T₁ to T₁₂)
- Lumbar (5 spinal nerves, from L₁ to L₅)
- Sacral (5 spinal nerves, from S₁ to S₅)

**Functions of the spinal cord**

- Contains ascending (sensory) and descending (motor) tracts
- Acts as an integrating center for spinal reflexes

**The sensory tracts (Ascending tracts)**

- The antero-lateral tract
- The dorsal column tract

**The motor tracts (Descending tracts)**

- The pyramidal tracts: (the corticospinal & the corticobulbar tracts)
- The extrapyramidal tracts: (the rubrospinal tract, the reticulospinal tract, the vestibulospinal tract & the tectospinal tract).

**The spinal reflexes**

- These are the reflexes which are integrated at the spinal cord.
- The basic structure features and the most important examples of these reflexes are described in the following section.
THE REFLEX ARC
- The reflex arc is the basic unit of integrated neural activity; it controls many autonomic and somatic functions.
- It consists of receptor, afferent, synapse (or center), efferent and effector.

**Fig 14.3: The reflex arc**

![Reflex Arc Diagram]

**The Receptors**
- Special structures found at the peripheral ends of afferent neurons.
- According to the site of receptors, reflexes are classified into:

1. **Superficial reflexes**
   - Receptors in the skin
   - Example: Withdrawal reflex, abdominal reflexes, plantar reflex & cremastric reflex.

2. **Deep reflexes**
   - Receptors are found deep within a muscle (intrafusal fibers or tendons)
   - Examples: Stretch reflex, Golgi tendon reflex & stepping reflex

3. **Visceral reflexes**
   - Receptors in viscera
   - Example: Micturition reflex, defecation reflex, vomiting reflex & erection reflex.
The Afferent
- Enters the spinal cord through the dorsal root. Its cell body is at the dorsal root ganglion.

The synapse (or center)
- The site of integration of the reflex. It represents a direct synapse between the afferent and the efferent neurons or an indirect synapse (through one or more interneurons).
- According to the number of synapses, the reflex can be:
  1. Monosynaptic
     - One synapse between the afferent and the efferent neurons
     - Example: Stretch reflex
  2. Bisynaptic
     - Two synapses between the afferent and the efferent neurons
     - Example: Golgi tendon reflex
  3. Polysynaptic
     - Many synapses between the afferent and the efferent neurons
     - Example: Withdrawal reflex

Fig 14.4: Types of reflexes
**The efferent**
- The motor neuron that leaves the spinal cord through the ventral root.

**The effector**
- The muscle or the myo-epithelial cell in a gland that perform the effect.

**THE STRETCH REFLEX**
- Deep / Monosynaptic / Spinal reflex (see above).

**The receptor**
- The muscle spindle (or the intrafusal fibers).
- The muscle spindle is few muscle fibers (up to 10 fibers), of less striations; enclosed within a connective tissue capsule; found deep within the substance of skeletal muscle.
- Its intrafusal fibers lie parallel to the other muscle fibers (or the extrafusal fibers).
- The fibers of the muscle spindle are two types:
  - Nuclear bag (with nuclei in a central dilatation).
  - Nuclear chain (with nuclei spreading in a chain).
- Nuclear bag fibers are two fibers: fiber-1 (with low myosin ATPase activity) & fiber-2 (with high myosin ATPase activity).
- Nuclear chain fibers are thinner & shorter but have higher number of fibers when compared to nuclear bag fibers.
- The central parts of the muscle spindle fibers (where afferents are attached) are sensitive to stretch whereas the ends (where gamma efferents are attached) are contractile.
- The muscle spindle can be stimulated by:
  - External stretch to the whole muscle.
  - Contraction of the ends of its fibers (by gamma efferent discharge, see below).
- The muscle spindle is not stimulated by contraction of the whole skeletal muscle (extrafusal fibers) because this causes shortening rather than stretch.

**The afferents**
- Two types:
  - Type (Ia); the primary sensory endings:
    - Rapidly conducting fibers.
    - Ends on both nuclear bag (1 & 2) and nuclear chain fibers.
    - The fibers wrap around the muscle spindle fibers to form terminations known as the "annulospiral endings".
  - Type (II) fibers; the secondary sensory endings:
    - Have lower conduction velocity than type Ia.
    - End only on the nuclear chain fibers.
    - Their terminations are known as the "flower spray endings".
- There are two types of afferent input carried by the primary sensory endings:
  - Dynamic: The rapid discharge while the muscle is being stretched (i.e. during stretching); comes from the nuclear bag fibers
  - Static response: The discharge from stretched muscle (i.e. during the period of static stretching); comes from the nuclear chain fibers

**The center (synapse)**
- The synapse in the spinal cord is a direct (single) synapse between the primary afferent neuron (Ia) and the cell body of the efferent neuron (A alpha); the neurotransmitter is glutamate.
- The afferent neuron (Ia) reaches the efferent at the anterior horn.
- The secondary afferent neuron (II) has little contribution to the reflex through both monosynaptic and polysynaptic connections.
The efferents

- Two types:
  - (A-alpha) efferents: supply the extrafusal fibers to do the effect; however, they also supply the intrafusal fibers.
  - (A-gamma) efferents: supply the intrafusal fibers to increase their sensitivity to stretch and generate muscle tone. They have two types of endings: plate ending on the nuclear bag fibers & trail endings: on the nuclear chain fibers.

- The dynamic and static afferent inputs mentioned above initiates dynamic (phasic) and static responses through the A α and A γ efferent neurons.
- The dynamic response increases sensitivity of the muscle spindle to rate of change in stretch whereas the static response increases its sensitivity to maintained stretch.
Role of A gamma discharge= generation of muscle tone

- The A gamma fibers are small motor neuron that supply the muscle spindles.
- They constitute 30% of all motor neurons in the ventral roots of the spinal cord.
- Their tonic discharge causes contraction of the ends of the intrafusal fibers; this stretches the sensitive areas in the fibers of muscle spindle “= the central portions” resulting in reflex contraction of the extrafusal fibers (i.e. A gamma discharge causes an indirect contraction of the extrafusal fibers).
- Some descending tracts from the brain inhibit the A gamma motor neurons to reduce their tonic discharge and minimize their indirect effect on the extrafusal fibers. But in spite of that, the A gamma discharge is still present.
- When trying to move a relaxed limb of a subject during clinical examination, one can feel slight degree of resistance to the passive movement of that limb. This resistance to the passive movement is known as the muscle tone.
- It is a normal finding as long as it is caused by the normal tonic discharge of the A gamma efferents. However, certain factors may affect the A gamma discharge resulting in either hypertonia or hypotonia.

Hypertonia:
- Occurs when the A gamma discharge is increased (a sign of UMNL, see below).
- The affected muscles are spastic or rigid, offering high resistance to passive stretch.
- Spasticity is present when hypertonia occurs in one group of muscles; e.g. flexors but not extensors.
- R rigidity is present when hypertonia occurs in both groups of muscles “agonists & antagonists”.
- Hypertonia is also described as:
  - Clasp knife (when the examiner of muscle tone feels resistance to passive stretch initially, then the resistance disappears). This typically occurs when someone closes a clasp knife. It occurs with spasticity rather than rigidity and it is explained by the lengthening reaction (see below).
  - Lead pipe (when the examiner of muscle tone feels resistance throughout the whole range of movement). It occurs with rigidity.
  - Cog Wheel (when the examiner of muscle tone feels interrupted resistance that appears and disappears many times). It occurs with rigidity.

**Hypotonia:**
- Occurs when the A gamma discharge is decreased (a sign of LMNL).
- The affected muscles are flaccid, offering very low resistance to passive stretch.

**The lengthening reaction:**
- Occurs in spasticity when the resistance to passive stretch appears initially then disappears because the antagonist muscle is hyperstretched.
- For example, during examination of the upper limbs in a patient with spasticity, flexing the forearm at the elbow joint initially causes stretch of triceps (the antagonist muscle that causes extension) followed by hyperstretch. The stretch stimulates the stretch reflex causing contraction of triceps (and therefore resistance to flexion), and then the hyperstretch stimulates the Golgi tendon reflex (see below) causing relaxation (and therefore disappearance of the resistance).
Factors affecting the discharge of A gamma

- Descending tracts from the brain:
  - The pyramidal tract: facilitatory (i.e. increases A gamma discharge)
  - The extrapyramidal tract: inhibitory (i.e. decreases A gamma discharge)
  - The cerebellum: facilitatory (i.e. increases A gamma discharge)

**Note:** Loss of inhibition to A gamma neurons as in transection of the spinal cord or basal ganglia lesions results in increased A gamma discharge and therefore increased muscle tone (hypertonia) whereas loss of facilitation as in cerebellar lesions results in decreased A gamma discharge and therefore decreased muscle tone (hypotonia).
- Anxiety: Increases A gamma discharge; that is why it is associated with hyperreflexia (see below).
- Unexpected movement: Increases A gamma discharge.
- Painful stimulus to the skin: Increases A gamma discharge to the flexors and decreases discharge to the extensors on the same side. The opposite occurs on the other side.
- Alpha-gamma linkage: Increased A\alpha discharge to a muscle to initiate its movement is associated with increased A gamma discharge to the muscle spindle to keep it sensitive to stretch during shortening of the skeletal muscle.
- Pullings the hands apart while hooking the fingers (Jendrassik’s maneuver): Increases A gamma discharge. This maneuver is usually performed during clinical examination of tendon reflexes. The increased A gamma discharge increases sensitivity of the muscle spindle and therefore makes the reflex more evident; that is why it is also known as “reinforcement”. Hard clenching of the teeth exerts the same effect.

**Clinical application of the stretch reflex**

- Clinical examination of deep reflexes (tendon jerks) is based on the stretch reflex. Here a hammer is used to stretch a muscle by a gentle blow on its tendon. The resulting stretch initiates a reflex that causes contraction of that muscle. The reflex contraction (or response) can be normal, increased or decreased/ absent.
- An abnormal reflex (increased or absent reflex) indicates either:
  - Upper motor neuron lesion (UMNL): when there is increased reflex contraction (hyperreflexia).
  - Lower motor neuron lesion (LMNL): when there is decreased or absent reflex contraction (“hyporeflexia” or “a reflexia”).
- In upper motor neuron lesions (UMNL) the motor neurons descending from the brain are damaged at the brain or the spinal cord (i.e. at the CNS).
- In lower motor neuron lesions (LMNL) the motor neurons leaving the spinal cord are damaged; either peripherally at the axons or centrally at the cell bodies in the spinal cord.

**Signs of UMNL:**

- Paralysis or weakness (paresis) of skeletal muscles
  - Due to interruption of the descending orders from the brain.
- No or minimal wasting of muscles
  - Generally, wasting does not occur in UMNLs; however, minimal wasting may occur due to disused atrophy.
- Hypertonia
  - Due to increased A gamma discharge, see above.
- Hyperreflexia of the deep tendon reflexes
  - Due to increased A gamma discharge, see above.
- Clonus
  - Occurrence of regular, rhythmic contractions of a muscle when subjected to sudden, maintained stretch.
  - The maintained stretch causes repetitive stimulation of the stretch reflex.
  - Examples: ankle clonus & patellar clonus.
- Absence of abdominal & cremasteric reflexes
  - These superficial reflexes are elicited by scratching the skin of the abdomen (from the outer side towards the midline) & the inner aspect of the upper thigh.
  - The normal responses are contraction of abdominal muscles (in abdominal reflex) & contraction of the cremaster muscle with
elevation of the scrotum (in cremasteric reflex). These responses are absent in both UMNLs and LMNLs.

- **Extensor plantar response**
  - The plantar reflex is a complicated polysynaptic superficial reflex that normally causes flexion of the toes.
  - It is stimulated by scraping a blunt object across the lateral side of the sole of foot (starting from the heel towards the small toe) and then arching medially towards the big toe.
  - A positive reflex (known as Babinski’s sign) is obtained when there is an extensor response (upgoing of the big toe with fanning of the other toes).
  - This abnormal response is normally inhibited by the lateral corticospinal tract. Therefore it appears in UMNLs.

- **Hoffmann’s sign**
  - A sign of UMNL elicited in the hands by tapping the terminal phalanx of the 3rd or 4th finger resulting in flexion of the terminal phalanx of the thumb (this response is inhibited in the normal states by descending tracts from the brain).
  - It is equivalent to the Babinski’s sign in the foot; but unlike the Babinski’s sign, it involves a monosynaptic reflex rather than a polysynaptic reflex.

**Signs of LMNL:**

- **Paralysis or weakness (paresis) of skeletal muscles**
  - Due to interruption of their motor supply (the Aα motor neurons).

- **Hypotonia**
  - Due to decreased A gamma discharge.

- **Hyporeflexia or a reflexia of the deep tendon reflexes**
  - Due to decreased A gamma discharge.
Fasciculation

- This is a small, local, involuntary twitching of muscle visible under the skin.
- Occurs early following the LMNL; due to hypersensitivity of skeletal muscles to preformed acetylcholine that is released spontaneously from the damaged motor neurons.
- It disappears later when the release of the preformed acetylcholine stops completely.

Wasting of muscles

- Due to loss of the trophic effect of the motor neurons.

Absence of superficial reflexes

- The abdominal cremasteric and plantar reflexes are absent in LMNLs; due to interruption of a reflex component (afferent, center or efferent).

**Significance of reflexes in localization of UMNLs**

- Reflexes are not only useful in differentiating between UMNL & LMNL, but also in localizing sites of lesions within the CNS. However, localization needs knowledge about the root values of reflexes (i.e. the roots of segments that integrate the reflexes). For example, a patient with hyperreflexia of the knee jerk with normal biceps reflex most probably suffers from an UMNL below C5 and above L2; accordingly investigations may be requested to visualize that site (e.g. CT myelography, MRI ...).

- The root values of the deep tendon reflexes (tendon jerks):
  - Biceps reflex for biceps muscle; (C5 & C6)
  - Triceps reflex for triceps muscle; (C6 & C7)
  - Supinator reflex for brachioradialis muscle; (C5 & C6)
  - Knee jerk for quadriceps muscle; (L2, L3 & L4)
  - Ankle jerk for gastrocnemius muscle; (S1)
- The root values of the superficial reflexes:
  - Plantar reflex (L4, L5, S1 & S2)
  - Abdominal reflexes (T8, T9 & T10 below & T10, T11 & T12 above the umbilicus).
  - Cremasteric reflex (L2 & L3)

OTHER REFLEXES

The Golgi tendon reflex
- This is a deep/ spinal/ bisynaptic reflex.
- Stimulus: strong stretch (hyperstretch) of skeletal muscle.
- Receptor: Golgi tendon organ (network of nerve endings within the tendon of a muscle).
- Afferent: Ib (myelinated, rapidly conducting neuron).
- Synapse: Bisynaptic (there is a single inhibitory interneuron between the afferent and the efferent neurons).
- Efferent: The Aα fibers (it is inhibited by the inhibitory interneuron).
- Effector: Skeletal muscle.
- Response: relaxation of the skeletal muscle.

Note: - This reflex is also known as the "inverse stretch reflex" because when its receptors are stimulated by strong stretch, its response is relaxation of skeletal muscle (rather than contraction).

**Fig 14.7: The Golgi tendon reflex**
Withdrawal reflex
- Deep/ polysynaptic/ spinal reflex.
- Stimulus: painful stimulus (or noxious stimulus).
- Response: Contraction of flexors and inhibition of extensors on the same limb to get a way from the stimulus. The opposite may occur on the other limb (contraction of extensors and relaxation of flexors to support the body (crossed extensor response).
- When contraction of flexors is accompanied by inhibition of extensors (or vice versa); this is known as reciprocal innervation (or inhibition). It is an important property of withdrawal reflexes. Other properties include local sign, irradiation, summation, recruitment, after discharge, fractionation & occlusion (see below).

**Fig 14.8: The withdrawal reflex**
GENERAL PROPERTIES OF REFLEXES

- **Adequate stimulus**
  - Each reflex is stimulated by a precise specific stimulus known as the adequate stimulus. For example, the adequate stimulus for stretch reflex is stretch, for withdrawal reflex is a painful stimulus and for scratch reflex in a dog is crawling of an insect across the skin, but not jumping!

- **Stereotyped response**
  - Reflexes provide stereotyped reactions to their adequate stimuli.
  - In spite of being stereotyped, some reflex responses may be modified by experience (e.g. habituation and sensitization; which are examples of non-associative learning in implicit memory "or memory of skills").
  - **Habituation**: when the stimulus is repeated many times, the subject becomes habituated to it and ignores it. It is associated with decreased Ca++ in the sensory endings resulting in decreased release of neurotransmitters (NTs) following the stimulation.
  - **Sensitization**: in spite of repetition of the stimulus, it produces greater response (opposite to habituation). It is associated with increased Ca++ in the sensory endings resulting in increased release of neurotransmitters following stimulation.

- **Local sign**
  - The pattern of the reflex response depends on the site of stimulation (i.e. it depends on the afferent neuron which carries sensation from that site).
  - Example: when the withdrawal reflex is stimulated from the medial side of the foot, the response includes flexion and some abduction of the lower limb; whereas when it is stimulated from the lateral side, the response includes flexion and some adduction.
• **Irradiation**
  - When the intensity of stimulation is very high, the impulses irradiate within the spinal cord to involve more and more segments (i.e. they activate more motor neurons). For example: in the withdrawal reflex of a lower limb, the upper limbs also respond to the stimulus.

  **Note:** Paraplegic patients with automatic bladder can scratch the skin of the inner aspect of the thigh; this causes stimulation and irradiation of impulses within the sacral segments of the spinal cord and other segments causing “a mass reflex” that includes micturition, defecation, sweating and fluctuation in blood pressure.

• **Summation**
  - Summation occurs within the spinal cord when the strength of a noxious stimulus is increased. This generates more EPSPs that may undergo either spatial or temporal summation resulting in activation of more motor neurons.
  - Spatial summation occurs when multiple EPSPs are generated simultaneously "at the same time" whereas temporal summation occurs when successive EPSPs are generated due to repeated stimulation.

• **Fractionation & occlusion**
  - Fractionation and occlusion occur in the withdrawal reflex. Here the total reflex response is less than what is expected on direct stimulation of the muscles. Fractionation is explained as follows: the afferent inputs reaching the spinal cord result in fractionation of the motor neurons (i.e. divide them into several independent groups). As a result, contraction occurs in a part of a muscle; not the whole muscle.
  - Occlusion occurs because several afferent inputs share the same motor neuron.
- **Final common pathway**
  - Many afferents converge on the same motor neuron (the efferent). For this reason, the motor neuron is regarded as the final common pathway for many afferent inputs (up to 10,000 synaptic knobs).

- **Response time (or reaction time)**
  - Depends on the conduction velocity of the afferent and efferent neurons & the central delay. Since a single synapse delays conduction for at least 0.5 ms, the central delay in a polysynaptic reflex is dependent on the number of synapses between the afferent and the efferent neurons (i.e. more synapses = more prolonged reaction time).

- **Reciprocal innervation (inhibition)**
  - Reflex contraction of agonist muscle is accompanied by inhibition of the antagonist muscle (reciprocal innervation) as occurs in the withdrawal reflex.

- **Recruitment & after discharge**
  - Recruitment occurs when repeated stimulation activates additional number of motor neurons.
  - After discharge is continuation of a response after cessation of the stimulus; due to repeated firing of the motor neuron (repeated firing requires “reverberating circuits”).

**Fig 14.9: The reverberating circuits**
SPINAL CORD TRANSECTION

Etiology
- Traumatic damage to the spinal cord may result from motor vehicle accidents, community violence, sport injuries and falls).
- Spinal cord damage can also occur due to tumors (primary or secondary intramedullary tumors), infections (e.g. tuberculosis of the spine), cervical spondylosis and cord infarction due to anterior spinal artery occlusion.

Severity
- Severity of spinal cord transection is related to the degree of transection (complete or partial) and the level of transection (higher lesions are more serious than lower ones); for example:
  - Upper cervical lesions cause quadriplegia (paralysis of both upper and lower limbs). If the lesion is above C4, it causes immediate death unless the patient is mechanically ventilated. This is because the diaphragm & other respiratory muscles are paralyzed.
  - Thoracic lesions: cause paraplegia (paralysis of both lower limbs).

Types
  - Complete transection
  - Hemisection (Brown-Séquard syndrome)

Complete transection of the spinal cord
- The patient passes through the following phases:
  - Spinal shock
  - Retention of reflexes
  - Extensor contraction

Spinal Shock
- The cause of spinal shock is unknown; it takes about 1-2 weeks in humans (but less than that in animals).
- It is characterized by the following below the level of the lesion:
  - Complete paralysis of muscles (i.e. power grade “0”).
  - Loss of all types of sensation
  - Hypotonia
  - Loss of all types of reflexes: (superficial, deep, visceral & autonomic reflexes)

**Note:** Deep reflexes reappear in the second phase and muscle tone returns back in the third phase (see below). However, power, sensation and superficial reflexes never return back.

**Retention of Reflexes**
- Reflexes start to reappear, usually higher than normal (hyperreflexia), after the spinal shock.
- Generally visceral reflexes return earlier than tendon reflexes & flexors before extensors; however, superficial reflexes like abdominal reflexes remain absent as a sign of UMNL.
- The retained visceral (or autonomic) reflexes include the automatic evacuation of the bladder and rectum and the spinal sexual reflexes (erection and ejaculation).
- The retained deep tendon reflexes show hyperreflexia.
- The threshold of the retained withdrawal reflex is very low, that is why it occurs in response to minor noxious stimuli. It also shows many features like irradiation and after discharge (the limb remains in flexion for long periods of time“= flexor spasm”).
- The mass reflex (see above) is sometimes used by paraplegic patients to control micturition & defecation. It involves stroking the skin of the upper thigh resulting in irradiation of impulses within the spinal cord; this stimulates many reflexes including micturition, defecation, sweating and limb withdrawal.
In spinal animals, the positive supporting reaction can be demonstrated. When a finger is placed on a sole of a foot, the limb extends following the finger as it is withdrawn (magnet reaction). This reflex can support these spinal animals to stand for 2-3 minutes.

**Extensor contraction**
- Occurs 3-4 weeks following the transection.
- Here tone returns back, usually higher than normal (hypertonia).

**Hemisection of the spinal cord (or Brown Sequard Syndrome)**
- Here there is transverse section of one half of the spinal cord.
- The same phases above will also occur.
- There are signs of LMNL at the level of the lesion (the damaged segments) and signs of UMNL below the level of the lesion (the segments that lost their connections with the brain).

**Fig 14.10: Hemisection of the spinal cord**

- There is characteristic sensory loss in Brown-Sequard syndrome:
  - Loss of dorsal column tract sensations on the same side of the lesion (fine touch and pressure, position sense, vibration and two point discrimination).
  - Loss of spinothalamic tract sensations on the other side (pain, temperature, crude touch and itching sensation).
- Hyperaesthesia: (Increased sensitivity to cutaneous stimulation due to a diminished threshold or an increased response to stimuli) occurs in the skin supplied by the segments immediately above the level of the lesion.

**Complications of spinal cord transection:**
- Immobilized patients suffering from quadriplegia or paraplegia develop serious complications that eventually lead to death. These include:
  - **Skin Breakdown:** (also termed “bed or pressure sores”). Occurs due to pressure of bones (especially bones of the buttock) on the skin blood vessels causing big ulcers; known as decubitus ulcers. These ulcers may become infected causing septicemia.  
    - They can be prevented by proper nursing (changing postion of the immobilized patient regularly, from one side to another).
  - **Protein breakdown:** Occurs in almost all immobilized patients (-ve nitrogen balance).
  - **Osteoporosis:** In immobilized patients (with decreased muscle activity and no bearing of weight) bones begin to lose protein matrix.
  - **Hypercalcemia & hypercalciuria:** Immobilization increases bone resorption. This results in hypercalcemia & hypercalciuria.
  - **Renal stones:** Loss of high amount of calcium in urine predisposes to stone formation.
  - **Hypoventilation & aspiration pneumonia:** Patients with spinal cord injuries above the T4 level are at increased risk to develop respiratory complications like hypoventilation & aspiration pneumonia.
  - **Autonomic Dysreflexia:** It is related to disconnection between the higher control mechanisms and their targets resulting in swinging of blood pressure and some bouts of sweating.
• **Deep vein thrombosis (DVT) & pulmonary embolism:** Immobilization causes stasis of blood and therefore predisposes to DVT & pulmonary embolism.

• **Urinary tract infection (UTI):** A very common complication of spinal cord transection. It is predisposed by urinary stasis (caused by bladder paralysis and stone formation).

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**THE PYRAMIDAL SYSTEM**

- The pyramidal system is a major motor system comprised of:
  - The corticospinal tracts (ventral & lateral)
  - The corticobulbar tract
- It is called “pyramidal system” because the descending axons of the lateral corticospinal tract form the pyramids in the medulla; however, other axons of the pyramidal system do not pass through the pyramids in the medulla and they are not described as “extrapyramidal”!
- The lateral corticospinal neurons are concerned with fine, skilled movements (movements of the distal limb muscles: fingers, hands & feet) whereas the ventral corticospinal neurons are concerned with postural adjustments and gross movements (movements of the trunk and proximal limb muscles).
- The corticobulbar neurons are involved with movements of the neck, face, oral cavity, and larynx.
- Damage to either the corticospinal or corticobulbar tracts above the level of the decussation in the medulla or the efferent cranial nerve nuclei (see below) in “humans”, results in inability to perform voluntary movements on the opposite side of the body.
Origin of the pyramidal system “The cortical motor areas”

- The corticospinal & corticobulbar tracts originate from the following motor areas in the cerebral cortex:
  
  ▪ The motor cortex
    - The area of the precentral gyrus in the frontal lobe (also known as the primary motor cortex, M1 or Brodmann’s area 4).
    - Represents the origin of about 30% of the neurons in the pyramidal system.
    - Receives projection from the supplementary motor area. This supplementary area is concerned with planning and programming motor sequence.
    - Also receives projection from the premotor cortex.
  
  ▪ The premotor cortex
    - Found on the lateral surface of the brain.
    - Represents the origin of about 30% of the neurons in the pyramidal system.
    - Connected to the motor cortex the postural control areas in the brain stem and the somatic sensory areas.
    - Its function is unknown; it may be concerned with setting suitable posture to perform planned movements.
  
  ▪ The posterior parietal lobe & the somatic sensory areas (I & II)
    - Somatic sensory area I (in post central gyrus) & area II (on the wall of Sylvian fissure).
    - Represents the origin of about 40% of the neurons in the pyramidal system.
    - Lesions affect motor performance of some learned, skilled movements.
Note:
- The body is represented in the precentral gyrus “upside-down”, with feet at the top and face at the bottom of the gyrus.
- The size of representation at the motor cortex is proportional to the degree of skill with which that part of the body moves. For example, the size of the areas that control hand and finger movements (especially the thumb) and speech movements (especially the lips and tongue) are very large, compared with the areas for trunk and proximal limb movements.
- These motor maps of the motor cortex are not rigid; a specific area may enlarge with experience or shift to another area when affected by a lesion (= plasticity of motor cortex).
- Each side of the motor cortex controls the opposite side of the body. However, the dominant hemisphere (usually the left one, see chapter 15) which mainly controls the right hand also participates in control of the left hand.

Fig 14.11: The cortical motor areas
The pathways of the corticospinal tracts

- The corticospinal tract is the largest descending pathway in humans.
- It originates from the pyramidal cells (Betz cells) in the motor cortex (and other brain cells in the premotor and somatosensory areas) in each side of the brain and descends through the posterior limb of the internal capsule, then through the cerebral peduncles of the midbrain and then the pyramids of the medulla.
- About 80% of the fibres from each hemisphere, decussate in the pyramidal decussation at the lower part of the medulla, and continue to descend in the white matter of the spinal cord as the lateral corticospinal tract of the opposite side.
- The remaining 20% continue to descend down ipsilaterally as the ventral corticospinal tract of the same side; however, the fibers of this tract end on interneurons at the spinal segments that supply the target muscles. The interneurons supply motor neurons on both sides.
- The crossed fibres comprise both sensory axons and motor axons. The sensory axons project into the dorsal horn of the grey matter, to exert feedback regulation of the input pathways. The motor axons, as mentioned above, terminate on motor neurons of the distal muscles either directly, or indirectly via interneurons.

The pathway of the corticobulbar tract

- This pathway connects the motor cortex to the motor nuclei of the cranial nerves in the brain stem that supply muscles of the face, head and neck. Its axons, as in the corticospinal tract, descend from the motor cortex through the internal capsule to the medial part of the cerebral peduncle.
- The axons then synapse with the motor neurons of the cranial nerve nuclei that are located in the brain stem (midbrain, pons and medulla).
Lesions affecting the pyramidal system

- Selective damage to the pyramidal lobe, without damaging extrapyramidal tracts, is expected to cause hypotonia and weakness (flaccid paresis) rather than hypertonia & complete paralysis (spastic paralysis). However, this selective damage rarely occurs clinically.

  - **Lesions at the cortex result in:**
    - Weakness in a limited area of the opposite side of the body (e.g. one limb “monoparesis”, face or hand); because the pyramidal fibers are widely distributed to be damaged by a localized lesion in the cerebral cortex.

      Note: this is the possible site of pure pyramidal lesions that cause hypotonia.

  - **Lesions at the internal capsule result in:**
    - Paralysis or weakness in the opposite side of the body (hemiplegia or hemiparesis); because fibers in the internal capsule are bundled...
together so closely that a small stroke can damage all fibers coming from one side of the motor cortex.

- **Lesions at the brain stem result in:**
  - Paralysis or weakness in the opposite side of the body (hemiplegia or hemiparesis) plus cranial nerve palsy contralateral to the hemiplegia.

- **Lesions at the spinal cord result in:**
  - Quadriplegia or paraplegia (in complete transection)
  - Hemiplegia or monoplegia (in hemisection)
  - The degree of motor deficit depends on the level of lesion (see above).

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**THE EXTRAPYRAMIDAL SYSTEM**

- The extrapyramidal system is the major motor system in non-mammalian species.
- In humans, it is the part of the motor system (excluding the pyramidal system) that is involved in regulation of posture, muscle tone, and involuntary movements.
- Unlike the pyramidal system, the neurons of the extrapyramidal system:
  - Do not pass through the medullary pyramids
  - Do not directly innervate motor neurons of the spinal cord or brainstem (i.e. do not synapse directly with the lower motor neurons).
- There is no definitive list of the extrapyramidal system structures, but all lists would include:
  - The basal ganglia
  - The subthalamic nucleus
  - The substantia nigra
  - The cerebellum (the lateral portions)
  - The red nucleus
The extrapyramidal tracts (which arise from the brain stem and subcortical structures) target the motor neurons in the spinal cord; they are modulated by various parts of the central nervous system (the basal ganglia, cerebellum, vestibular apparatus and cerebral cortex).

- They include:
  - Rubrospinal tract
  - Tectospinal tract
  - Vestibulospinal tract
  - Reticulospinal tract

THE BASAL GANGLIA

- These are a group of interconnected subcortical nuclear masses found bilaterally within the white matter of the brain. They include the following structures:
  - Caudate nucleus
  - Putamen
  - Globus pallidus
  - Two other “functionally related” structures:
    - The subthalamus
    - The substantia nigra

- Historically, the amygdaloid nucleus (which is part of the limbic system) was included with the basal ganglia; however, its function is different.

- The caudate + putamen form the corpus striatum.
- The globus pallidus + putamen form the lenticular nucleus.
- The globus pallidus has two segments: Internal segment & external segment.
The substantia nigra (meaning the black substance because its neurons are pigmented with melanin) has two parts: Pars compacta & pars reticularis.

**Fig 14.13: The basal ganglia**

![Diagram of the basal ganglia](image)

**Connections**

**The main afferent inputs to the corpus striatum:**

- From the cerebral cortex (excitatory input by releasing glutamate; in addition, some interneurons release acetylcholine).
- From substantia nigra (from pars compacta; inhibitory input by releasing dopamine. Damage to this pathway, dopaminergic nigrostriatal pathway, causes Parkinson’s disease)
  
  - Remember that the substantia nigra also inhibits the thalamus & brain stem by releasing GABA.
- Other afferent inputs to the corpus striatum come directly from the limbic system and indirectly from the brain stem (through the thalamus).
The main efferent outputs from the corpus striatum:

- To both internal and external segments of globus pallidus (direct and indirect pathways; inhibitory outputs by releasing GABA).
- To substantia nigra (pars reticularis) which receives inhibitory output from the corpus striatum by GABA.
Remember that: The efferent pathways towards the globus pallidus are two pathways: direct and indirect. The direct pathway directly inhibits the internal segment whereas the indirect pathway inhibits the external segment that inhibits the internal segment (= indirect). The external segment also inhibits subthalamus (see below).
- The inhibitory output from the corpus striatum to the globus pallidus cancels the inhibitory effect of globus pallidus on the thalamus (see below).

The main efferent outputs from the globus pallidus:
- Outputs from the external segment of the globus pallidus to the subthalamus (inhibitory outputs through GABA).
- The subthalamus feeds back to the globus pallidus (internal and external segments) through excitatory neurons that release glutamate.
- Outputs from the internal segment of the globus pallidus pass to the thalamus.
  - This is the principal output from the basal ganglia.
  - It is an inhibitory output; the neurotransmitter is GABA
  - The thalamus sends excitatory impulses to the cortex (the prefrontal and the premotor cortex) to complete a loop.
- Other inhibitory outputs from the internal segment pass to the brain stem.

Functions of the basal ganglia
- Still unknown; however, lesions in experimental animals and diseases affecting the basal ganglia in humans suggest that they are concerned with:
  - Planning and programming of voluntary movement.
Initiation of voluntary movement (discharge from the basal ganglia and lateral portions of the cerebellum is noticed before a movement starts).
- Associated movements (e.g. swinging the upper limbs while walking).
- Inhibition of muscle tone.
- Posture taken to perform some voluntary movements.
- Cognitive function (the caudate nucleus).

**DISEASES OF THE BASAL GANGLIA**

- Damage to the basal ganglia has little effect on animals, but severe effects on humans. In general, diseases of the basal ganglia are characterized by: Hyperkinesia (excessive movement), hypokinesia (poverty of movement) or both.

**Parkinson’s disease (Paralysis agitans or Shaking palsy)**

- “Parkinsonism” is a neurological syndrome characterized by the triad of rigidity, akinesia and tremor, plus many other signs including stooped posture and shuffling gait (see below).
- It is caused by a wide range of etiologies but the most common cause of Parkinsonism is “Parkinson’s disease” which was originally described by James Parkinson in 1817.

**Pathogenesis of Parkinson’s disease**

- Parkinson’s disease occurs due to degeneration of the dopaminergic nigrostriatal neurons. This usually occurs in old subjects (above 65 y) due to the aging process; however, the degree of degeneration in Parkinson’s disease is accelerated due to unknown cause (= idiopathic).
- Loss of the dopaminergic nigrostriatal neurons releases the corpus striatum (especially the putamen) from the inhibitory effect of dopamine whereas the excitatory effect of acetylcholine becomes unopposed.
This results in imbalance at the globus pallidus because of the higher inhibition from the corpus striatum, especially on the external segment (through the indirect pathway).

Accordingly, the internal segment of the globus pallidus receives less inhibition (through the indirect pathway) and more excitation (from the subthalamus).

Therefore, the inhibitory discharge from the internal segment of the globus pallidus to the thalamus is increased, and the excitatory discharge from the thalamus to the cerebral cortex is decreased resulting in the clinical features of the disease.

**Fig: 14.15: Pathogenesis of Parkinson’s disease**

![Diagram of Pathogenesis of Parkinson's Disease]

**Other causes of Parkinsonism**

- Damage to the substantia nigra or loss of the dopaminergic nigrostriatal neurons may also occur due to:
  - Dopamine antagonists which block D2 receptors. These include:
    - Antipsychotic drugs like haloperidol & chlorpromazine
    - Antiemetic drugs like metoclopramide
    - Antidepressant drugs like the tricyclic antidepressants
- Repeated head trauma (such as injuries sustained in boxings)
- Toxins like MPTP (1-methyl-4-phenyl-tetrahydrodpyridine) which is a byproduct of an improper technique for synthesizing a form of synthetic heroin
- Cerebral atherosclerosis
- Encephalitis
- Parkinson’s Plus syndromes (Group of neurological disorders characterized by neuronal degeneration at various parts of the CNS. They have complex clinical presentations; however, since they have Parkinsonian features in common, they are known collectively as Parkinson’s Plus syndromes). They include:
  - Multiple system atrophy
  - Shy Drager syndrome
  - Olivopontocerebellar atrophy
  - Striatal Nigral Degeneration
  - Progressive supranuclear palsy
  - Corticobasilar ganglionic degeneration

**Note:** The Parkinson’s Plus syndromes differ from Parkinson’s disease in that: they show no response to dopamine, they may present with ocular signs (e.g. failure of upward & downward gaze) and they may present with early onset of dementia, postural instability and autonomic dysfunction (e.g. postural hypotension or urinary incontinence).

**Clinical features of Parkinson’s disease**
- Symptoms appear when the majority of the nigrostriatal neurons are lost (loss of 60-80%).
- The major feature is the triad of rigidity (hypertonia), akinesia and tremor:
  - Rigidity
    - Defined as hypertonia in both agonists and antagonists
- Types of rigidity (hypertonia) in Parkinson’s disease:
  - Lead pipe & cog-wheel
- Hypertonia affects flexors more than extensors (resulting in stooped posture) & proximal muscles more than distal muscles.
- Akinesia
  - Defined as poverty of movements
  - Failure to initiate movement is an example of akinesia
- Tremor
  - Regular rhythmic tremor (with a rate of about 4-8 Hz).
  - Because of the thumb movements, it is described as pill-rolling tremor.
  - Occurs mainly at rest, increases with emotions & disappears with activity.
  - Occurs due to regular, alternating contractions of agonist and antagonist muscles.

Note: Akinesia is a hypokinetic feature whereas tremor and rigidity are hyperkinetic features (= Both hyper and hypokinetic features are present).

-Other signs:
  - Expressionless face (mask face)
  - Decreased blinking (detected by the glabellar reflex)
  - Loss of associated movements
  - Failure to elevate the lower limbs while walking (Shuffling gait); with progressive increase in speed of walking (festination)
  - Soft & slow monotonous speech (due to reduced movements of the muscles involved in speech and failure to initiate sentences)
  - Difficulty in writing (micrographia)
  - Drooling of saliva (due to decreased frequency of swallowing)
  - Anxiety & depression
- Impaired recent memory
- Dementia (late sign)

**Diagnosis**
- The diagnosis of Parkinson’s disease is based on medical history and neurological examination. There is no specific test for confirmation.

**Treatment**

**Dopamine (in form of L-dopa “levodopa”):**
- This is to replace the lost dopamine in the basal ganglia
- Levodopa “a precursor of dopamine” is given because dopamine cannot cross the blood brain barrier (BBB) whereas levodopa can. However, L dopa should be combined with a decarboxylase inhibitor (e.g. Carbidopa) that prevents decarboxylation of L dopa to dopamine in the peripheral tissues (to prevent the side effects of dopamine).
- Example of this combination: SINEMET ® (Carbidopa-Levodopa).
- Dopamine agonists (like Bromocriptine) are also helpful.
- The therapeutic effects of dopamine disappear in 5-7 years

**Anticholinergics**
- To decrease the excitation of the corpus striatum by the cholinergic neurons
- Example: Artane ® (Trihexyphenidyl)

**Surgery**
- Still under development but may help to control symptoms refractory to medical treatment). Surgical procedures include:
  - Pallidotomy (lesions in the globus pallidus “internal segment”)
  - Implanting electrodes “deep brain stimulation”
  - Implantation of dopamine secreting tissues in the region of basal ganglia (e.g. Patient’s own adrenal medulla, carotid body or fetal striatal tissue).
Hyperkinetic abnormalities

Chorea
- Due to damage to the caudate nucleus (with or without the putamen) resulting in less release of GABA & therefore less inhibition of the globus pallidus.
- Characterized by spontaneous, uncontrolled, non-repetitive dancing movements of the distal extremities and muscles of the face, tongue, and pharynx.
- It increases with emotions (e.g. when a patient is aware of being watched).
- Associated with hypotonia.
- Causes:
  - Rheumatic fever (chorea is one of the cardinal features of rheumatic fever).
  - Huntington’s disease (genetic problem inherited as AD; appears between 30-50 years of age. Its abnormal gene in chromosome 4 is characterized by multiple trinucleotide repeats of cytosine-adenine-guanine “CAG”).
- Treatment: Dopamine antagonists (e.g. haloperidol).

Athetosis
- Occurs due to damage to the globus pallidus.
- Characterized by involuntary, continuous, slow writhing (twisting) movements of the hands, and feet (distal parts of the body); but other parts like the neck & face may be affected.
- Associated with spasm of the affected muscles (varying degrees of hypertonia).
- Treatment: Anticholinergic drugs.
**Ballism**
- Occurs due to lesions to the subthalamic nucleus.
- Characterized by violent, flailing contractions of the proximal limb muscles (arms and legs).
- Usually affects one side of the body (= Hemiballismus) as in unilateral stroke.
- May be associated with hypotonia.
- Treatment: Dopamine antagonists (e.g. haloperidol or phenothiazines).

**THE CEREBELLUM**

**Structure**
- The cerebellum (= the little brain) is the part of the nervous system that is concerned with coordination of motor functions of the brain.
- It lies in the posterior fossa, dorsal to the brain stem and inferior to the occipital lobe.
- It is connected to the brain stem by three bundles of white matter:
  - Superior peduncle
  - Middle peduncle
  - Inferior peduncle
- It consists of:
  - Vermis (lies in the central part of the cerebellum; divided into 10 smaller lobules).
  - Two hemispheres (lie lateral to the vermis).
- Compared to the cerebral surface, the surface of the cerebellum has:
  - Less weight (about 10% of that of the cerebral cortex)
  - Less surface area (about 75% of that of the cerebral cortex)
  - More extensive folds and fissures (these increased the surface area to a relatively high degree if compared with the low weight).
Divisions of the cerebellum

Anatomical divisions:
- Divided by two fissures (the primary fissure and the posterolateral fissure) into 3 lobes:
  1. Anterior lobe
  2. Posterior lobe
  3. Folliculo-nodular lobe

Functional divisions:
  1. Vestibulocerebellum
    - The flocculonodular lobe
    - Has vestibular connections (receives input from the semicircular canals and the vestibular nuclei and sends output back to the vestibular nuclei).
    - Also receives input from the visual cortex through the pons (the cortico-ponto-cerebellar pathway).
    - Concerned with equilibrium (balance) and eye movement.
  2. Spinocerebellum
    - The vermis + adjacent medial parts of the hemispheres.
    - Receives proprioceptive sensation through the spinal cord (spinocerebellar tracts) and a copy of motor plan from the cerebral cortex; by comparing them, it coordinates movements of the body.
    - The vermis controls movement of axial and proximal limb muscles.
    - The hemispheres control movement of distal limb muscles.
    - It also receives input from the trigeminal nerve, the visual and the auditory systems.
    - It sends fibers to the deep cerebellar nuclei which in turn project to the brain stem and the cerebral cortex (to modulate the descending motor plan).
3. The neocerebellum
   o = Cerebro-cerebellum
   o Well developed in humans than animals.
   o Participates in planning and programming of movements.
   o It receives input exclusively from the cerebral cortex (especially the parietal lobe) via the pontine nuclei (forming cortico-ponto-cerebellar pathways).
   o It sends fibres mainly to the ventrolateral nuclei of the thalamus.

**Fig 14.16: Devisions of the cerebellum**

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**The deep cerebellar nuclei & the cerebellar cortex**
- The gray matter of the cerebellum is formed by the cerebellar nuclei (deep) and the cerebellar cortex (superficial). They are separated from each other by white matter.

The deep cerebellar nuclei include:
- Dentate nucleus
- Globose nucleus
- Emboliform nucleus
- Fastigial nucleus

- Note: Globose + emboliform = Interpositus nucleus.

The cerebellar cortex contains 5 types of cells:
- Purkinje cells (inhibitory; release the neurotransmitter GABA)
- Granular cells (excitatory; release the neurotransmitter Glutamate)
- Basket cells (inhibitory; release the neurotransmitter GABA)
- Golgi cells (inhibitory; release the neurotransmitter GABA)
- Stellate cells (inhibitory; release the neurotransmitter GABA)

The cerebellar cortex consists of 3 layers:
- Superficial molecular layer:
  - Contains two types of inhibitory cells: stellate and basket cells.
  - It also contains the dendritic arbors of purkinje cells and parallel fibers from the granular cells. These form many synapses with each other.
- Middle (Purkinje) layer:
  - Contains the Purkinje cells (very big cells with extensive dendrites).
  - The Purkinje cells receive excitatory input from:
    - The climbing fibers (coming from the inferior olivary nucleus in the medulla)
    - The parallel fibers (from the granular cells)
  - The Purkinje cells receive inhibitory input from:
    - The Basket cells
  - The Purkinje cells send inhibitory output to:
    - The deep cerebellar nuclei.
- Deep granular layer:
  - Contains two types of cells: granular cells and golgi cells.
  - The granular cells are the most numerous neurons in the brain.
- They receive excitatory input from Mossy fibers (coming from the pontine nuclei) and inhibitory feedback from the golgi cells (note that the golgi cells are excited by the granular cells and Mossy fibers).
- They send T-shaped axons (known as parallel fibers to the superficial molecular layer to synapse with the dendrites of the Purkinje cells).

**Fig 14.17: Connections within the cerebellum**

The cerebellar inputs and outputs:
- The main afferent input to the cerebellar nuclei and cortex comes through:
  - Climbing fibers
    - Excitatory to the Purkinje cells and the deep cerebellar nuclei.
    - Comes from the medulla (inferior olivary nucleus).
**Mossy fibers**
- Excitatory to the granular cells, Golgi cells and the deep cerebellar nuclei.
- Comes from the pons (pontine nuclei).
- Efferents from the cerebellar cortex to the deep cerebellar nuclei pass through the axons of Purkinje cells, the only cells that leave the cerebellar cortex.
- Efferents from the cerebellar cortex to outside of the cerebellum are always excitatory.

- They pass from and to the following sites:
  - From the vestibulocerebellum to the brain stem (pass directly, not through the deep nuclei).
  - From the spinocerebellum to the deep nuclei (all the nuclei except the dentate) and then to the brain stem.
  - From the neocerebellum to the dentate nucleus and then to the ventrolateral thalamus.

**Functions of the cerebellum**
- Coordination of voluntary movements (controls the rate, range and direction of movement).
- Increases muscle tone (send facilitatory impulses to the Ay motor neurons).
- Controls posture and balance (has connections with the vestibular apparatus).
- Makes adjustments and predictions (based on prior learning and experience) to make the repeated motor tasks easier (i.e. can be done with greater speed, greater accuracy and less effort). After some time these tasks can be done automatically.
Note: About learning in the cerebellum:
- Learning in cerebellum depends on the input from the olivary nuclei to the Purkinje cells; through the climbing fibers. Each Purkinje cell receives input from one climbing fiber. However, its dendrites make a lot of synapses with it.
- The input from the climbing fibers produces a large and complex spike in the Purkinje cell. This spike modifies the pattern of input from the mossy fibers to the same Purkinje cell.

**Cerebellar ataxia**
- Ataxia (meaning lack of coordination) is defined as incoordination of voluntary motor activity due to errors in rate, range, force and direction of movement.
- There are many types of ataxia (e.g. cerebellar ataxia, sensory ataxia, vestibular ataxia …).
- Cerebellar ataxia also comprises many types of ataxia resulting from damage to various parts of the cerebellum (e.g. deep cerebellar nuclei, spinocerebellum, vestibulocerebellum or neocerebellum).
- Generally, damage to the deep cerebellar nuclei produces more generalized defects than damage to the other parts of the cerebellum.
- In general, cerebellar ataxia is caused by:
  - Toxic substances like alcohol and some drugs (e.g. anticonvulsants, barbiturates …)
  - Tumors of the cerebellum
  - Autoantibodies (e.g. paraneoplastic cerebellar degeneration)
  - Viral encephalitis and cerebellar abscess
  - Hereditary problems (Spinocerebellar ataxia, Friedreich’s ataxia …)
  - Congenital problems (e.g. Arnold Chiari malformation)
- Signs of cerebellar ataxia:
  - Wide based, unsteady gait (described as drunken man gait)
  - Nodding of the head (yes-yes or no-no movements)
  - Nystagmus (jerky movements of the eyeball; usually horizontal in this type of ataxia)
  - Dysarthria (slurred speech; described as scanning speech)
  - Tremor (irregular, large amplitude, coarse tremor, absent at rest, occurs when a patient stretches his hand out to reach something; therefore it is described as kinetic or intention tremor).
  - Past pointing or dysmetria (due to loss of the braking effect of the cerebellum)
  - Dysdiadochokinesia or adiadochokinesia (failure to do rapid alternating opposing movements; e.g. repeated supination & pronation of the hands).
  - Hypotonia (due to loss of the facilitatory effect on the Aγ discharge)
  - Rebound phenomenon (due to loss of the braking effect of the cerebellum; for example, when a patient is asked to flex his forearm against resistance and then the resistance is suddenly released, he can not stop the forearm before striking his face or shoulder).
  - Decomposition of movement (the patient performs actions that require simultaneous movements of more than one joint in stepwise manner; i.e. each joint at a time).
  - Difficulty in swallowing (due to incoordination; appears as coughing or choking).
CONTROL OF POSTURE

- Control of posture is due to integration of reflexes at various levels of the CNS. Centers of integration include:
  - Spinal cord
  - Medulla
  - Midbrain
  - Cerebral cortex
- These centers of integration send multiple inputs that converge on the cell bodies of spinal motor neurons and the equivalent neurons in the cranial nerves.
- It is the integrated activity of these multiple inputs that regulate posture of the body.
- The spinal reflexes are simple whereas the reflexes which are integrated at higher levels are more complex.
- Postural reflexes not only maintain the body in an upright, balanced position; but also produce the necessary adjustments in posture before and during the voluntary activity.
- Therefore they can be grouped into:
  - Static reflexes (produce sustained contraction of muscles to maintain posture).
  - Dynamic or phasic reflexes (produce transient movements for postural adjustments).
- As mentioned above, these postural reflexes are affected by neural pathways from various levels in the CNS. Therefore, a transection in the CNS releases reflexes below the level of transection from control of higher centers; therefore they appear to be accentuated.
- For this reason, postural reflexes were studied in experimental animals in which the neural axis was transected at various levels.
- Sites of transection in experimental animals include:
  - At the superior border of the pons:
    - Results in decerebrate rigidity
    - This rigidity is in fact “spasticity”; it develops immediately (no neuronal shock) in the extensors of the four limbs in animals (i.e. antigravity muscles).
    - It can be explained by increased Aγ discharge & by direct increased excitability of Aα neurons.
  
  Note:
  - Decerebrate rigidity allows study of medullary reflexes in animals. It is rare in humans because it is incompatible with life. However, animals like cats and dogs can stand, walk and run after complete destruction of the pyramidal tracts.
  - In patients with decerebrate posturing, the head is arched back, the arms are extended by the sides, and the legs are extended (= known as extension posturing).

**Fig 14.18: Posture of decerebrate rigidity**

- At the superior border of the midbrain:
  - Results in extensor rigidity similar to decerebrate rigidity.
The rigidity develops due to increased A gamma discharge. However, it appears only at rest and not during movement; because during movement it is obscured by the phasic postural reflexes.

Note: This level of transection in animals allows study of the midbrain reflexes “midbrain animals”. These animals can stand walk and right themselves (i.e.correct their posture). Therefore, unlike the medullary reflexes, midbrain reflexes include righting reflexes.

- At the cerebral cortex:
  - Results in decorticate rigidity
  - The rigidity develops due to loss of the cortical area that inhibits the A gamma discharge. However, as in midbrain animals, it appears only at rest and not during movement; because during movement it is obscured by the phasic postural reflexes.
  - All the reflexes in midbrain animals are also present in decorticate ones. In addition, decorticate animals can survive for longer periods of time. In humans, decorticate rigidity can be seen in hemiplegic patients.
  - Patients with decorticate posturing present with the arms flexed, or bent inward on the chest, the hands are clenched into fists, and the legs extended (= known as flexion posturing).

**Fig 14.19: Posture of decorticate rigidity**
It is important to note that most of the postural reflexes are present in humans during the early neonatal period (therefore they are known as primitive reflexes); however, they disappear after a few months (after full development of the nervous system). Persistence of these reflexes after infancy indicates congenital brain damage (= cerebral palsy).

**Spinal cord reflexes**

- As mentioned above, transection of the spinal cord allows study of spinal cord reflexes.
  - These reflexes include:
    - **Stretch reflex**
      - Receptors: Muscle spindle (stimulated by stretch)
      - Response: Muscle contraction
    - **Withdrawal reflex**
      - Receptors: Skin receptors (stimulated by noxious stimuli)
      - Response: flexion of the same limb (to get away from the stimulus) & extension of the other (to support the body)
    - **Positive supporting reaction**
      - Receptors: Proprioceptors in distal flexors
      - Response: Extension of the lower limbs to support the body
  - When a finger is placed on a sole of a foot, the limb extends following the finger as it is withdrawn (magnet reaction). This reflex can support the spinal animals to stand for 2-3 minutes.
    - **Negative supporting reaction**
      - Receptors: Proprioceptors in extensors
      - Response: Release of the positive supporting reaction
  - When the sole of the foot is raised up from the supporting surface, the limb is flexed (the opposite response to the above reflex).
Medullary reflexes
- As mentioned above, decerebrate rigidity allows study of medullary reflexes in animals.
- Appearance of spasticity after decerebration in the extensors of the four limbs explains how these static (or tonic) reflexes support the body against gravity.
- Investigations in animals showed that the pattern of decerebrate rigidity is affected by:
  - Position of the body (whether the animal stays prone, on its side or on its back; the change in position is detected by the otolithic organ in the inner ear “the labyrinth” and the resulting reflexes are known as labyrinthine reflexes. These medullary reflexes are static “tonic” since no correction of posture occurs (i.e. no righting reflex)).
  - Movement of the head relative to the body (this produces static (tonic) medullary reflexes that support the body in its new position; the receptors that detect the movement of the head are proprioceptors in the neck and the responses are flexion in some limbs and extension in others).
The medullary reflexes include:

- Tonic labyrinthine reflexes
  - Receptors: Otolithic organ in the inner ear (detects change in position of the body in relation to gravity)
  - Response: increase or decrease in the tone of antigravity muscles.
  - Example: Placing a decerebrate animal on its back (supine position) produces extension in all limbs, on its side decreases the rigidity and on the prone position decreases it further to a very minimal degree in extensors (but increases rigidity in flexors).

**Fig 14.21: Tonic labyrinthine reflexes in a child with cerebral palsy**

- Tonic neck reflexes
  - Receptors: Neck proprioceptors (detect movement of the head relative to the body)
  - Response: extension in some limbs and flexion in others
  - Examples: Turning the head to:
    - Left side: causes extension of limbs in the left & decreases rigidity in the right side; the opposite occurs on turning the head to the other side.
    - Up: causes flexion of lower limbs and extension of upper limbs
- Down: causes flexion of upper limbs and extension of lower limbs

**Fig 14.22: Tonic neck reflexes in a neonate**

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**Midbrain reflexes**

- As mentioned above, midbrain reflexes were studied in midbrain animals.
- The rigidity appears due to midbrain static responses (in the absence of phasic responses).
- The phasic responses (known as righting reflexes) appear due to stimulation of various receptors including the otolithic organ, muscle spindle, visual cues and exteroceptors. They act to maintain the normal upright position of the head and the body. They include:
  - **Labyrinthine righting reflexes**
    - Receptors: Otolithic organs (stimulated by tilting the head)
    - Response: contraction of the neck muscles to upright the head
  - **Body on head righting reflex**
    - Receptors: Exteroceptors on one side of the body (stimulated by pressure on that side; when the animal is laid on its side)
    - Response: contraction of the neck muscles to upright the head (even if the labyrinthine is destroyed).
- Neck righting reflexes
  - Receptors: Muscle spindle in the neck muscles (stimulated when the head is upright but the body is tilted)
  - Response: Contraction of the neck muscles to correct the thorax then abdomen and pelvis.

- Body on body righting reflex
  - Receptors: Exteroceptors on one side of the body (stimulated by pressure on that side; when the animal is laid on its side)
  - Response: Muscle contraction to upright the body even if the head is prevented from righting.

- Vestibular placing reaction
  - Receptors: Otolithic organs (stimulated by lowering a blindfolded animal rapidly)
  - Response: Preparation of the animal to land (by extending its legs and spreading its toes).

Note: if the eyes of the animal are not blindfolded, they act as receptors to another type of placing reaction integrated in the cerebral cortex, see below.

**Cerebral cortex reflexes**
- Cortical reflexes are lost in decorticate animals. They include:
  - Optical righting reflexes
    - Receptors: The eyes (stimulated by visual cues)
    - Response: Upright posture (righting) in the absence of labyrinthine or body stimulation.
  - Placing reactions
    - Receptors: Various visual, exteroceptors and proprioceptors
- Response: Feet (or hands) placed firmly on a supporting surface

- Hopping reactions
  - Receptors: Muscle spindles (stimulated by lateral displacement of an animal while standing)
  - Response: Hopping to maintain the limbs in position to support the body.

**Fig 14.23: Optical placing reaction in a neonate**

**CONTROL OF VOLUNTARY MOVEMENT “SUMMARY”**
- First, it is worth noting that much is still unknown about control of voluntary movement.
- Before ordering and executing a voluntary movement it should be planned.
- Planning occurs at the cortical association area, basal ganglia and lateral parts of the cerebellum (the neocerebellum). Impulses from these sites are transmitted to the ordering sites (the premotor and motor cortex) either directly or through the thalamus.
The premotor and motor cortex send their orders through the corticospinal and corticobulbar tracts to the motor neurons to execute the movement. They also send feedback information to the basal ganglia and the neocerebellum; and a copy of the motor plan to the spinocerebellum.

- The spinocerebellum, to co-ordinate the movement, projects to the brain stem which sends its main descending tracts (rubrospinal, reticulospinal, vestibulospinal and tectospinal tracts) to the spinal motor neurons.

- The brain stem also receives direct input from the motor cortex and collaterals from the corticospinal and corticobulbar tracts. Therefore its tracts, in addition to co-ordination and regulation of posture, are also concerned with voluntary movements.

  The muscles which execute the movement and the, joints, ligaments and skin send feedback information to the motor area and the spinocerebellum.
## QUESTIONS FOR SELF ASSESSMENT-10 (MCQS)

1. Long standing lower motor neuron lesions are characterized by:
   a. Clonus
   b. Fasciculation
   c. Extensor plantar response
   d. Wasting of affected muscle
   e. Rigidity

2. The gamma motor discharge is inhibited by:
   a. Motor area 4 of the cerebral cortex
   b. The cerebellum
   c. The vestibular nuclei
   d. Medullary reticular formation
   e. Pontine reticular formation

3. The spinal shock phase of complete spinal cord transaction is characterized by:
   a. Muscle wasting
   b. Rigidity
   c. A reflexia
   d. Loss of touch sensation just above the lesion
   e. Fasciculation

4. The muscle spindle:
   a. Is the receptor of the inverse stretch reflex
   b. Is supplied by A alpha motor neurons
   c. Results in relaxation of extrafusal fibers in response to over stretch
   d. Is Stimulated when extrafusal fibers contract
   e. Is stimulated by the gamma motor discharge

5. All the following statements about Renshaw cells are correct except that they are:
   a. Inhibitory interneurons
   b. Found in the grey matter of the spinal cord
   c. Excited by collaterals from alpha motor neurons as they leave the spinal cord via the ventral root
   d. Representative of negative feedback mechanism that controls firing of alpha motor neurons
   e. Cholinergic neurons

6. The muscle spindle is not:
   a. Stimulated by stretch
   b. Innervated by la afferents
   c. Covered by a connective tissue capsule
   d. Acting as a receptor of a deep reflex
   e. Found in tendons of muscles

7. The following is a polysynaptic reflex:
   a. The knee jerk reflex
   b. The withdrawal reflex
   c. The ankle jerk reflex
d. The biceps jerk reflex  
e. The inverse stretch reflex

8. The inverse stretch reflex is:  
   a. Caused by stimulation of the la sensory afferents  
   b. Caused by stimulation of alpha motor efferent  
   c. Induced by over stretch of the muscle tendon  
   d. Protective against over excitation of the muscle spindle  
   e. A monosynaptic reflex

9. In a lower motor neuron lesion there is:  
   a. Exaggerated abdominal reflexes  
   b. Hypotonia  
   c. Persistent fasciculation  
   d. Minimal muscle wasting  
   e. Hyperreflexia

10. Cog wheel rigidity is a feature of:  
   a. Pyramidal lesions  
   b. Cerebellar ataxia  
   c. Parkinsonism  
   d. Chorea  
   e. Spinal cord transaction

11. Parkinson's disease is characterized by:  
   a. Muscle weakness  
   b. Muscle wasting  
   c. Kinetic tremors  
   d. Spasticity  
   e. Brady-kinesia

12. Athetosis is caused by damage to:  
   a. Corpus striatum  
   b. Substantia nigra  
   c. Subthalamus  
   d. Globus pallidus  
   e. Thalamus

13. The following does not occur in Parkinson's disease:  
   a. Clonus  
   b. Akinesia  
   c. Mask face  
   d. Rigidity  
   e. Tremor

14. Chorea occurs due to damage to the:  
   a. Caudate nucleus  
   b. Lenticular nucleus  
   c. Globus pallidus  
   d. Substantia nigra  
   e. Subthalamus

15. The following is not a basal ganglia structure:  
   a. Putamen
b. Subthalamic nucleus
c. Thalamus
d. Globus pallidus
e. Caudate nucleus

16. Which of the following is characterized by muscle paralysis:
   a. Syringomyelia
   b. Cerebellar ataxia
   c. Parkinson’s disease
   d. Hemibalismus
   e. Vestibular damage

17. Athetosis is caused by damage to:
   a. Corpus striatum
   b. Substantia nigra
   c. Subthalamus
   d. Globus pallidus
   e. Thalamus

18. The following represents a spinocerebellar function:
   a. Planning of voluntary movement
   b. Initiation of involuntary movement
   c. Coordination of voluntary movement
   d. Inhibition of muscle tone
   e. Control of bladder function

19. Cerebellar lesions result in:
   a. Resting tremor
   b. Muscle wasting
   c. Dysmetria
   d. Micrographia
   e. Exaggerated reflexes

20. The stretch reflex is:
   a. Polysynaptic reflex
   b. Superficial reflex
   c. Integrated in the spinal cord
   d. Exaggerated in lower motor neuron lesions
   e. Not found in children

21. All the following abnormalities are characterized by tremors except:
   a. Cerebellar disease
   b. Subthalamic lesion
   c. Substantia nigra lesion
   d. Hyperthyroidism
   e. Stress

22. The optical righting reflex is integrated at:
   a. The spinal cord
   b. The medulla oblongata
   c. The midbrain
   d. The cerebral cortex
   e. The cerebellum
23. The stretch reflex is:
   a. Polysynaptic reflex
   b. Visceral reflex
   c. Integrated in the brain stem
   d. Absent in lower motor neuron lesions
   e. Not found in children

24. Which of the following is a medullary postural reflex:
   a. The positive supporting reaction
   b. The corneal reflex
   c. The tonic labyrinthine reflex
   d. The hopping reaction
   e. The body on body righting reflex

25. The following does not occur in Parkinson's disease:
   a. Stooped posture
   b. Shuffling gait
   c. Kinetic tremor
   d. Hypertonia in both agonists and antagonists
   e. Bradykinesia

26. A lesion at superior border of the pons in an experimental animal results in all the following except:
   a. Decerebrate rigidity
   b. Easy demonstration of tonic neck reflexes
   c. Hypertonia that develops immediately
   d. Extended posturing
   e. Appearance of righting reflexes

27. The deep cerebellar nuclei are directly inhibited by:
   a. Granular cells
   b. Purkinje cells
   c. Climbing fibers
   d. Mossy fibres
   e. Golgi cells

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CHAPTER (15)
AWAKE & SLEEP STATES

INTRODUCTION
- Perception of the various sensory impulses that ascend through the sensory pathways requires processing in the alert or conscious brain.
- Radiation of impulses within the cerebral cortex, especially between the thalamus and the cortex, produces characteristic patterns in the EEG (see below) and correlates well with the behavioral state (i.e. degree of alertness).
- Afferents from the specific nuclei of the thalamus (the medial & lateral geniculate bodies and the ventrobasal nuclei) terminate on layer IV of the neocortex whereas afferents from the non specific nuclei (the midline and the intralaminar nuclei) terminate on the layers I-IV.
- The behavioral states range from deep sleep through light sleep, REM sleep, and the two awake states: relaxed awareness and full awareness with concentrated attention.

THE RETICULAR FORMATION
& THE RETICULAR ACTIVATING SYSTEM
- The reticular formation is a complex area of small interconnected neurons located within the brain stem and has ascending and descending extensions.
- The ascending extension (known as the reticular activating system “RAS”) projects to all areas of the cerebral cortex. It is composed of several neurons connecting the brain stem with the cerebral cortex. It is concerned with arousal, attention and sleep (see below).
- The descending extension participates in control of motor activity (see below).
Functions of the reticular formation:

- **Motor functions:**
  - Receives collaterals from the spinothalamic tract and receives input from the cerebral cortex and the red nucleus and projects to the cerebellum.
  - Sends 2 descending tracts (= medial and lateral reticulospinal tracts) that carry motor commands generated in the reticular formation itself.
  - The descending tracts also receive input from the cerebral cortex and the basal ganglia.

- **Sensory functions:**
  - Sends descending tracts to inhibit some sensory pathways in the spinal cord (related to pain perception).
  - Receives collaterals from ascending sensory tracts.

- **Visceral functions:**
  - Contains many of the areas concerned with regulation of heart rate, blood pressure and respiration.
Level of consciousness.

- Sends ascending tracts (ascending reticular activating system “RAS”) to make direct connections with the thalamus, hypothalamus, basal ganglia and cerebral cortex. Those to the thalamus terminate in the intralaminar nuclei and from there project to widespread area in the cerebral cortex.
- These ascending tracts “RAS” are concerned with arousal, attention and sleep.
- Bilateral damage to these tracts results in coma.

### THE ELECTROENCEPHALOGRAM “THE EEG”

- A record of the electrical activity of the brain using electrodes.
- The electrodes are placed on the scalp or directly on the surface or within the cortex of the brain.
- The recording may be unipolar or bipolar.

**Types of normal EEG waves:**

- **Alpha waves**
  - Frequency 8-12 Hz (or cycle/s) in humans; slightly more rapid in some animals.
  - Amplitude about 50-100 microvolt (when recorded from the scalp).
  - Appear mainly on the parieto-occipital region (but also observed in other areas).
  - Recorded when the adult subject is a wake, relaxed and closing his eyes.
  - Disappears or replaced by rapid low voltage waves upon opening the eyes or during emotional tension; this is known as “alpha block”.
**Fig 15.2: Alpha waves**

- **Beta waves**
  - Have higher frequency: 18-30 Hz & less amplitude.
  - Seen on the frontal region.
  - Recorded during emotional tension; however, highly concentrated attention may result in appearance oscillations with more rapid frequency (> 30 Hz). These are known as “gamma oscillations”.

**Fig 15.3: Beta waves**

- **Theta waves**
  - Have less frequency: 4-7 Hz & higher amplitude: about 100 microvolt.
  - Recorded in children from the parietal and temporal regions.
  - Can be recorded in adults during sleep (stage 2&3).

**Fig 15.4: Theta waves**
- **Delta waves**
  - Have the least frequency: 1-3.5 Hz & the highest amplitude.
  - Recorded in children from the occipital regions.
  - Can be recorded in adults during sleep (stage 4).

**Fig 15.5: Delta waves**

![Delta waves](image)

**Note:**
- The type of the EEG rhythm is affected by the following factors:
  - Age (alpha rhythm in the occipital lobe appears during adolescence).
  - Behavioral state (ranging from deep sleep to concentrated attention).
  - Hypoglycemia (decreases frequency of alpha waves).
  - Hypothermia (decreases frequency of alpha waves).
  - Hypercapnia (decreases frequency of alpha waves).
  - Addison’s disease (decreases frequency of alpha waves).
  - Hyperventilation (used to induce EEG abnormalities).

**Clinical uses of the EEG**

1. **Diagnosis of epilepsy:**
   - Appearance of multiple spikes indicates grand mal epilepsy

**Fig 15.6: Grand mal epilepsy**

![Grand mal epilepsy](image)
- Appearance of spikes and waves (typically 3 spike & wave discharges per second) indicates petit mal epilepsy (or absence seizures).

**Fig 15.7: Alpha waves**

![Alpha waves](image)

2- Localization of space occupying lesions (e.g. brain tumor or subdural hematoma):
- For example by appearance of unilateral delta waves in the EEG.

**Fig 15.8: Delta waves**

![Delta waves](image)

**Epilepsy**
- Epilepsy is a common neurological disorder characterized by recurrent unprovoked seizures.
- The seizures are transient signs and/or symptoms caused by abnormal, excessive synchronous discharge of the neurons in the brain.
There are two types of seizures:

- Partial (or focal seizures): when the source of the seizure in the brain is localized. These are further divided into simple partial seizure (when there is no loss of consciousness) or complex partial seizure (when there is loss of consciousness).
- Generalized seizures: when the source of the seizure in the brain is distributed. These are further divided according to their effects on the body into: absence (or petit mal), tonic-clonic (or grand mal), myoclonic, clonic and atonic seizures.

The type of epilepsy can be diagnosed from history, examination and investigations like the EEG, CT scan, MRI and other investigations.

Epilepsy can be controlled by anti-epileptic drugs (e.g phenytoin, carbamazepine ...).

Note: Absence seizure (or petit mal seizure) occurs most often in children. It involves a brief, sudden lapse of consciousness; during which the child appears as staring into space for a few seconds. Although mild, the attacks may be dangerous if they occur during certain activities like swimming. In addition, they may occur hundreds of time each day thus interfering with the school performance.

- Tonic-clonic seizure (or grand mal seizure) starts with loss of consciousness and falling down. This is followed by a period of muscle rigidity (tonic phase) lasting for about 15 to 20 seconds. Then a period of violent, rhythmic convulsions (clonic phase) lasting for 1 to 2 minutes. During the attack, some patients may pass urine or feces (= sphincteric disturbance). Most seizures last from 30 seconds to five minutes. After the seizure, patients may feel headache, drowsiness or confusion. Seizures often occur randomly, but in some cases they are triggered by sleep deprivation, excessive alcohol consumption and stimuli like light & sound.
Sleep

- Sleep is a state of transient loss of consciousness from which a subject can be aroused by appropriate stimuli.

**Stages of sleep (from the EEG recording):**

**Alert wakefulness**
- Beta waves (high frequency).

**Quiet wakefulness**
- Alpha waves (subject is relaxed, quiet and cloding his eyes).

**Light sleep (stage 1)**
- Rapid low-voltage waves broken by sleep spindles.

**Slow-wave sleep (stages 2-4)**
- Theta waves (stage 2 & 3)
- Delta waves (stage 4)

**Types of sleep**
- There are two different types of sleep:
  - Slow-wave sleep (Non rapid eye movement; non REM)
  - Rapid eye movement (REM)

**Slow-wave sleep (Non REM)**
- Constitutes 75% of sleep time
- Exceedingly restful
- Associated with:
  - Decrease in peripheral vascular tone
  - Decrease in BP
  - Decrease in respiratory rate
  - Decrease in metabolic rate
  - Delta and theta waves on the EEG
- Not associated with dreams:
  - Called dreamless sleep
- Dreams may occur but cannot be remembered (because it is not consolidated in the memory).

**Rapid eye movement sleep (REM)**

- Occurs in episodes of 5-30 min, every 90 min.
- Constitutes 80% of total sleep in premature babies, 50% in neonates and 25% in older children and adults; then falls further in old subjects.
- Tiredness decreases the duration of each episode, but as the person becomes restful, the duration is increased.
- A person is more difficult to be awakened during the REM sleep.
- REM sleep is associated with:
  - Rapid movement of the eyes
  - Active dreaming (can be remembered later)
  - Muscle tone is depressed (hypotonia)
  - Excitation of reticular inhibitory centers
  - Heart & respiratory rates may become irregular
  - Ponto-geniculo-occipital spikes (PGO) & β waves in the EEG

**Fig 15.9: Types of sleep**

- **Awake**
- **Light sleep**
- **REM sleep**
- **Deep sleep**
The ponto-geniculo-spikes (PGO) & beta waves in sleep:

- The PGO spikes are large phasic potentials that originate in the pons and pass to the lateral geniculate body and then to the occipital cortex (i.e. ponto-geniculo-occipital). They stimulate the inhibitory reticular area and are therefore responsible for the hypotonia in REM sleep.
- The Beta waves indicate increased brain activity inspite of sleep (therefore REM sleep is called paradoxical sleep).

Mechanism of sleep

- Sleep is an active process (not only an absence of wakefulness). This was confirmed by many observations in experimental animals; for example: Stimulation of certain sites in the brain causes sleep and EEG pattern of sleep and inhibition of some parts of the RAS produces alertness.
- Stimulation of the following sites may cause sleep:
  o The diencephalon (including the posterior hypothalamus & the intralaminar and anterior nuclei of the thalamus. The suprachiasmatic nuclei of the hypothalamus are responsible for sleep circadian rhythm.
  o The reticular formation in the medulla oblongata (areas around the nucleus of tractus solitarius “NTS”).
  o The Basal forebrain (the preoptic area and the diagonal band of Broca).
  o Mechanoreceptors in the skin (produce sleep possibly via the brain stem).

Neurotransmitters in sleep

- The neurotransmitter responsible for sleep is still unknown.
- The following neurotransmitters may have a role:
  o Adenosine is a sleep producing factor; that is why caffeine “adenosine antagonist” inhibits sleep.
- Prostaglandin D2 causes sleep.
- Prostaglandin I2 causes wakefulness.
- Noradrenaline contributes to wakefulness.
- Serotonin suppresses sleep (serotonin agonists suppress sleep whereas serotonin antagonists (ritanserin) increase slow-wave sleep)

**Disorders of sleep**

**Insomnia**
- A sleeping disorder characterized by difficulty in falling sleep or insufficient sleep despite an adequate opportunity.
- Can be transient, acute or chronic.
- Causes include medications (caffeine, amphetamines ...), hormonal disturbance (menstruation, hyperthyroidism ...), stress or mental disorder (depression, anxiety ...).

**Fatal familial insomnia**
- Progressive prion disease (prion diseases are spongiform encephalopathies transmissible to animals). It is characterized by neuronal loss and gliosis of some thalamic and meullary nuclei.
- Patients suffer from increased insomnia, dementia and impaired motor and autonomic functions.

**Sleep walking (somnambulism)**
- Occurs during the non REM sleep.
- Subjects eat, dress themselves or even walk with open eyes and avoid obstacles, but they can not remember the episode.

**Narcolepsy**
- Episodic sudden loss of muscle tone (cataplexy) and un-resistable urge to sleep even during day time activities. This is explained by early and
sudden occurrence of REM sleep (i.e. not after a period of non-REM sleep as occurs normally).

- Patients may also suffer from sleep paralysis (inability to talk or move while waking), frightening hallucinations and automatic behavior (i.e. continue to talk or put things away while sleeping).

**Obstructive sleep apnea**
- Occurs during REM sleep (when the hypotonic pharyngeal muscles obstruct the airways).
- Obstruction of the airways results in loud snoring, carbon dioxide retention and sudden awakenings when breathing stops; for this reason patient is usually sleepy during the day time.

**REM behavior disorder**
- Here there is no hypotonia during REM sleep.
- Patients seem to act out their dreams (move or even jump out of bed).
- Responds to treatment with benzodiazepines.

**Night terror**
- An abrupt awakening from sleep with behavior consistent with terror.
- Occurs during non-REM sleep.

**Nocturnal enuresis (or bed wetting)**
- Also occurs during the non-REM sleep (see the renal system).
CHAPTER (16)

HIGHER FUNCTIONS OF THE NERVOUS SYSTEM

- The term higher functions of the nervous system includes memory, learning, speech, judgment and many other functions of the mind.
- These functions distinguish humans from animals. They enable them to learn, read, communicate and earn high university degrees; however, some of these functions can be demonstrated in some animals. For example, the conditioned reflex in dogs and some sort of language communication in some monkeys (chimpanzees).
- The techniques used for studying these functions in humans are very advanced and highly sophisticated. They include:
  - PET scanning (Positron Emission Tomography; a nuclear medicine medical imaging technique often used to measure local glucose metabolism).
  - fMRI (Functional Magnetic Resonance Imaging; is the use of MRI to measure the hemodynamic response, e.g. increase in blood flow to an area in the brain following neuronal activity. This increase in blood flow is due to increased oxygen consumption by the neurons during their activity.
  - Other techniques include direct stimulation of the cortex & use of implanted electrodes.

MEMORY & LEARNING

Definition
- Memory is the ability of the brain to store, retain, and subsequently retrieve (recall) information.
- Learning is the acquisition of memories (or information) to alter behavior.
**Stages of memory**

- There are four stages of memory:
  - Reception of sensory information
  - Formation of memory trace
  - Consolidation of memory trace
  - Recall of memory trace (or retrieval)

**Reception of sensory information**

- The information is received and interpreted in the sensory cortex.

**Formation of memory trace**

- A memory trace is a chemical change in tissue that represents formation of a memory. Its exact site within the cerebral cortex is unknown. May be the temporal lobe.
- Before the process of consolidation (i.e. during the first minutes of formation); the memory trace is vulnerable to loss by trauma or drugs (because it requires at least 5 to 10 minutes for minimal consolidation).

**Consolidation**

- The process by which the information is stored and becomes resistant to erasing.
- Involves protein synthesis in neurons.
- Involves the hippocampus and its connections.

**Recall (or retrieval)**

- The process by which the stored information is called back.
- The information may be called back (remembered) by one of the following mechanisms:
  - Recollection: Pieces of memories fit together based on an event or clue (e.g. an essay question in an exam).
  - Recall: Regeneration of the memory without being provided any clue (e.g. filling the blank spaces in a question).
Recognition: The ability to identify something as a memory when the stimuli from the memory are experienced again (e.g. multiple choice or a matching question).

Relearning: When someone takes less time in memorizing information that is learned in a previous time (e.g. one takes less time in reading a book for the second time compared to the first time).

Classification of memory

There are several ways for classification of memories. For example it can be classified according to the duration of memory retention or according to the type of information.

- Classification according to the duration of memory retention

1. Immediate (or sensory memory):
   - Its duration is less than one second
   - Either fades away or changes into primary or secondary memory

2. Primary (short term or recent memory).
   - Lasts for few minutes. It develops from the sensory memory
   - Rely mostly on an acoustic code (listening) and to a lesser extent a visual code
   - The capacity of the brain for this type of memory is small, but its recall is rapid (=the working memory)

3. Secondary (long term or remote memory)
   - This is the memory that lasts for long time (up to several years)
   - It develops from either sensory or primary memory by either repetition of information or practice
   - The hippocampus is essential to the consolidation of information from short-term to long-term memory, although it does not seem to store information itself
Classification according to the type of information

1. Explicit memory
   - Also known as declarative or recognition memory
   - Associated with awareness
   - Its retention depends on the hippocampus and the temporal lobes
   - Can be divided into:
     - Episodic memory (memory for events)
     - Semantic memory (memory for words, rules and language)

2. Implicit memory
   - Also known as non-declarative or reflexive memory
   - Not associated with awareness
   - Its retention does not depend on the hippocampus; however, the cerebellum and the basal ganglia are involved.
   - Includes skills, habits and conditioned reflexes
   - Can be divided into two types:
     - Non-associative learning (i.e. learning about one stimulus).
     - Associative learning (learning about two stimuli related together).

Examples of non-associative learning

1- Habituation: when the stimulus is repeated many times, the subject becomes habituated to it and ignores it. It is associated with decreased Ca++ in the sensory endings resulting in decreased release of neurotransmitters following the stimulation.

2- Sensitization: in spite of repetition of the stimulus, it produces greater response (opposite to habituation). It is associated with increased Ca++ in
the sensory endings resulting in increased release of neurotransmitters following the stimulation.

**Examples of associative learning**

1- The conditioned reflex: A reflex response to a stimulus that previously had no effect, after pairing it repeatedly with another stimulus capable of producing the response. It was first described by Pavlov in the 1890s.

- In his famous experiment, Pavlov used a bell (= conditioned stimulus) to call a dog to his meal (= unconditioned stimulus that normally causes salivation). After a few repetitions; the dog learned that the bell is followed by food; so it started to salivate in response to the bell.

**Note:**

- Explicit memory (and many forms of implicit memory) can be retained for short periods of time (sensory or short term memory) or long periods of time (long term memory); see above.

- Riding a bicycle initially requires the explicit memory (e.g. the rules); then after learning, it requires the implicit memory (i.e. it becomes a skill).

**Mechanism of memory**

- Memories are caused by enhancement of synaptic transmission. This is achieved by:
  - Activation of reverberating circuits.
  - Short term (post-tetanic) synaptic potentiation (increased intracellular calcium).
  - Structural (anatomical) changes in the presynaptic terminal (e.g. increase the number of the transmitter vesicles)
Table 16.1: The role of hippocampus and its connections in memory

<table>
<thead>
<tr>
<th>Structure</th>
<th>Role in memory</th>
<th>Note</th>
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<tbody>
<tr>
<td>Hippocampus</td>
<td>Formation of long term memory (consolidation)</td>
<td>Lesions (as in Alzheimer's disease) results in failure to form new long term memories</td>
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<tr>
<td>Prefrontal cortex</td>
<td>Temporary storage of working memory</td>
<td>Recall of words is related to the left frontal lobe &amp; pictures to the right frontal lobe</td>
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<tr>
<td>Mamillary bodies</td>
<td>Formation of recent memory</td>
<td>Lesions (as in alcoholics) develop impairment of recent memory</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Encodes emotions related to memory</td>
<td>Events associated with strong emotions are remembered better than those without</td>
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<tr>
<td>Temporal lobe</td>
<td>Interpretation of the surroundings as familiar or not</td>
<td>Lesions may result in “déjà vu” (feeling familiar in strange places) or “jamais vu” (feeling strange in familiar places).</td>
</tr>
</tbody>
</table>

**Amnesia**

- Amnesia or loss of memory has the following types:
  - Retrograde amnesia: inability to recall memories from the past, specially the recent events (i.e. before consolidation of the memory trace). It is caused by brain concussion or an electrical shock.
  - Anterograde amnesia: inability to form new Long-term memories (but the already stored are intact); caused by lesions of the hippocampus.
  - Hysterical (psychogenic) amnesia: occurs due to severe psychological stresses, and it often recovers completely.
  - Global amnesia: occurs in extensive brain lesions; resulting in both retrograde & anterograde amnesia.
THE NEOCORTEX

- The neocortex is the part of the cerebral cortex that is involved in higher functions such as conscious thought and language.
- In humans it constitutes 90% of the cerebral cortex.
- It is made up of six layers, labeled I (superficial) to VI (deep). These layers contain different types and sizes of neurons. The fibers of these neurons (association, commissural and projection fibers) form complex connections and feedback control on the cells of origin.
- The projection fibers to extra-cortical sites originate mainly from layer V (the layer of the large pyramidal cells “Betz cells”) and also from layer VI (to a lesser extent); whereas afferents from the specific nuclei of the thalamus end in layer IV.
- The neocortex includes the following three major association areas:
  o Frontal association area
    • Infront of the premotor area
  o Parietal-temporal-occipital area
    • Between the somatesthetic and visual cortices
  o Temporal area
    • From the lower portion of the temporal lobe to the limbic system

Functions of the neocortex

- One of the most important functions of the neocortex is related to language (see below); however, this function is localized to one of the two hemispheres.
- The hemisphere that is concerned with language is known as the categorical (or dominant) hemisphere whereas the other is known as the representational (or non-dominant) hemisphere.
- The categorical hemisphere is the left hemisphere in almost all right handed and most left handed subjects (e.g. in some populations: the left hemisphere is dominant in 96% of right handed and 70% of left handed people).

**Functions of the categorical hemisphere**

- Language functions

  Note: Lesions in this hemisphere produce language disorders (see below) and apraxia.

- Apraxia is defined as a disorder of skilled movement not caused by weakness, akinesia or any other organic movement disorder.

- A patient with apraxia has no paralysis but lost the information about how to do skilled movements. This is usually associated with left sided lesions; however, right sided lesions also may be implicated. Examples include:
  - Constructional apraxia: inability to copy 3-dimensional assemblies (associated with left or right parietal lobe lesions and may be other sites in the brain).
  - Dressing apraxia: associated with right parietal lobe lesions (part of the neglect syndrome; see below).

**Functions of the representational hemisphere**

- Identification of objects by their form
- Recognition of musical themes
- Recognition of faces

**Important clinical points:**

- Lesions in the representational hemisphere cause agnosias and hemi-neglect.

- Agnosias are group of disorders caused by right brain lesions (especially the parietal lobe), characterized by inability to identify objects, persons, sounds, or smells while the sensory modality is intact. Examples include:
- Astereognosis (inability to identify objects by feeling them)
- Finger agnosia (inability to distinguish fingers of the hand)
- Prosopagnosia (inability to recognize familiar faces; see below)
- Auditory agnosia (inability to hear environmental sounds such as a dog barking).

- Hemineglect (or sensory inattention) is caused by lesions in the inferior parietal lobule. Affected patients ignore stimuli coming from one half of their bodies.

**Fig 16.1: The neocortex**

![Image of the neocortex](image)

**LANGUAGE “SPEECH”**

- Language (spoken or written) is a key part of human culture; it is the mean of communication between people.
- It requires integrity of the categorical (dominant) hemisphere which is the left cerebral hemisphere.
- It has two aspects:
  1. Sensory aspect (language input)
  2. Motor aspect (language output)

- Sensory aspect (language input):
  - Requires integrity of the **Wernicke's area** at the posterior end of the superior temporal gyrus.
  - This area is concerned with understanding auditory and visual information (i.e. spoken and written speech).
  - It projects via the arcuate fasciculus to the Broca's area.

- Motor aspect (language output):
  - Requires integrity of the **Broca's area** at the frontal lobe (infront of the inferior end of the motor area).
  - After processing the information received from the Wernicke's area; it projects to the motor cortex to initiate movements of the lips, tongue and larynx to produce words.

**Fig 16.2: The speech areas**
Language disorders (Aphasias)
- Aphasia is defined as loss of the ability to produce and/or comprehend language, due to injury to the brain areas specialized for these functions.
- It is caused by lesions in the categorical hemisphere (i.e. the left hemisphere in most cases). For example stroke, head injury or brain tumors.
- It can be classified into fluent, non-fluent and pure types:

- **Fluent aphasias:**
  - **Wernicke’s aphasia (sensory aphasia):**
    - Caused by damage to the Wernicke’s area.
    - The patient can see and hear words but he can not understand the speech of others.
    - May speak in long sentences that have no meaning and add unnecessary new words.
  - **Anomic aphasias:**
    - Caused by lesions affecting the angular gyrus in the dominant hemisphere without affecting the Wernicke’s or Broca’s areas.
    - The angular gyrus is concerned with processing of visual information. The resulting abnormality is failure in understanding pictures and written language.
  - **Conduction aphasia:**
    - Caused by damage to the arcuate fasciculus (it appears that the affected areas are in and around the auditory cortex).
    - Auditory comprehension is near normal, and oral expression is fluent with occasional paraphasic errors and poor repetition ability.
- **Non-fluent aphasias:**
  - **Motor aphasia:**
    - Caused by lesions involving the Broca's area.
    - Patient understands both, spoken & written words, but he can not talk easily (= non fluent aphasia). He can produce short, meaningful phrases with great effort.
    - He often omits small words such as "is", "and", and "the". For example, a person with Broca's aphasia may say, "Walk dog" meaning, "I will take the dog for a walk".
    - Unlike the sensory aphasia, patients with motor often have right sided hemiplegia.
  - **Global (general aphasia):**
    - Caused by severe lesions of the categorical hemisphere (involving motor and sensory speech).
    - Patients have severe communication difficulties and will be extremely limited in their ability to speak or comprehend language.

- **Pure aphasias:**
  - **Agraphia (writing aphasia):**
    - Selective impairment in writing.
    - Caused by damage to the writing center in the area of hand skills.
  - **Dyslexia (inability to read or word blindness):**
    - Selective impairment in reading. Its cause is unknown but probably related to a defect in the visual association area.
  - **Pure word deafness:**
    - Caused by damage to Wernicke's area or disruption of auditory input to this region.
    - It exhibits itself as inability to comprehend the meaning of speech, but in most cases still being able to hear, speak, read, and write.
Other speech disorders:

- **Stuttering:**
  - Stuttering (or stammering) is a speech disorder in which the flow of speech is disrupted by involuntary repetitions and prolongations of sounds or words and involuntary silent pauses or blocks.
  - The exact etiology of stuttering is unknown; however, it is found to be associated with right cerebral dominance and widespread over activity in the cerebral cortex and cerebellum.

- **Damage to the non-dominant hemisphere:**
  - Lesions of the representational hemisphere have no effect on speech; however, some patients lose the ability to tell stories or jokes.

<table>
<thead>
<tr>
<th>Other abnormalities in the higher functions</th>
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<tr>
<td>- Many abnormalities in the higher functions are studied in patients with neurological lesions (e.g. strokes and head injuries). When a patient presents with such abnormality, the fMRI and PET are used to localize the site of the lesion.</td>
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<tr>
<td>- The following are examples of some these abnormalities:</td>
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<td><strong>Prosopagnosia “face blindness”</strong></td>
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<td>- Patients fail to recognize faces of familiar people (family and friends); however they can recognize them by their voices.</td>
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<td>- Due to lesion in the right inferior temporal lobe “fusiform gyrus” (but the left is also involved in recognition of faces).</td>
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<td><strong>Acalculia</strong></td>
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<td>- Patients have difficulty in performing simple mathematical tasks, such as adding, subtracting, multiplying and even simply stating which of two numbers is larger.</td>
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</table>
Due to lesion in the inferior portion of the left frontal lobe.
Also caused by lesions affecting the left angular gyrus. Here the agraphia is associated with “agraphia” (inability to write), “finger agnosia” (difficulty in naming and differentiating among the fingers) and “left-right disorientation” as in Gerstmann’s syndrome (a neurological disorder associated with lesions in the dominant (usually left) side of the angular and supramarginal gyri near the junction between the temporal and parietal lobes).

**Failure of navigation**
- Failure to locate places is caused by lesions involving the right hippocampus (concerned with learning locations of places) and the right caudate nucleus (facilitates movement to the places).
- Men are better than women in spatial skills and navigation (may be because they have larger number of brain cells and larger size of brain!).

**Personality change & Lack of concern “Disinhibition”**
- Anti-social behavior is a characteristic of frontal lobe lesions.
- Because these patients also do not bother about tensions and pain (= lack of concern); prefrontal lobotomy was used for treatment of severe intractable pain and incapacitating tensions associated with phobias, delusions and compulsions.

**Dementia**
- Dementia is progressive decline in cognitive function of the brain; to a degree above what is expected from normal aging.
- The affected areas in cognition (especially at the later stages of the disease) include memory, attention, orientation, language and problem solving.
- It is more common in the elderly population (senile dementia); however, it may occur in younger age groups (pre-senile dementia).
Types of dementia

1- Cortical dementias

- Alzheimer disease
  - The commonest cause of senile dementia (in the Western countries).
  - Characterized by progressive loss of short term memory followed by general loss of cognitive function and eventually death.
  - Atrophy of the hippocampus appears on the MRI before the onset of symptoms.
  - Pathological features: cytoplasmic neurofibrillary tangles (abnormally phosphorylated tau protein that normally binds the microtubules) and senile plaques (extracellular deposition of beta-amyloid protein).

- Vascular dementia
  - The next common cause of dementia in the elderly (in the Western countries).
  - Also known as multi-infarct dementia.
  - Caused by poor circulation of blood to the brain (due to multiple tiny strokes).

- Dementia with Lewy bodies
  - Exhibits clinical overlap between Alzheimer’s disease and Parkinson’s disease.
  - Pathologically, it is characterized by development of abnormal proteinaceous cytoplasmic inclusions, called Lewy bodies, throughout the brain.

- Alcohol induced dementia
  - Caused by long term excessive drinking of alcohol, resulting in neurological damage and memory loss.
May be associated with Wernicke’s encephalopathy and Korsakoff’s psychosis.

Wernicke’s encephalopathy is caused by acute thiamine deficiency (vitamin B1) due to alcohol and Korsakoff’s psychosis is the chronic complication of that deficiency.

Signs of Wernicke’s encephalopathy:
- Aataxia
- Nystagmus
- Ophthalmoplegia
- Coma

Signs of Korsakoff’s psychosis:
- Confusion
- Amnesia (anterograde and retrograde)
- Confabulation (description of events that never occurred)

2- Subcortical dementias

Dementias due to Hypothyroidism, hypoglycemia, Parkinson’s disease, Huntington’s disease, deficiency of vitamin B1, deficiency of vitamin B12 & deficiency of folate.
### QUESTIONS FOR SELF ASSESSMENT-11 (MCQS)

1. **Multiple spikes in the EEG are signs of:**
   - a. Brain death
   - b. Head injury
   - c. Epilepsy
   - d. Sensory ataxia
   - e. Normal brain activity

2. **A patient with sensory aphasia:**
   - a. Cannot obey commands
   - b. Cannot speak in long sentences
   - c. Has normal wernicke’s area
   - d. Is unable to write words
   - e. Is unable to recognize objects by feeling them

3. **Which of the following is true?**
   - a. Hypotonia of sleep is more marked during the non rem type
   - b. Damage to the hippocampus results in impaired recent memory
   - c. Temporal lobe damage causes retrograde amnesia
   - d. Acoustic neuroma causes conductive deafness
   - e. Linear acceleration is detected by the semicircular canals

4. **Eeg signs of stage IV sleep include:**
   - a. Alpha waves
   - b. Dominance of sleep spindles
   - c. Beta waves
   - d. Delta waves
   - e. Spikes and waves

5. **Long term memory:**
   - a. Is lost in dementia
   - b. Formation requires the hippocampus
   - c. Is stored in the temporal lobe
   - d. Lasts for several hours
   - e. Formation requires mamillary bodies

6. **The following is a fast eeg rhythm:**
   - a. Beta waves
   - b. Delta waves
   - c. Alpha wave
   - d. Theta wave
   - e. None of the above

7. **Which of the following may show unilateral slowing of EEG activity:**
   - a. Head injury
   - b. Epilepsy
   - c. Brain tumor
   - d. Meningitis
   - e. Parkinson’s disease

8. **Sensory aphasia is caused by damage to:**
   - a. Frontal lobe
b. Auditory pathway
c. Broca's area
d. Wernicke's area
e. Cerebellum

9. **Dyslexia is caused by damage to:**
   a. The hippocampus
   b. Temporal lobe
   c. Broca's area
   d. Wernicke's area
   e. Visual association area

10. **Motor aphasia is caused by damage to:**
    a. Frontal lobe
    b. Auditory pathway
    c. Broca's area
    d. Wernicke's area
    e. Cerebellum

11. **Rapid eye movement sleep:**
    a. Constitutes 80% of sleep in adults
    b. Decreases in duration as the subject becomes restful
    c. Is dreamless
    d. Is associated with profound hypotonia
    e. Is associated with delta waves in EEG

12. **Which of the following sleep disorders occur during REM sleep:**
    a. Sleep walking
    b. Narcolepsy
    c. Obstructive sleep apnoea
    d. Nocturnal enuresis
    e. Both b & c

13. **Riding a bicycle is an example of:**
    a. Explicit memory
    b. Implicit memory
    c. Associative learning
    d. Episodic memory
    e. Sensitization

14. **Inability to recognize objects by feeling their forms is:**
    a. Caused by lesions of dominant hemisphere
    b. Known as apraxia
    c. Known as asteriognosis
    d. Explained by loss of sensation in the hands
    e. Due to an abnormality in prefrontal cortex

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FURTHER READING


(الحمد لله الذي ينعمه تتم الصالحات)