



GIT & NUTRITION

THEORETICAL HANDBOOK

Zagazig National University
2024- 2025

**ZAGAZIG NATIONAL UNIVERSITY ZNU
MEDICINE & SURGERY PROGRAM**

FIRST YEAR

SEMESTER 2

**GIT& NUTRITION MODULE THEORETICAL
HANDBOOK**



2024-2025

Learning outcomes

I- Anatomy:

- **Outline** anatomy of the oral cavity
- **Identify** anatomy palate
- **Describe** anatomy of tongue
- **Describe** anatomy of salivary glands
- **Describe** anatomy of oropharynx
- **Outline** anatomy of anterior abdominal wall
- **Describe** anatomy of inguinal canal and **identify** inguinal hernia
- **Describe** anatomy of the posterior abdominal wall
- **Describe** anatomy of peritoneum
- **Explain** anatomy of esophagus and stomach
- **Describe** anatomy of small and large intestine
- **Identify** anatomy rectum and anal canal
- **Describe** anatomy of pancreas and spleen
- **Identify** anatomy liver
- **Describe** blood supply of GIT

II- Histology:

- **Outline** histology of the oral cavity
- **Describe** histology of tongue
- **Describe** histology of salivary glands
- **Explain** histology of esophagus and stomach
- **Describe** histology of small and large intestine
- **Identify** histology of anal canal

- **Describe** histology of pancreas
- **Identify** histology of liver and gall bladder

III- Physiology:

- **Explain** function of enteric system in the process of mastication and salivation
- **Explain** secretions and motility of stomach, small and large intestine with their clinical correlation
- **Describe** exocrine pancreatic secretion and its control
- **Explain** function of liver and biliary secretion with their clinical correlation
- **Explain** basal metabolic rate and specific dynamic action
- **Explain** control of food intake and obesity.

IV- Biochemistry:

- **Know** digestion and absorption of carbohydrates
- **Outline** glycolysis
- **Outline** pyruvate dehydrogenase (PDH) & Tricarboxylic acid cycle (TCA)
- **Outline** gluconeogenesis
- **Identify** glycogen Metabolism
- **Describe** pentose phosphate pathway
- **Know** electron transport chain (ETC)
- **Know** lipids digestion
- **Know** digestion of Proteins
- **Outline** overall Nitrogen Metabolism
- **Outline** metabolism of Ammonia
- **Discuss** amino acid metabolism
- **Describe** inborn error of amino acids
- **Describe** heme Synthesis
- **Know** catabolism of Hemoglobin, Hyperbilirubinemia and Jaundice

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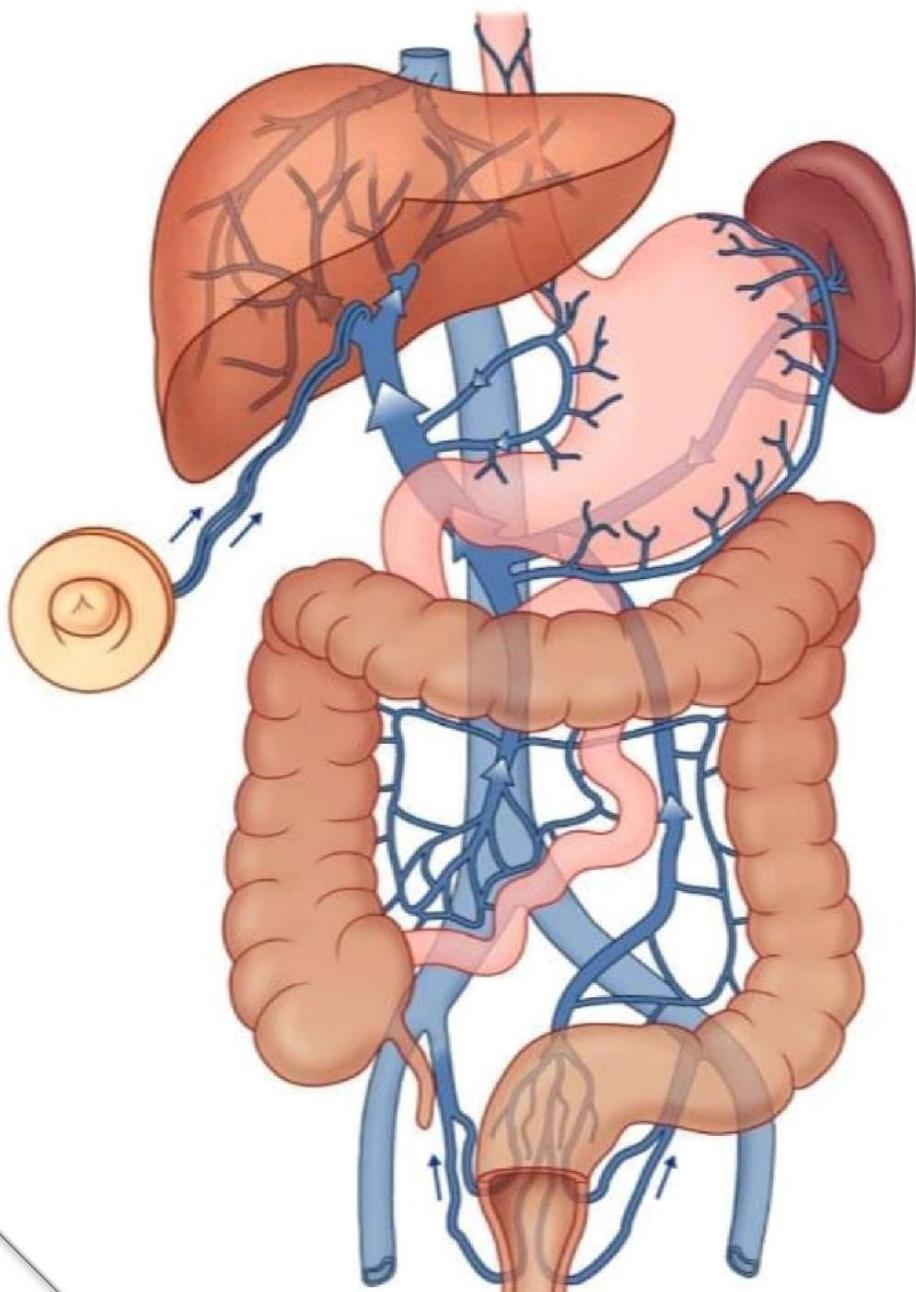
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Anatomy of GIT and Nutrition



Chapter 1: Oral Cavity and oropharynx

Anatomy of the oral cavity

The oral cavity is separated into two regions by upper and lower dental arches consisting of the teeth and alveolar bone that supports them:

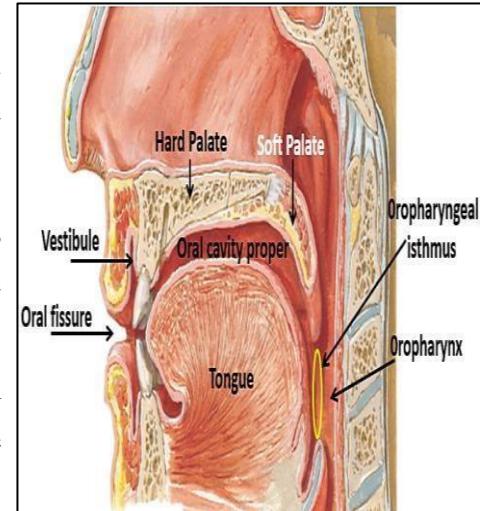
- The outer oral vestibule**, which is horseshoe shaped, is between the dental arches and the deep surfaces of the cheeks and lips. It opens into exterior by the oral fissure.
- Oral cavity proper**: the space enclosed by the dental arches. Posteriorly it opens into the oropharynx by the oropharyngeal isthmus, which is bounded:
 - superiorly by the soft palate.
 - inferiorly by the tongue
 - on each side by the palatoglossal arches.

The approximation of these arches shuts off the mouth from oropharynx and is essential to deglutition

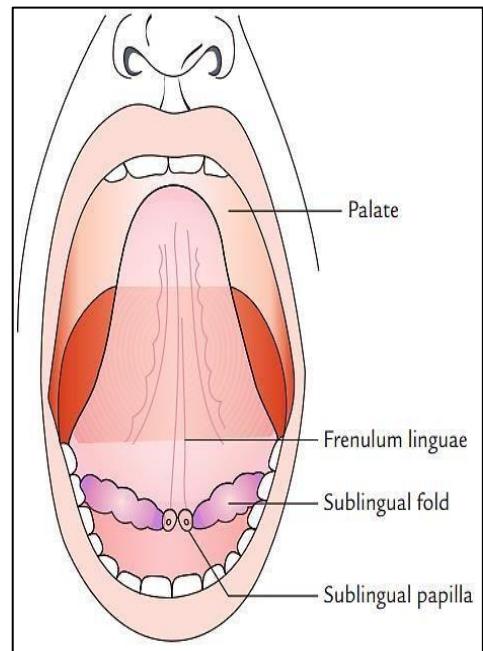
When the jaws are closed, the two parts of the mouth cavity are connected by the space behind the last molar tooth.

The floor of the mouth presents the following features:

- Lingual frenulum (frenulum lingula)**: a median fold of mucus membrane which connects the lower surface of the tongue with the floor of the mouth.
- Plica fimbriata**: fold of mucus membrane on the sides of the frenulum.
- The sublingual fold**: a small ridge on each side of the lingual frenulum. It is formed by the underlying sublingual gland, and it receives the openings of its ducts.
- The sublingual papilla**: a small conical elevation on the anteromedial end of the sublingual fold. The submandibular duct opens on its top.



Sublingual region seen when tongue is turned upwards



The Lips: two folds of skin and subcutaneous tissue surround the oral fissure and join each other at the angles of the mouth. Each lip has a fold of mucus membrane called **labial frenulum** connect it with the gum in the median plane. The outer surface of upper lip has a depression in median plane called philtrum.

The cheeks: The cheeks lie on the sides of the oral fissure. They are covered externally by skin and lined internally by mucus membrane.

Gums (Gingiva): These are highly vascular folds of dense fibrous tissue fixing the teeth in the alveolar arches of the jaws.

The Teeth: They are either primary (deciduous) or permanent teeth.

A- Primary teeth:

- These teeth are temporary, and they erupt during the 1st two years after birth. They are 20 in number, 10 in each jaw.
- They are arranged as 2 incisors, 1 canine & 2 molars in each half of jaw (Rt. or Lt.).

B- Permanent teeth:

They begin to replace deciduous teeth at the age of 6 y. They are 32 in number, 16 in each jaw. They are arranged as 2 incisors, 1 canine, 2 premolars and 3 molars (in each half of the jaw).

Anatomy of the palate

It forms the roof of the mouth cavity separating it from nasal cavity and is formed of hard & soft palate.

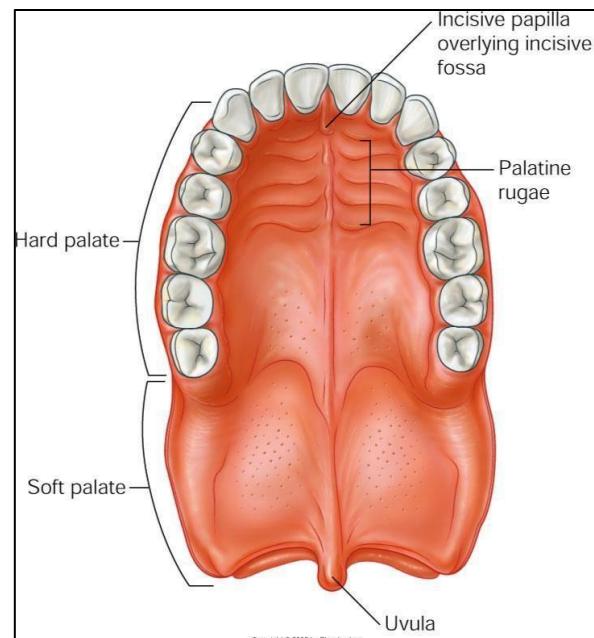
- **Hard palate:** It is formed from Rt. & Lt. halves separated from each other by interpalatal suture. Each half is formed from two parts:

- 1- Anteriorly: the palatine process of maxilla. It forms about the anterior $\frac{3}{4}$.
- 2- Posteriorly: the horizontal plate of palatine bone. It forms the posterior $\frac{1}{4}$.

The 2 parts are separated from each other by palatomaxillary suture.

- **Soft palate (palatine aponeurosis):**

- It is a mobile fold of fibrous tissues covered by mucus membrane.
- It is attached anteriorly to the posterior border of the hard palate.
- Its posterior border has a conical median projection called **the uvula**.
- The soft palate swings up and down to separate the nasopharynx from the oropharynx (acts as a policeman) during deglutition.



Muscles of the palate: These are 4 muscles (see practical).

- Tensor palati
- Levator palati
- Palatopharyngeus
- palatoglossus

Nerve supply of the palate:

A. Motor: all muscles of the palate are supplied by the pharyngeal plexus except tensor palati muscle which is supplied by a branch from mandibular n. (n. to med.pterygoid).

B. Sensory: derived from the following nerves:

- a. Greater and lesser palatine nerves and the naso-palatine nerve. These are branches from maxillary nerve.
- b. Branches from the glossopharyngeal nerve.

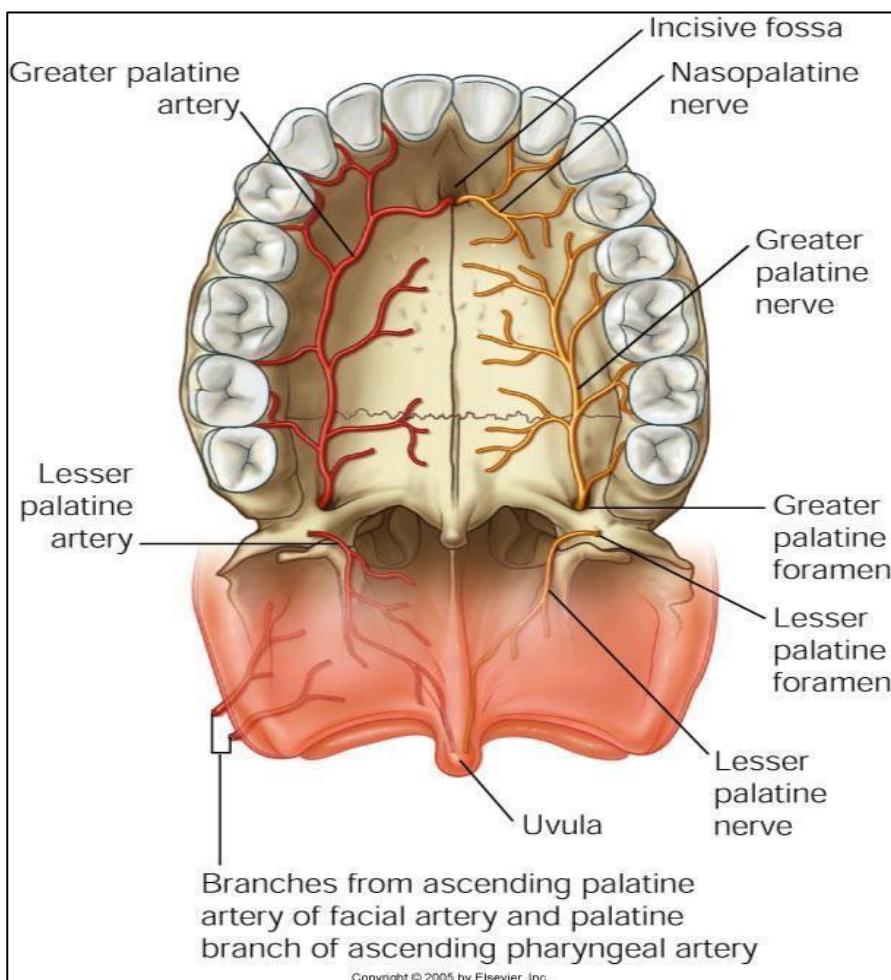
Blood supply of the palate:

A. Arterial:

- a) Greater palatine a.: branch from the 3rd part of maxillary a.
- b) Ascending palatine a.: branch from the facial a.
- c) Twigs from the ascending pharyngeal a.

B. Venous drainage: the veins of palate drain into the pharyngeal venous plexus which end by two pharyngeal veins in the internal jugular vein.

- **Lymph drainage of palate:** drains into the deep cervical lymph nodes.



Anatomy of the Tongue

- It is a muscular organ concerned with speech, taste sensations & deglutition.
- It has an apex, base, and two surfaces: dorsal (upper) and ventral (lower).

1) The apex (tip): directed forwards. It lies behind the incisor teeth.

2) The base: directed backwards. It is attached to the mandible by genioglossus muscle & attached to hyoid bone by hyoglossus muscle.

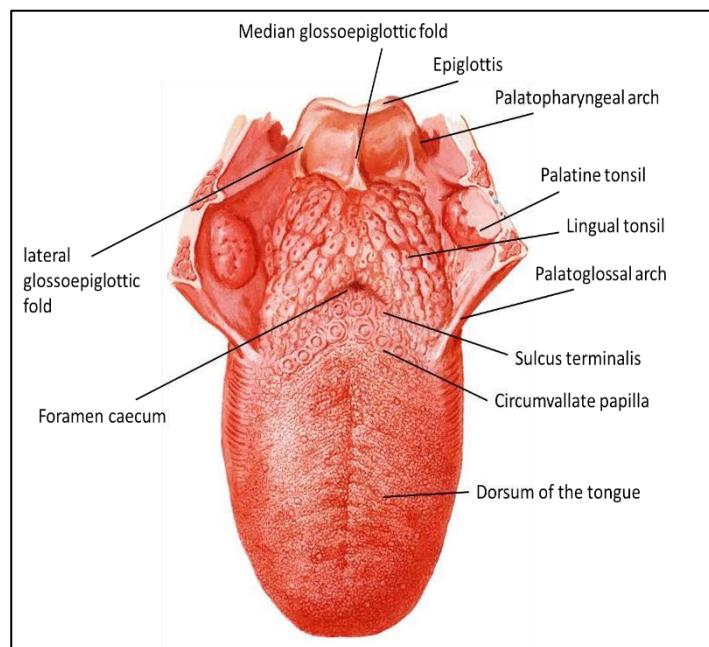
3) The dorsal (upper) surface: directed upwards towards the palate. It is divided by V- shaped sulcus called sulcus terminalis into two parts:

- a. The anterior 2/3 (called the oral part): lies Infront of the sulcus terminalis in the floor of the mouth.
- b. The posterior 1/3 (called the pharyngeal part): lies behind the sulcus terminalis in the anterior wall of the oro-pharynx.

The apex of sulcus terminalis is directed backwards, and it has a narrow pit called foramen caecum which is the embryonic remnant of the thyroglossal duct. This duct gives origin to thyroid gland in fetus.

4) The ventral surface: Its mucus membrane is smooth, and it is reflected from the lower surface of the tongue into the floor of the mouth. It presents special features described with the floor of mouth.

- **Lingual papillae:** These are folds of mucus membrane on the dorsum of the anterior two thirds of the tongue. They increase the surface area of the mucus membrane which comes in contact with the food. They are Vallate, Fungiform, and Foliate papillae.
- **The lingual tonsil:** These are collections of lymphoid follicles in the submucosa of the dorsal surface of the posterior 1/3 of the tongue.



Muscles of Tongue:

1. **Intrinsic muscles:** see practical
2. **Extrinsic Muscles:** see practical

Blood supply of the tongue:

1- Arterial Supply of the Tongue:

- a- Lingual artery: carries the main arterial supply of tongue.
- b- Tonsillar branch of facial a. supplies post. part of tongue.
- c- Twigs from ascending pharyngeal artery: supply the posterior part of the tongue.

2- Venous Drainage of the Tongue:

The tongue is drained by 2 groups of veins that lies superficial and deep to the hyoglossus muscle. They join at the posterior border of the hyoglossus to form the common lingual veins that end either in the internal jugular v. or in common facial v.

Nerve supply of the tongue:

1- Motor: All muscles of tongue (intrinsic and extrinsic) are supplied by hypoglossal n. except the palatoglossus muscle which is supplied by the pharyngeal plexus.

2- Sensory:

a. The ant. 2/3:

1. General sensations carried by the lingual nerve (branch of mandibular n.).
2. Taste sensations carried by chorda tympani which is a branch from facial n.

b. The post. 1/3: both general & taste sensations are carried by glossopharyngeal n.

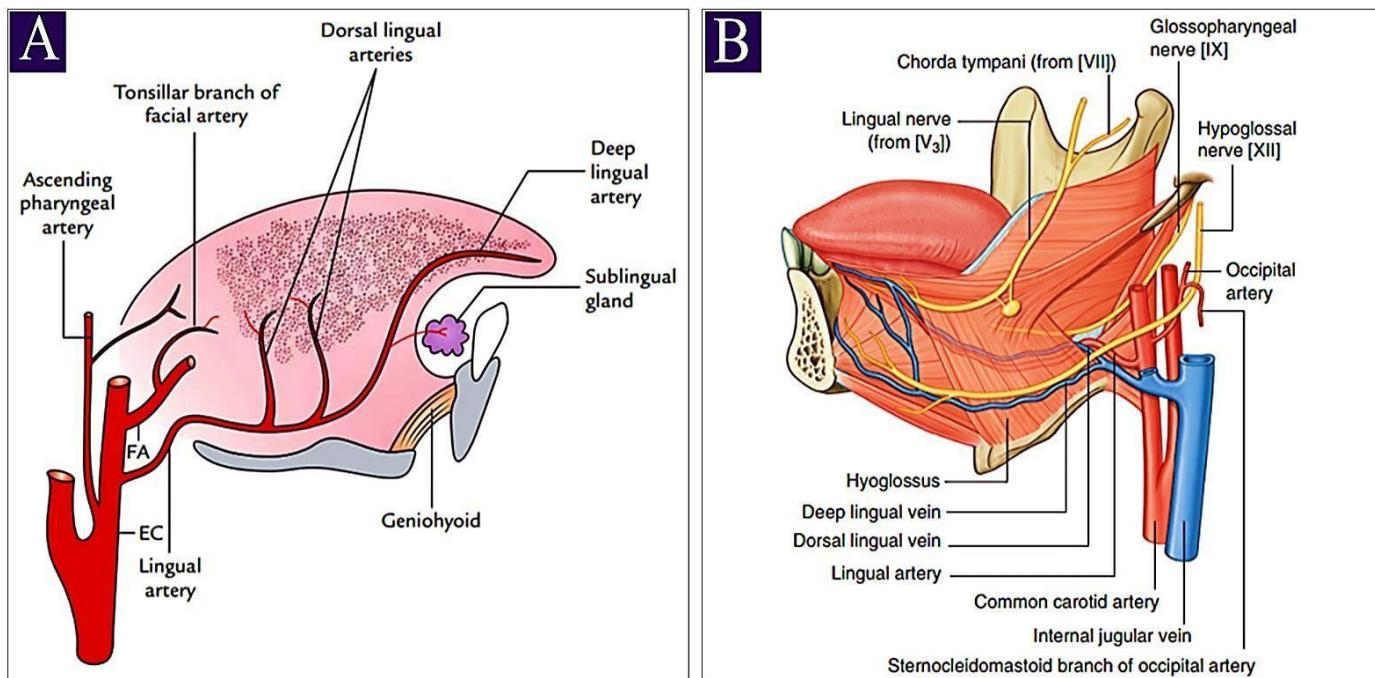
c. Root of the tongue (posterior part): both general and taste sensations are carried by the internal laryngeal nerve (branch of the vagus nerve).

Lymphatic drainage of the tongue:

a. Anterior 2/3:

1. The tip drains into the submental L.N.
2. The margins drain into the submandibular L.N. of its side.
3. The central part drains into the submandibular L.N. of both sides.

b. Posterior 1/3: drain into the deep cervical L.N. of both sides.



A) arterial supply of tongue. B) Veins of the tongue

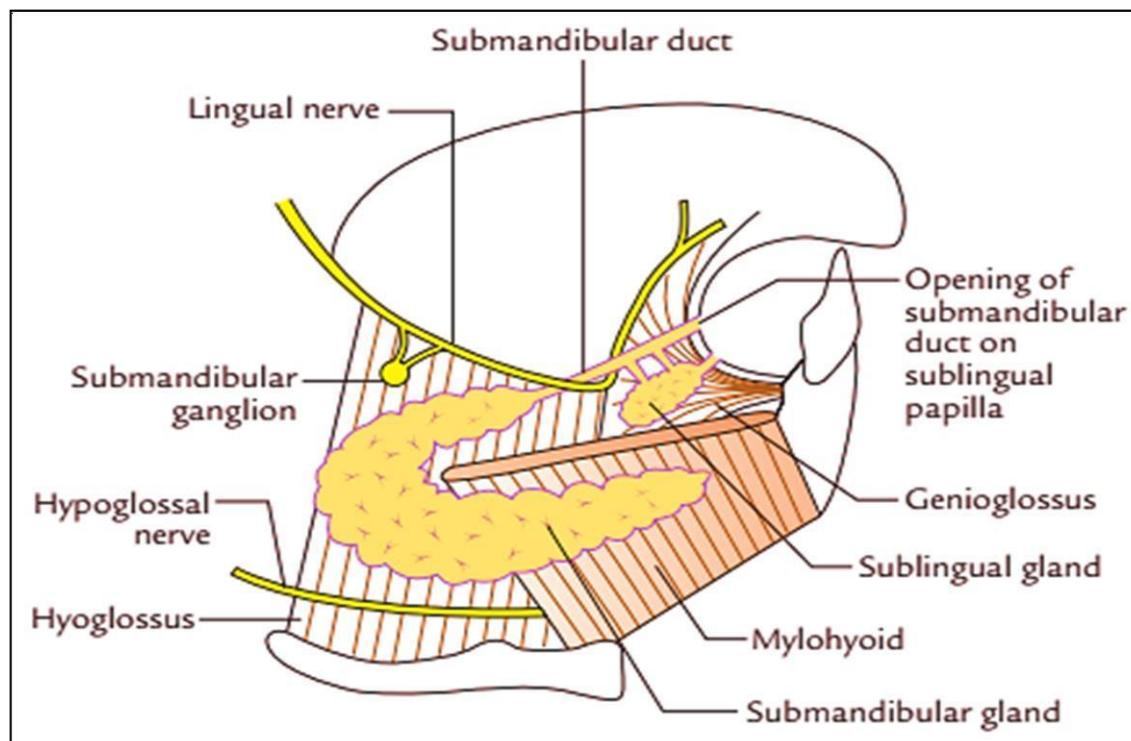
Anatomy of Salivary glands

1-Submandibular salivary gland

The submandibular gland is one of the three pairs of salivary glands is situated partly below and partly deep to the posterior half of the mandible weights about 10–20 g.

Parts: It consists of two parts: (a) a large superficial part and (b) a small deep part. They are superficial and deep to mylohyoid muscle subsequently. The two parts are continuous with each other around the post. border of mylohyoid muscle.

- a. **A-Superficial part:** The superficial part presents two ends anterior and posterior and three surfaces inferior, lateral, and medial. The anterior end extends up to the anterior belly of the digastric muscle. The posterior end extends up to the stylomandibular ligament, which separates the submandibular gland from the parotid gland.
- b. **B- Deep Part:** It's situated on the lateral surface of the hyoglossus below the lingual nerve and the submandibular ganglion and above the hypoglossal nerve. It is related laterally to mylohyoid.



The submandibular and sublingual glands

The submandibular duct:

It is 5 cm long. It arises from the deep part of the submandibular gland. It runs forwards between the hyoglossus and the mylohyoid muscles. Then it passes between the genioglossus medially and the sublingual salivary gland (laterally) where it is hooked by the lingual nerve. Finally, it opens in the floor of the mouth on an elevation called the sublingual papilla on the side of the frenulum of the tongue

2-The Sublingual gland

This is the smallest of the three pairs of large salivary glands. It lies in the floor of the mouth between the mucus membrane and the mylohyoid muscle. It is almond-shaped and rests in the sublingual fossa of the mandible. It is separated from the base of the tongue by the submandibular duct. It is mostly mucus in nature and weighs about 3–4 g. The gland pours its secretion by a series of ducts, about 15 in number, into the oral cavity on the sublingual fold, but a few of them open into the submandibular duct.

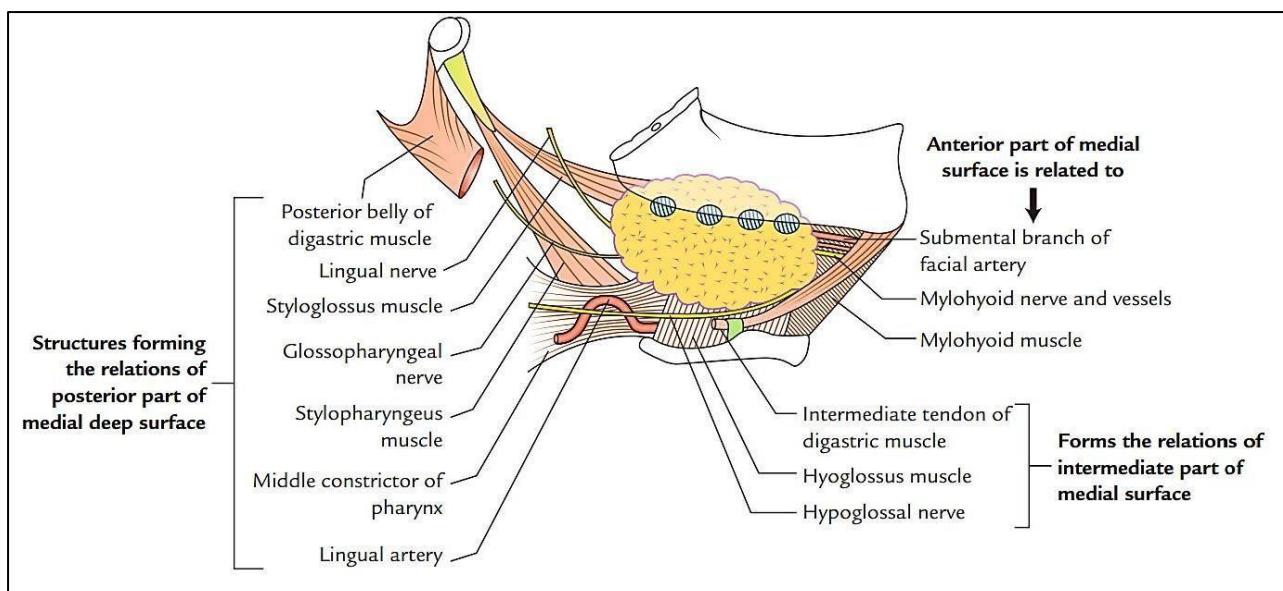
Blood supply the submandibular and sublingual glands: The glands are supplied by facial and lingual arteries and drained by common facial & lingual veins.

Nerve supply of the submandibular and sublingual glands:

1- **Sensory:** from the lingual nerve.

2- **Sympathetic:**

- Submandibular gland: from the plexus around the facial artery
- Sublingual gland: from the plexus around the lingual artery.



3- Parasympathetic:

Preganglionic parasympathetic fibers from the superior salivary nucleus (in the pons) pass with the facial nerve then with its chorda tympani branch.

The chorda tympani join the lingual nerve in the infratemporal fossa. The parasympathetic fibers relay in the submandibular ganglion. Postganglionic fibers pass directly to supply the submandibular and sublingual salivary glands.

Submandibular ganglion

- It is a parasympathetic ganglion which lies in the submandibular region. It lies on the superficial surface of hyoglossus muscle suspended from the lingual nerve.
- **Roots:** 1) **Sensory:** branch from lingual nerve.
2) **Sympathetic:** from the plexus around the lingual artery.
3) **Parasympathetic:** mentioned above (parasympathetic nerve supply of submandibular and sublingual salivary glands).

Branches: supply the submandibular and sublingual salivary gland

3-The Parotid gland

- It is the largest salivary gland in the body.

Site: It lies below the external acoustic meatus between the angle of mandible & sternomastoid muscle.

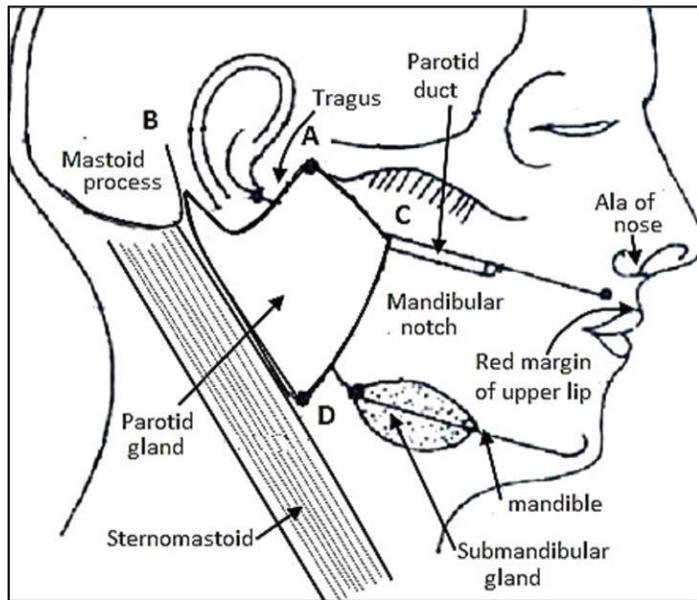
Shape: roughly pyramidal in shape. It has:

- a- **2 ends:** upper and lower.
- b- **3 borders:** anterior, posterior & medial border.
- c- **3 surfaces:** superficial (lateral), anteromedial & postero-medial surfaces.

Surface anatomy of the parotid gland:

It is represented by the four points:

- Point **A:** at the tragus of the auricle.
- Point **B:** at the mid-point of the anterior border of the mastoid process.
- Point **C:** at the midpoint of the mandibular notch.
- Point **D:** at a point on the anterior border of sternomastoid muscle 2cm below and behind the angle of the mandible.



Surface anatomy of parotid gland and its duct.

The borders of the gland are represented by the following lines:

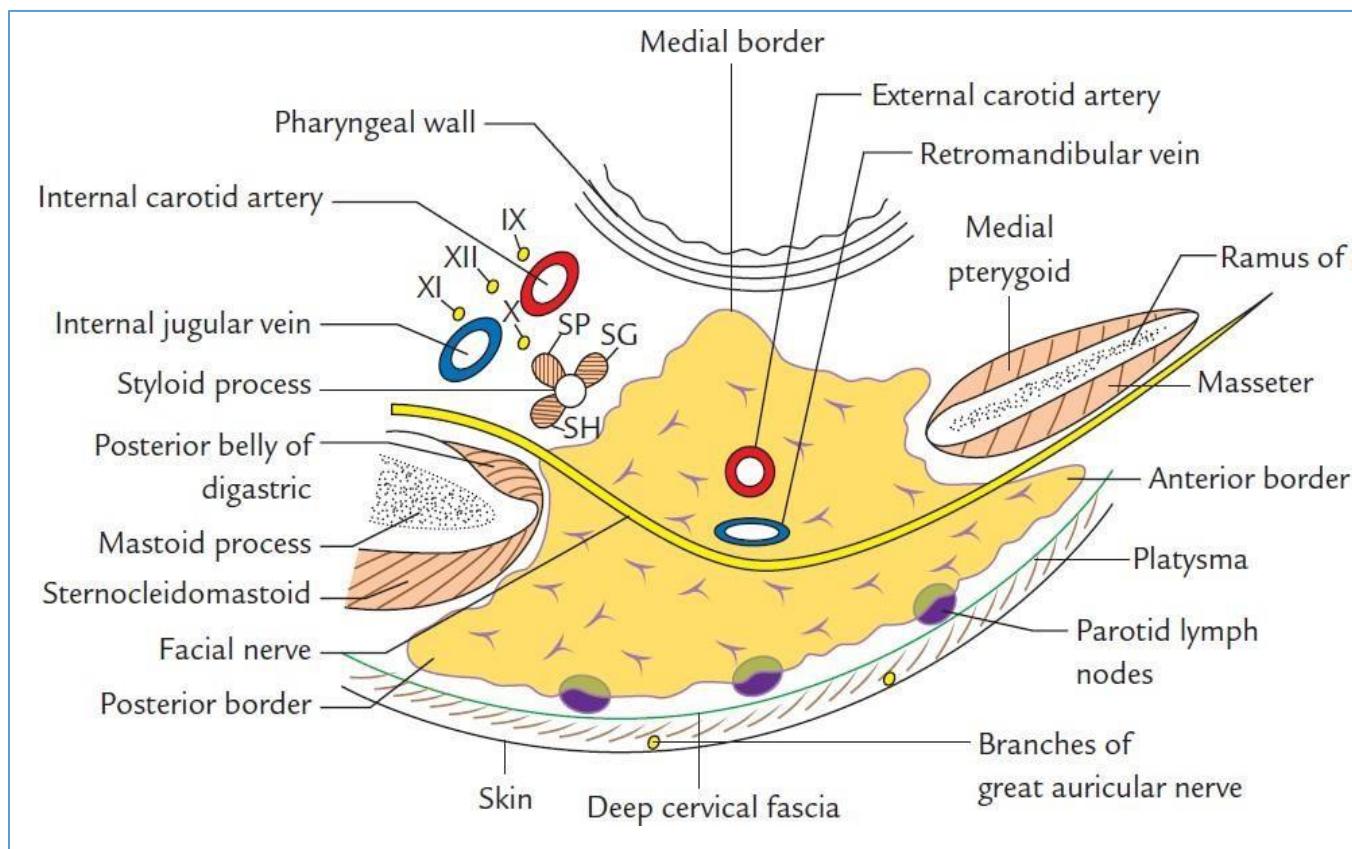
Upper end	by a line concave upwards between points A and B. It fits into the external acoustic meatus
Anterior border	by a line from point A downwards and forwards to point C then it curves downwards and backwards to point D
Posterior border	by a line on the ant. border of sternomastoid muscle between points B and D.
Surface anatomy of parotid duct:	represented by the middle third of a line drawn between 2 points: <ul style="list-style-type: none"> • The tragus. • A point halfway between ala of nose & red margin of upper lip.

The capsule of the parotid gland: It has two capsules:

1. **True (inner) capsule:** formed by condensation of the connective tissue of the gland.
2. **False (outer) capsule:** formed from the deep cervical fascia which is splitted into two layers; one passes superficial and the second passes deep to the gland. The deep layer is attached between the styloid process and the angle of the mandible to form the **stylomandibular ligament**. This ligament separates the parotid from the submandibular gland.

Clinically: when the parotid gland is inflamed as in mumps. It is enlarged. The patient suffers from severe pain due to firm enclosure of the gland by false capsule (deep cervical fascia).

Relations of the parotid gland:



The parotid duct & its course:

The parotid duct is 2 inches (5 cm) long. It emerges from the anterior border of the gland and passes forwards on the masseter muscle, finger breadth below the zygomatic arch.

At the anterior border of the masseter, it curves inwards and pierces the following structures:

- 1) Buccal pad of fat.
- 2) Buccopharyngeal fascia.
- 3) Buccinator muscle.
- 4) Mucus membrane of the mouth.

Finally, it opens into vestibule of the mouth opposite ***upper 2nd molar tooth***.

- Before it opens in the mouth the parotid duct passes a short distance between the buccinator muscle & mucus membrane of the mouth. This oblique passage forms a valve like mechanism which prevents inflation of the duct system during violent blowing.
- It can be felt in the living by rolling a finger at upper part of the anterior border of masseter muscle during clenching of teeth.

Structures inside the parotid gland:

- 1-Facial n. & its branches are superficial
- 2-External carotid a. is deep
- 3-Retromandibular v. (posterior facial v.) lies in between
- 4-Auriculo-temporal n.
- 5-Deep parotid lymph nodes.

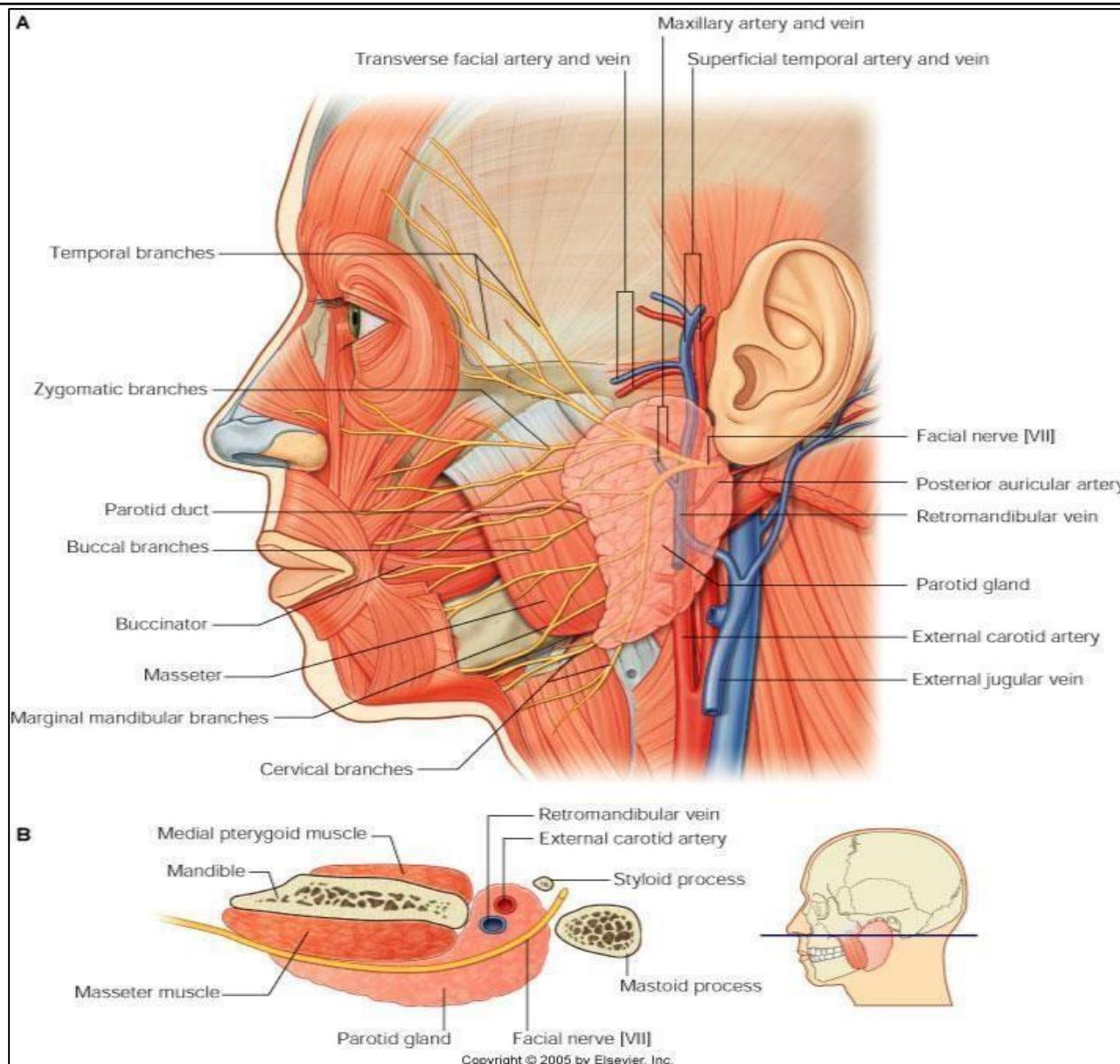
How these structures enter and leave parotid gland?

- 1- Facial n.:** enters the gland through its postero-medial surface & divides inside it into 5 terminal branches. These branches are.:

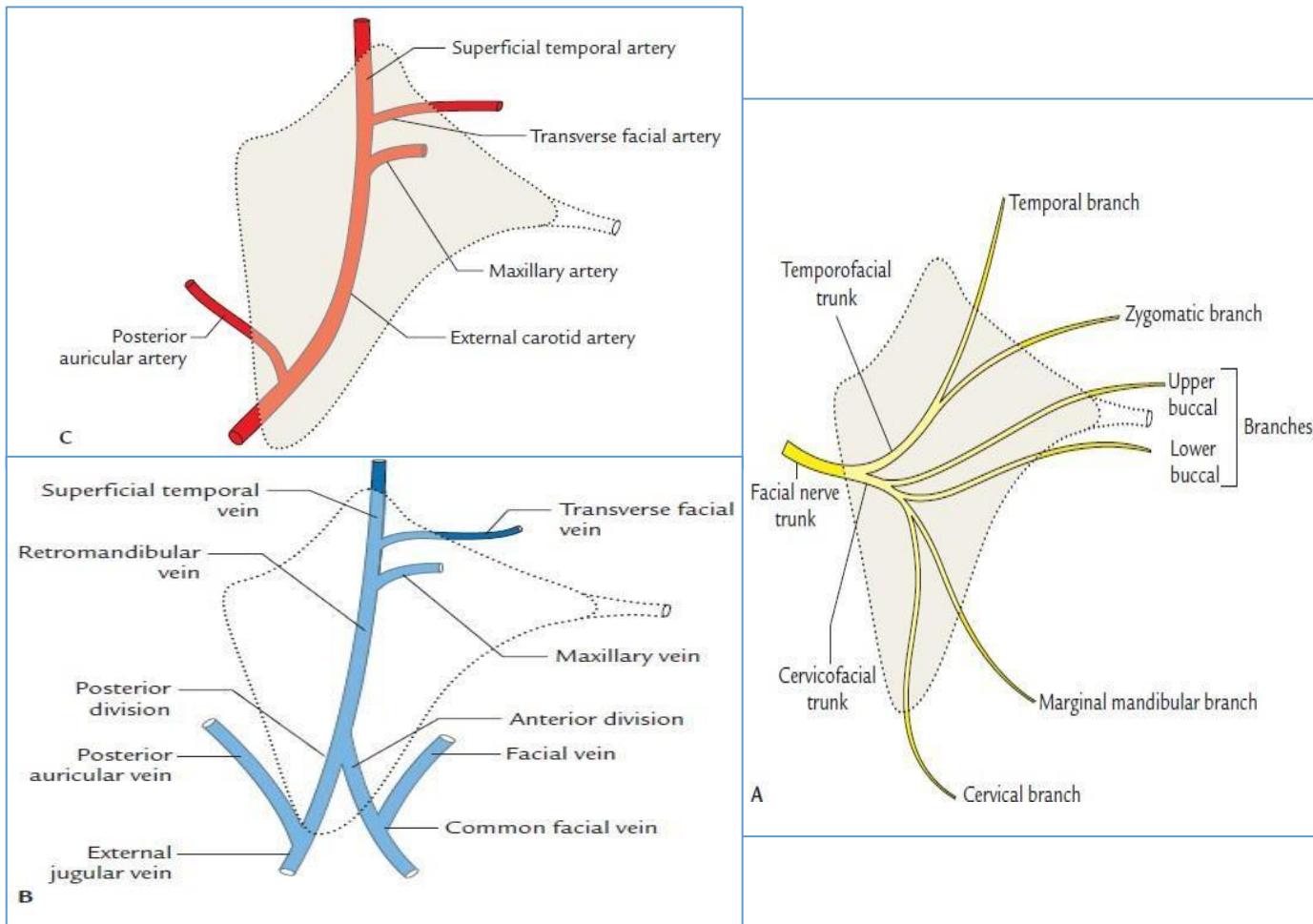
• Temporal	Leaves the gland through its upper end
• Zygomatic • Buccal • Mandibular	leave the gland through its anterior border. One or more of these branches may be double.
• Cervical	Leaves the gland through its lower end

- 2- External carotid artery** enters the gland through its postero-medial surface and divides inside it into its **2** terminal branches: superficial temporal a. & maxillary a.

- The superficial temporal artery leaves the gland through its upper end.
- The maxillary artery leaves the gland through its antero-medial surface.



- 3- The retromandibular vein:** formed inside the gland by union of:
- Superficial temporal vein** enters the gland through its upper end.
 - Maxillary vein:** enters the gland through its anteromedial surface. Within the gland, the retromandibular vein divides into anterior & posterior divisions which leave the gland through its lower end.
- 4- Auriculo-temporal nerve** enters the gland through its anteromedial surface and leaves it through its upper end.



The accessory parts of the parotid gland:

- 1- The anterior border of the gland extends forwards above the parotid duct superficial to masseter muscle. This part may be separated from the main part of the gland to form **the accessory parotid gland**.
- 2- The upper part of gland may extend behind **temporomandibular joint to enter the mandibular fossa**. So, patient with mumps feels severe pain during mastication.

Blood supply of parotid gland: **Arterial:** receives branches from external carotid a. & its terminal branches. **Veins:** drain into the retromandibular vein.

Lymph drainage: lymph vessels from the parotid gland drain into the parotid lymph nodes which in turn drain into the upper deep cervical lymph nodes.

Nerve supply of the parotid gland:

1- **Sensory**: from the auriculo-temporal nerve.

2- **Sympathetic**: from the plexus around the external carotid artery.

3- **Parasympathetic (Very important)**:

- a) Preganglionic parasympathetic fibres arise from the inferior salivary nucleus in the medulla oblongata and pass with the glossopharyngeal nerve.
- b) passes in the jugular foramen the glossopharyngeal nerve gives its tympanic branch which enters the middle ear to supply its mucosa and gives the lesser petrosal nerve.
- c) The lesser petrosal nerve leaves the middle ear cavity and passes through foramen ovale. It enters the infra-temporal fossa to relay in the otic ganglion.
- d) Postganglionic parasympathetic fibres arise from the otic ganglion and pass with the **auriculo-temporal nerve** (branch from the posterior division of mandibular nerve) to reach to and supply the parotid gland.

- **Clinically:**

- Tumor in the parotid gland may compress the facial nerve causing unilateral facial paralysis.
- The terminal branches of facial nerve run horizontally in the parotid gland. So surgical incisions must be done transverse to avoid injury of these branches.
- The parotid duct is relatively superficial. It may be damaged in face injuries.

Anatomy of pharynx

- It is a musculo-membranous tube which acts as passage for air and food.
- It begins at the pharyngeal tubercle at base of the skull and ends at the level of C6 where it continues with the oesophagus. It is 3.5 cm wide at its beginning and 1.5 cm at its end, so it is wider above than below.
- **Divisions:** as it descends it lies behind the nose, the mouth and the larynx and opens into each of these three parts.
- **It is formed from three parts:**
 - 1- **Nasopharynx:** lies behind the nose
 - 2- **Oropharynx:** lies behind the mouth and opens into it by oropharyngeal isthmus.
 - 3- **Laryngo-pharynx** lies behind the larynx and opens into it by the laryngeal inlet.

Anatomy of Oropharynx:

Extension: It lies behind the oral cavity and extends from the level of the soft palate down to the level of the upper end of the epiglottis.

Communications:

Anteriorly, with the mouth cavity via the oropharyngeal isthmus.

Inferiorly, continues with the laryngopharynx

Features:

- A. **Anteriorly:** (i) posterior 1/3 of the tongue containing lingual tonsil.
(ii) upper free end of epiglottis.
(iii) median and two lateral (Rt & Lt) gloss-epiglottic folds with epiglottic vallecula in between.
- B. **Posteriorly:** body of C2 vertebra and upper part of the body of C3 vertebra.
 - **Laterally:** **palatine tonsils.** one on either side. It is located into a triangular fossa (**tonsillar fossa**) bounded anteriorly by palatoglossal arch and posteriorly by palatopharyngeal arch.

Palatine tonsils: two masses of lymphoid tissue, one on either side. It reaches its normal maximum size in early childhood. It gradually atrophies after puberty. It is located into a triangular fossa (**tonsillar fossa**). The fossa bounded by:

- **Anteriorly** by palatoglossal arch (runs downwards and forwards from palate to the lateral margin of the tongue).

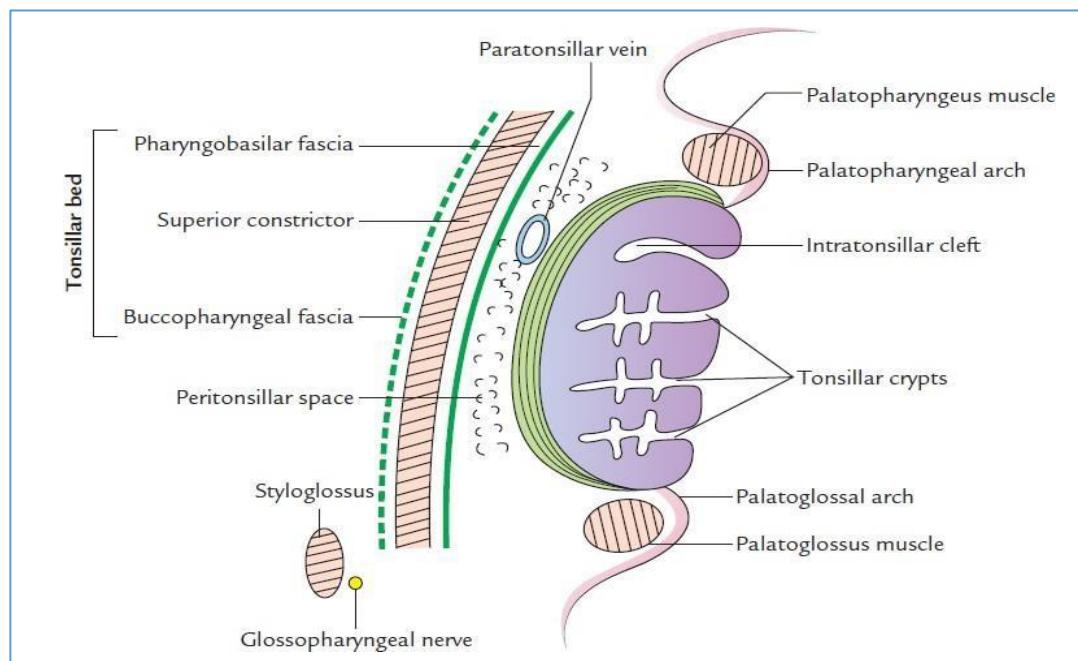
- **Posteriorly** by palatopharyngeal arch (runs downwards and backwards to the pharyngeal wall where it fades out).
- **Superiorly:** the soft palate.
- **Inferiorly:** the posterior third of the tongue.
- **Laterally:** *An incomplete fibrous capsule* surrounds its lateral surface. This layer allows the surgeon to decorticate the tonsil from its bed during tonsillectomy. Paratonsillar (external palatine) vein lies in this layer: *Injury of this vein during the tonsillectomy leads to severe bleeding.*

Blood supply

- 1- Tonsillar and ascending palatine branches of facial artery.
- 2- Twigs from the ascending pharyngeal artery.
- 3- Twigs from the greater palatine artery (branch from the 3rd part of maxillary artery).
- 4- Twigs from the dorsalis lingual arteries.

Lymph drainage: End in the upper deep cervical lymph nodes especially ***the jugulodigastric*** lymph nodes.

Waldeyer's Ring: Circum-pharyngeal ring of mucosa-associated lymphoid tissue that surrounds the openings into the digestive and respiratory tracts. It is made up anteroinferior by the lingual tonsil, laterally by the palatine tonsils, and poster superiorly by the pharyngeal tonsil



Chapter II: Abdominal Wall

Anatomy of Anterior abdominal wall

Superficial fascia: It is a layer of variable amount of fat. Below the level of the umbilicus, it is divided into 2 layers, superficial fatty layer, and deep membranous layer.

- The deep membranous layer: **called Scarpa's fascia** has the following characters:
 - 1- firmly attached to fascia lata (deep fascia of thigh) along a line parallel to the inguinal lig.
 - 2- Continues with **Colle's fascia** (membranous layer of perineal superficial fascia).

The linea alba (linea= line, alba= white or bloodless):

It is a fibrous cord in the median plane of the anterior abdominal wall. It extends from the xiphoid process to the upper border of the symphysis pubis. It is formed by interlacing of the aponeurosis of the 3 muscles of lateral abdominal wall. It is wider above the umbilicus than below it.

The umbilicus: a fibrous structure situated slightly below the middle of the linea alba. It is variable in position.

- a- In children it is lower due to incomplete development of the pelvis.
- b- In adults it lies at level of the highest point of iliac crest opposite the (L3/ L4 disc).

Layers of anterior abdominal wall:

- | | |
|-----------------------------|----------------------------------|
| 1- Skin. | 3- Muscles. |
| 2- Superficial fascia: | 4- Fascia transversalis. |
| a. Superficial fatty layer. | 5- Extraperitoneal fatty tissue. |
| b. Deep membranous layer. | 6- Parietal peritoneum. |

Muscles of anterior abdominal wall

- These are divided into two groups:
 - A) Muscles of the anterolateral part of the anterior abdominal wall: (**see practical**)

1- External abdominal oblique.	3- Transverses abdominis.
2- Internal abdominal oblique.	
 - B) Muscles of the medial part of the anterior abdominal wall: (**see practical**)

4- Rectus abdominis.	
5- Pyramidalis.	

The rectus sheath:

- It is an envelope which surrounds the rectus abdominis muscle.
- It is formed by the aponeurosis of the three muscles of the lateral abdominal wall.
- The sheath is divided by two lines into three parts.
 - o The first line lies at the level of the costal margin.
 - o The second line lies midway between the umbilicus and the symphysis pubis.

- **Structure of each part of the sheath:**

1. First part: it lies above the line at level of the costal cartilage:

- a- Anteriorly: aponeurosis of the external abdominal oblique.
- b- Posteriorly: 5th, 6th, and 7th costal cartilages.

2. Second part: it lies between the two lines:

- a- Anteriorly: aponeurosis of the external abdominal oblique and the anterior lamellae of the aponeurosis of the internal abdominal oblique muscle.
- b- Posteriorly: the posterior lamellae of the aponeurosis of the internal abdominal oblique muscle, and the transverses abdominis muscle and the fascia transversalis.

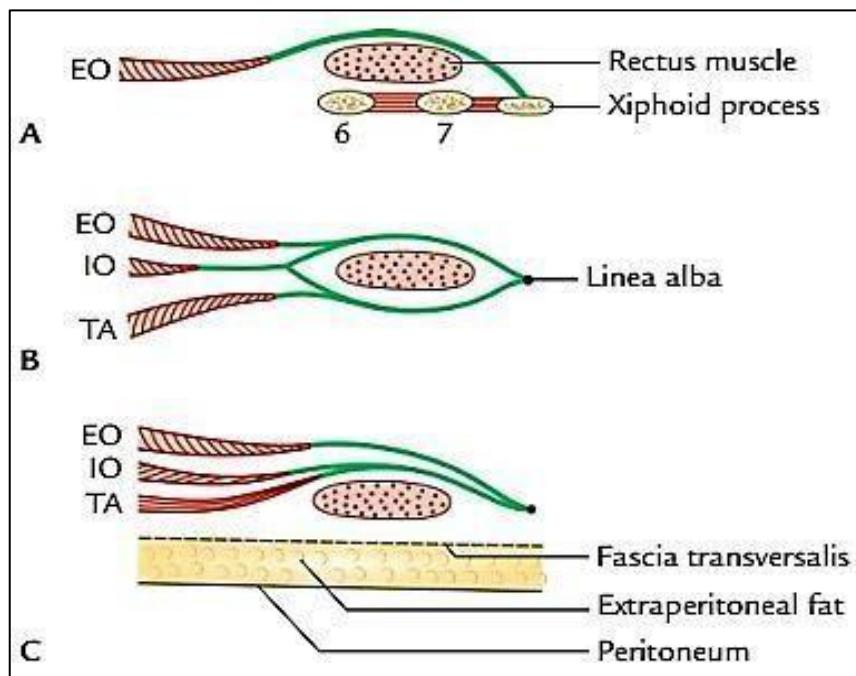
3. Third part: it lies below the second line:

- a- Anteriorly: the aponeurosis of the external abdominal, the internal abdominal and the transverses abdominis.
- b- Posteriorly: the posterior wall of the sheath is deficient and is formed by the fascia transversalis only.

The posterior wall of the rectus sheath ends at the second line in a curved line concave downwards called arcuate line.

- **Contents of the rectus sheath:**

- 1- Two muscles: Rectus abdominis and Pyramidalis.
- 2- Two vessels: Superior epigastric vessels and Inferior epigastric vessels.
- 3- Lower five intercostal and subcostal nerves and vessels.



Rectus sheath at 3 levels: A, above costal margin; B, between costal margin & arcuate line; C, below arcuate line (EO = external oblique, IO = internal oblique, TA = transversus abdominis)

Inguinal ligament: The aponeurosis of the external abdominal oblique between the pubic tubercle and the anterior superior iliac spine (ASIS). It's free (has no attachment) and is folded upwards and backwards on itself to form the inguinal ligament.

- **The lower aspect** of the ligament is round.
- **Its upper aspect** presents a groove which forms the floor of inguinal canal.
- **Lacunar Ligament:** the deep fibres from the medial end of inguinal ligament curve horizontally backward to the medial part of the pecten pubis forming lacunar ligament.
 - It is triangular.
 - ✓ **Apex:** attached to the pubic tubercle.
 - ✓ **Lateral edge:** sharp and forms the medial boundary of the femoral canal.
- **Reflected Part of Inguinal Ligament:** The superficial fibres from the medial end of the inguinal ligament expand upward and medially to form this ligament. It lies behind the superficial inguinal ring and in front of the conjoint tendon.
- **Mid-inguinal point:** It is a point on the inguinal ligament midway between the symphysis pubis and the ASIS. The femoral a. passes deep to this point.

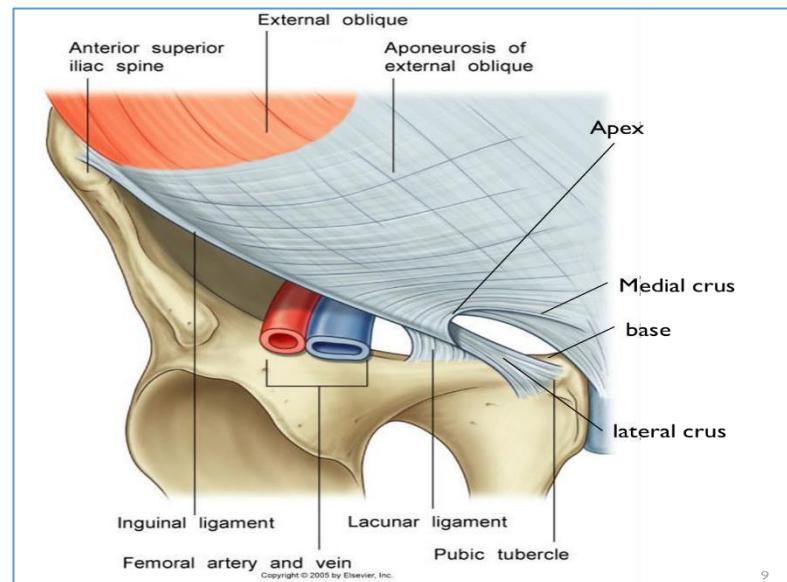
Mid-point of the inguinal ligament: It is a point on the inguinal ligament midway between the pubic tubercle & ASIS. It lies $\frac{1}{2}$ inch lateral to the mid-inguinal point.

Fascia transversalis:

- This is a layer of deep fascia which lines the deep surface of the transversus abdominis muscle. It is separated from the parietal peritoneum by extra-peritoneal fatty tissue.

Superficial inguinal ring:

- It is a \blacktriangle opening in the aponeurosis of external abdominal oblique muscle. It lies immediately above & lateral to the pubic tubercle. It has an apex, base & 2 crura; medial & lateral.
 - Apex: directed upwards & laterally.
 - Base: formed by pubic crest.
- Structures passing through ring:
 1. The spermatic cord in males or the round ligament of uterus in females.
 2. The ilioinguinal nerve in both sexes.

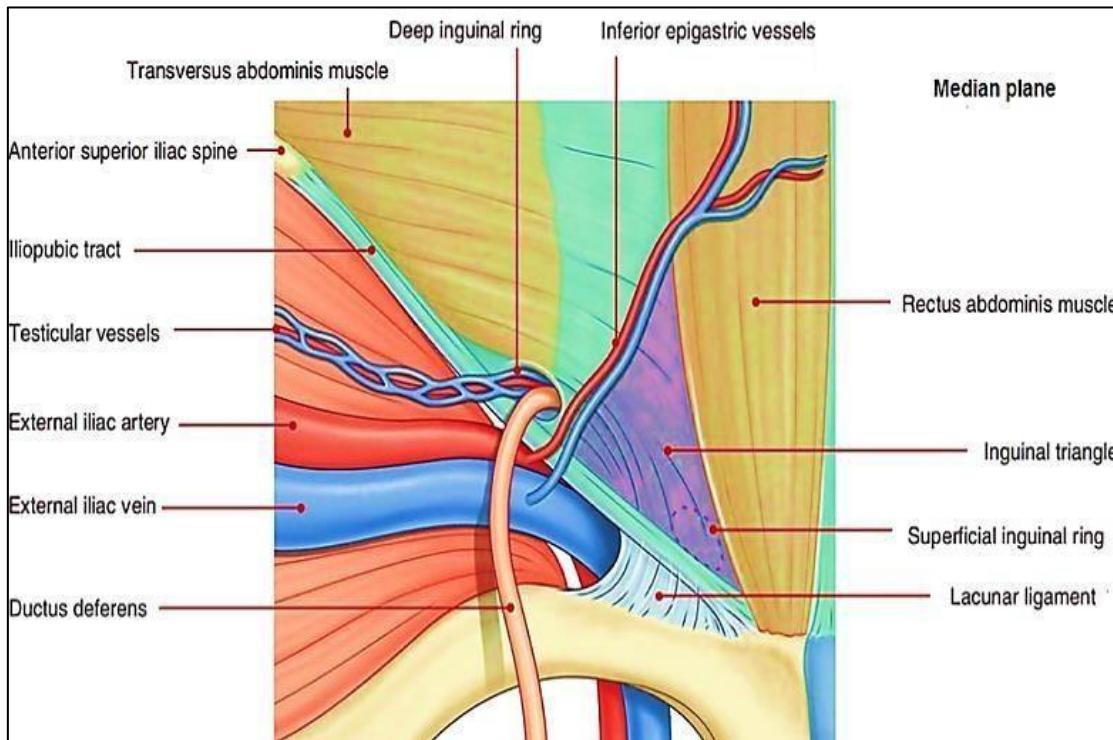


Superficial inguinal ring

The deep inguinal ring: a rounded opening in the fascia transversalis lying half an inch above the mid-inguinal point.

It has very important relations:

- 1- The external iliac a. descends behind fascia transversalis. Just below the ring the external iliac a. gives 2 branches:
 - a. Inferior epigastric a. ascends upwards and medially behind fascia transversalis to enter the rectus sheath in front of the arcuate line. Just after its origin it gives a small but important branch called cremasteric a. which re-enters the ring to continue into inguinal canal.
 - b. Deep circumflex iliac a. ascends upwards & laterally up to anterior superior iliac spine.



Deep inguinal ring

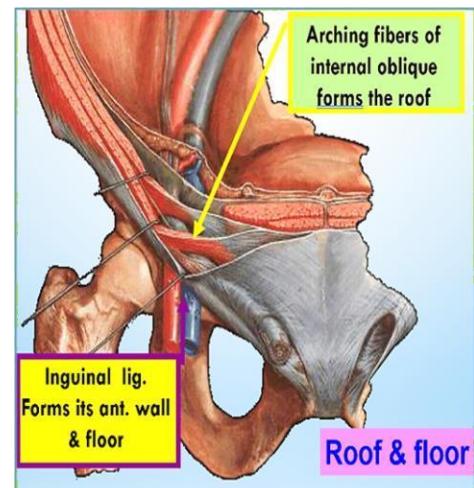
The inguinal canal

Definition: Oblique intermuscular passage about 4 cm long lying above the medial ½ of inguinal lig.

Extent and direction: extend from deep inguinal ring to the superficial inguinal ring. It is directed downward, forward, and medially. On the body surface, the canal is marked by **2** parallel lines (1 cm apart and 4 cm long) just above the medial ½ of inguinal lig.

The boundaries of the inguinal canal:

- **Anterior wall:** It is formed from superficial to deep by:
 - (a) Skin
 - (b) Superficial fascia in the whole extent.
 - (c) External oblique aponeurosis.
 - (d) internal oblique muscle fibers, in lat. 1/3.



Roof & floor of inguinal canal.

- **Posterior wall:** It is formed from deep to superficial by:
 - (a) Fascia transversalis, in the whole extent
 - (b) Conjoint tendon, in medial 2/3
 - (c) Reflected part of the inguinal ligament, in medial most part.
- **Roof:** It is formed by the lower arched fibers of internal oblique and transversus abdominis muscles.
- **Floor:** It is formed by: (a) Grooved upper surface of the inguinal ligament in the whole extent (b) Abdominal surface of the lacunar ligament at the medial end.

Contents: In male: spermatic cord and ilioinguinal nerve. **In female:** round ligament of the uterus and ilioinguinal nerve.

Inguinal triangle (Hasselbach's Triangle):

Boundaries:

- Medially: Rectus abdominis.
- Laterally: Inf.epigastric vessels.
- Inferiorly: Inguinal lig.

Inguinal Hernia

Definition: A protrusion of abdominal viscera (e.g., loops of intestine) into the inguinal canal. Clinically it presents as a pear-shaped swelling above and medial to pubic tubercle, above the inguinal ligament.

Types of inguinal hernias:

	Indirect inguinal hernia	Direct inguinal hernia
incidence	<ul style="list-style-type: none"> • Common in children & young adults. • More often in males > females. • commoner > direct inguinal hernia 	It is common in elderly due to weak abdominal muscles.
Course	It occurs if the hernial sac enters the inguinal canal through the deep inguinal ring, lateral to the inferior epigastric artery.	It occurs if the hernial sac enters the inguinal canal directly by pushing the posterior wall of the inguinal canal forward, medial to inferior epigastric artery through the Hasselbach's triangle.

Types	<p>The indirect inguinal hernia may be congenital or acquired</p> <p>a) Congenital indirect inguinal hernia: It occurs due to patent processus vaginalis.</p> <p>b) Acquired indirect inguinal hernia: It occurs due to increased intra-abdominal pressure as during weightlifting.</p>	<p>It is of two types:</p> <ul style="list-style-type: none"> a) Lateral direct inguinal hernia. b) Medial direct inguinal hernia.
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Complications of hernia: 1. Pain. 2. Obstruction. 3. Bowel necrosis. 4. Perforation.

The inguinal hernia must be differentiated from the femoral hernia:

	Inguinal hernia	Femoral hernia
Incidence	More common in males	More common in females
	Occurs in young age	in middle and old age
Site of protrusion of hernial sac	<ul style="list-style-type: none"> Deep inguinal ring (in oblique hernia) Through inguinal ▲ (in direct hernia) 	Through the femoral ring
Descent of hernia	Into inguinal canal	Into femoral canal
Site of the hernial sac	Lies above and medial to pubic tubercle	Lies below and lateral to the pubic tubercle

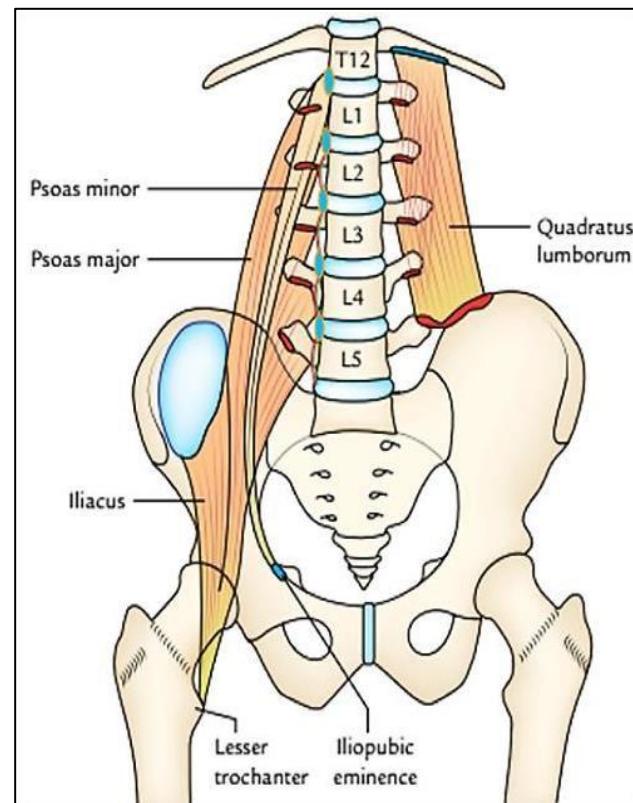
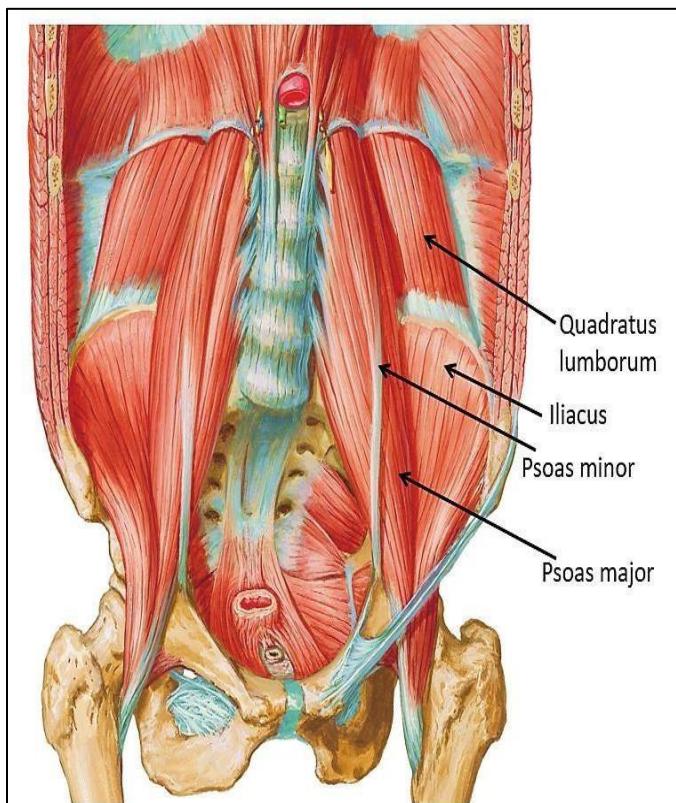
Anatomy of Posterior Abdominal Wall

The posterior abdominal wall extends from the 12th rib above to the pelvic brim below. It is strong and stable because it is constructed by bones, muscles, and fasciae. It supports retroperitoneal organs, vessels, and nerves.

The posterior abdominal wall is constructed as follows:

1. Bony part: In the median plane, it is made up by lumbar vertebrae & intervertebral discs. Laterally it is made up by iliac crest, iliac fossa, and inner surfaces of the 12th rib.
2. Muscular part: Above the iliac crest, from medial to lateral sides, it is made up of psoas major, quadratus lumborum, and transversus abdominis muscles. Below the iliac crest on either side of the lumbar vertebral column from *medial to lateral sides*, it is made up of psoas major and iliocaudis muscles.

Muscles of the posterior abdominal wall: Three muscles psoas major, iliocaudis, and quadratus lumborum, on each side of the vertebral column form most of the posterior abdominal wall.



Origin and insertion of the psoas major, psoas minor, iliocaudis, and quadratus lumborum muscles.

Psoas Major

Origin: The muscle arises from 14 fleshy slips that are as follows:

1. five slips from intervertebral discs between T12–L5 vertebrae and adjoining margins of the bodies of these vertebrae.
2. Five slips from anterior surfaces & lower borders of transverse process of L1-5.
3. Four slips from tendinous arches bridging the constricted sides of the bodies of lumbar vertebrae. The lumbar vessels pass deep to these arches.

Insertion: From the site of origin, the muscle descends along the pelvic brim and enters the thigh behind the inguinal ligament and inserted into the anterior surface of the tip of the lesser trochanter of the femur.

Nerve Supply: by direct branches from ventral rami of L2, L3, L4 spinal nerves.

Actions: These are as follows:

1. Acting from above, it is the chief flexor of the thigh at the hip joint.
2. Acting from below, it flexes the trunk on the thigh, as in raising the trunk from recumbent to sitting position.

Psoas minor:

This muscle is present in about 50% individuals. When present, it runs downward in front of psoas major.

Origin: It arises from the side of the intervertebral disc between T12 and L1 vertebrae and adjoining parts of their bodies.

Insertion: From the site of origin, the muscle runs in front of the psoas major and ends in a long flat tendon, which is inserted into the iliopubic eminence.

Nerve Supply: It is by a branch of L1 spinal nerve.

Action: It is a weak flexor of the trunk.

Iliacus

It is a fan-shaped muscle and forms the lateral component of the iliopsoas muscle.

Origin: It arises from the upper two thirds of the floor of iliac fossa, inner lip of iliac crest and upper surface of the lateral part of the sacrum.

Insertion: The fibres converge on and fuse with the lower part of the psoas major medially and inserted with it on the anterior surface of lesser trochanter of the femur and an area (2.5 cm long) below it.

Nerve Supply: It is by the femoral nerve.

Actions: with psoas major, it causes flexion of thigh & lumbar part of vertebral column.

Quadratus Lumborum

Origin: It arises from:

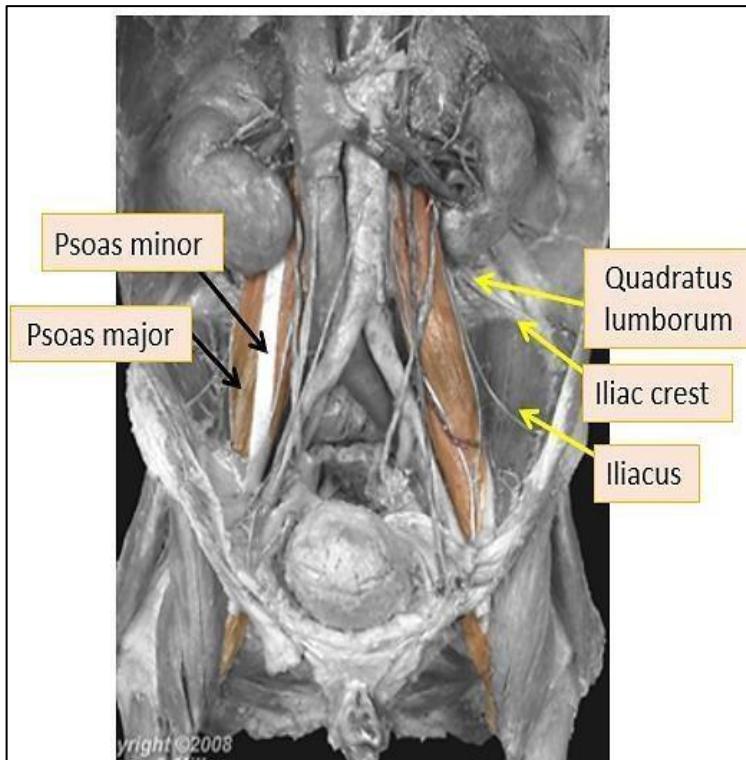
- (a) Posterior one-third of the inner lip of the iliac crest and Iliolumbar ligament.
- (b) Lower two to four transverse processes of lumbar vertebrae.

Insertion: The muscles run upward and medially pass posterior to the lateral arcuate ligament to be inserted into the medial part of the anterior surface of the 12th rib. It is also inserted into upper lumbar transverse processes, post. to its slips of origin.

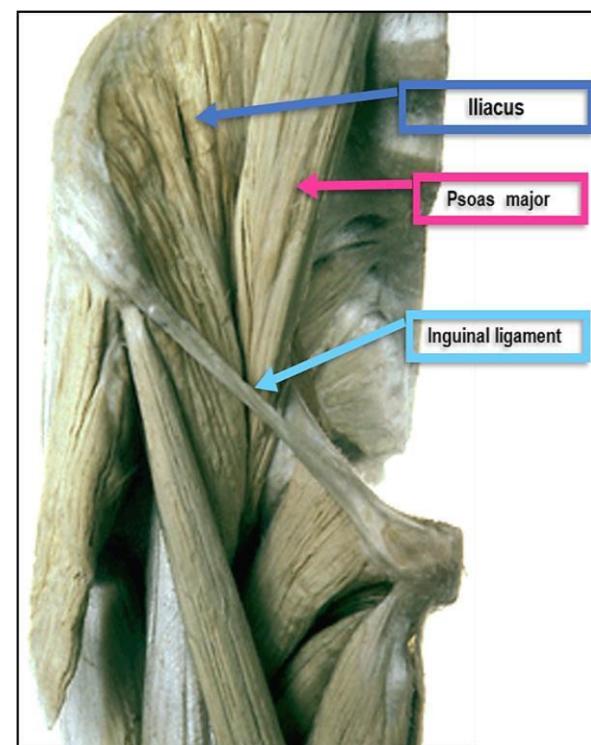
Nerve Supply: It is by ventral rami of T12–L3/L4 lumbar spinal nerves.

Actions: These are as follows:

1. it is a lateral flexor of the lumbar vertebral column.
2. It fixes the 12th rib during inspiration for effective contraction of the diaphragm.
3. Muscles of both sides acting together extend the lumbar vertebral column.



Posterior abdominal wall muscles (real anatomy)



Relation of iliocostalis & psoas major muscles to inguinal lig.

Chapter III: Esophagus and Stomach

Abdominal cavity

The abdominal cavity is divided into nine regions by four imaginary planes (2 vertical & 2 horizontal) on ant. abdominal wall.

1. Superior horizontal plane (transpyloric plane):

(transpyloric plane): It is placed midway between the suprasternal notch and the pubic symphysis. It lies at the level of lower border of L1 vertebra and cuts costal margin at 9th costal cartilages.

N.B. the subcostal plane is used in preference to the transpyloric plane. This is drawn through the lowest parts of the costal margins at the 10th costal cartilages and lies at the level of the body of L3 vertebra.

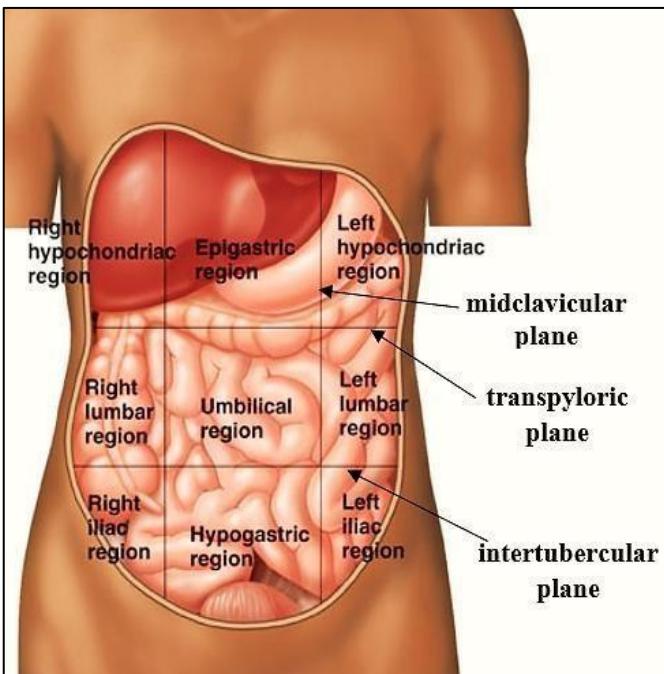
2. Inf. horizontal plane (intertubercular plane):

(intertubercular plane): It is drawn at the level of tubercles of the iliac crests. It lies at the level of upper border of L5 vertebra.

3. Rt. & Lt. vertical planes (midclavicular planes): from the midpoint of the clavicle to the mid-inguinal point (a point midway between anterior superior iliac spine & symphysis pubis).

Nine regions marked out are arranged into three horizontal zones of abdomen: upper, middle, and lower. They are arranged from right to left

- In upper abdomen (**Rt. hypochondrium, epigastric region & Lt. hypochondrium**).
- In the middle abdomen (**Rt. lumbar region, umbilical region & Lt. lumbar region**).
- In the lower abdomen (**right iliac fossa, hypogastric region, and left iliac fossa**).



Planes and regions of abdominal cavity.

Anatomy of Peritoneum

Definition: is a large thin serous membrane, which lines the interior of the abdominopelvic cavity. It forms the largest serous sac of the body.

The invaginations by the organs have different forms:

- Some organs invaginate the peritoneum and develop a peritoneal fold connecting them with the posterior abdominal wall. These organs become covered completely by peritoneum except at the line of attachment to the peritoneal fold.
- Other organs invaginate the peritoneal sac to a lesser degree and become covered by peritoneum on the front and sides only.
- Some other organs don't invaginate the peritoneal sac and covered by the peritoneum anteriorly only e.g., the duodenum.

Due to the invagination of the peritoneal sac by the organs and formation of peritoneal folds and the ligaments the peritoneal sac is divided into two sacs; greater and lesser sac, completely separated from each other except at an opening called **epiploic foramen (of Winslow)** or opening into lesser sac.

- Layers of the peritoneal sac:

The peritoneum covering the organs is called visceral peritoneum, and that which lines the abdominal wall is called parietal peritoneum. The 2 layers are separated from each other by a potential space called the peritoneal sac which contains a film of serous fluid called the peritoneal fluid. The peritoneum is a completely closed sac except the opening of the uterine tube in female.

- Folds of the peritoneum:** These folds stretch between the organs covered by peritoneum and the abdominal wall or other organs. They function to allow free mobility of the included organs. These folds have different names according to the organ included as omentum, ligament or mesocolon but the structure is the same. As a role each peritoneal ligament irrespective to its name is formed from two layers except the greater omentum as it is reflected on itself hence formed of 4 layers:

A- Peritoneal folds:

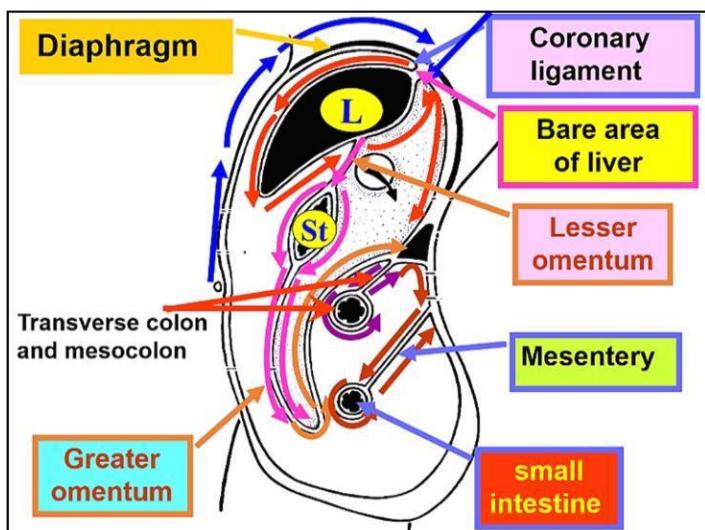
1. **Omenta:** Lesser & Greater omentum.

B- Mesenteries:

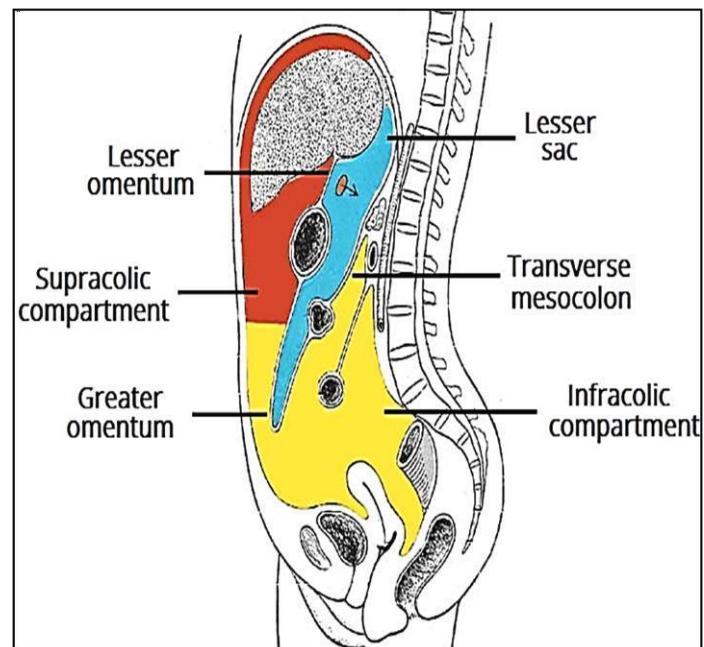
1. Mesentery of small intestine.
2. Transverse mesocolon.
3. Pelvic (sigmoid) mesocolon.

C- Ligaments:

1. Falciform ligament.
2. Gastroplenic ligament.
3. Gastrophrenic ligament.
4. Phrenicocolic ligament.
5. Lienorenal ligament.



Peritoneal folds.



Subdivisions of Peritoneal Cavity.

Lesser omentum: stretched between the lesser curvature of the stomach and the margins of the porta hepatis of the liver. Its right border is free and forms the anterior boundary of the opening into the lesser sac.

Greater omentum: stretched between the greater curvature of the stomach and the transverse colon. It is formed by the peritoneum covering the anterior and the posterior surfaces of the stomach. The 2 layers descend in the abdominal cavity till the pelvis acting as a rope to protect the abdominal organs then reflected backwards and upwards forming posterior two layers up to the anterior border of the pancreas where they diverge. The ant. one ascends on the ant. surface of pancreas & the post. passes on its inferior surface.

Subdivisions of the peritoneal cavity:

- The peritoneal cavity is a completely closed sac subdivided in lesser and greater sacs, which communicate together through the epiploic foramen.
- **The lesser sac**, or omental bursa, is situated behind the stomach & lesser omentum.

Contents of the right free border of lesser omentum:

- Portal v. (posteriorly).
- Hepatic a. (in front of portal v. and to the left of common bile duct).
- The common bile duct (in front of portal v. & to the right of hepatic a.).

Epiploic foramen (of Winslow) is a short, vertical slit in the upper part of the right border of the lesser sac .

- It leads into the greater sac.
- It is 3 cm in height in adults.

Boundaries:

- Anterior: The thickened right edge of the lesser omentum.
- Posterior: The peritoneum covering the I.V.C.
- Above: caudate lobe of liver.
- Below: 1st inch of 1st part of duodenum.

Anatomy of oesophagus

- It is a muscular tube 25 cm long 2cm wide.
- **Begin:** at the level of **C6** as a continuation of the pharynx.
- **End:** ends at the cardiac end of the stomach at level of **T11** corresponding to xiphoid process of sternum.
- It has a slight sinuous course but mostly lies in the midline. It starts in the **midline** then inclines to the **left** as far as the root of the neck then gradually returns to the **midline** then deviates to the **left** again to reach its opening in the diaphragm.

Parts of the oesophagus: it has 3 parts:

- a- **Cervical part (in the neck):** the most upper part in lower part of the neck.
- b- **Thoracic part (in the thorax):** it descends anterior to the vertebral column through the sup. & Post. mediastina until reaching oesophageal opening of diaphragm (one inch to the left of the median plane at the level of **T10**).
- c- **Abdominal part (in the abdomen):** It is very short (1–2.5 cm in length) and ends in the cardiac end of stomach. It lies behind the oesophageal groove of the lt. lobe of liver.

Oesophageal constrictions (see practical):

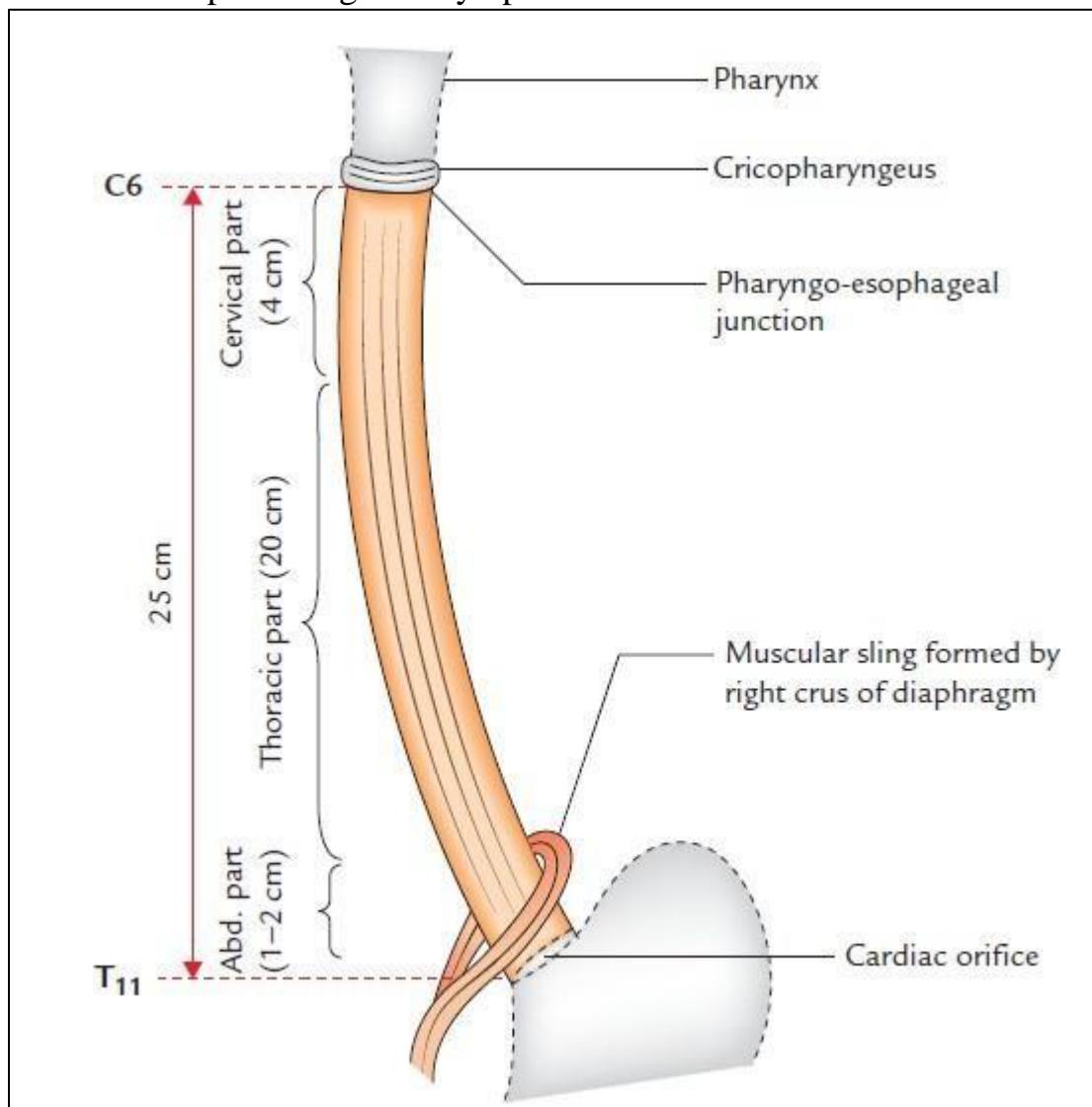
1st constriction (upper oesophageal sphincter)	<ul style="list-style-type: none"> • at the beginning point. It is the 2nd narrowest point of alimentary tract (the narrowest is the veriform appendix). • It is located 15 cm after maxillary central incisor teeth. • corresponds to body of 6th cervical vertebra
2nd constriction	<ul style="list-style-type: none"> • It is made by aortic arch & corresponds to T4. • It is located 22.5 cm after maxillary central incisor teeth.
3rd constriction	<ul style="list-style-type: none"> • located at crossing point of oesophagus & lt. main bronchium. • located at level of T5. It is 27.5 cm after maxillary central incisor teeth
4th constriction (lower oesophageal sphincter)	<ul style="list-style-type: none"> • made by oesophageal opening in the right crus of diaphragm. • located at level of T11. It is 40 cm after maxillary incisor teeth • It is a physiological sphincter mechanism made by muscle fibers of right crus of diaphragm

Blood supply:

- 1- Cervical part: the inferior thyroid artery & vein.
- 2- Thoracic part: from descending aorta and drains into azygos & hemiazygos veins.
- 3- Abdominal part: the left gastric artery & vein.

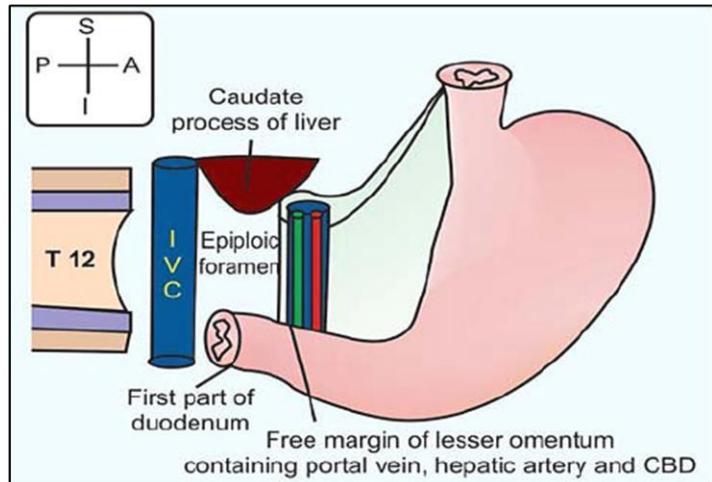
Lymphatic drainage: lymph vessels from the oesophagus drain into the following L.N:

- 1- Cervical part: paratracheal and the lower deep cervical lymph nodes.
- 2- Thoracic part: posterior mediastinal lymph nodes.
- 3- Abdominal part: left gastric lymph nodes



Anatomy of stomach

- It is most dilated part of the gut.
- Shape: the stomach is J-shaped.
- It lies in the upper part of the left side of the abdominal cavity in the epigastrium, umbilical region & left hypochondrium.
- **It has:**
 1. Two openings; cardiac and pyloric,
 2. Two curvatures; lesser and greater
 3. Two surfaces; anterior and posterior.



Boundaries of epiploic foramen and contents of the right free border of lesser omentum.

Openings:

- 1- **Cardiac opening:** connects the stomach with oesophagus. It lies one inch to the left of the median plane, at the level of the 11th thoracic vertebra, opposite the left 7th costal cartilage, four inches deep to the anterior abdominal wall.
- 2- **Pyloric opening:** connects the stomach with the duodenum. It lies one inch to the right of the median plane, at the level of L1 (transpyloric plane).

Curvatures:

- 1- Lesser curvature: begins at the right border of the cardiac orifice. It is concave to the right side. Near its pyloric end, it has a notch called angular notch or incisura angularis. It gives attachment to the lesser omentum. The right and left gastric vessels run along it.
- 2- Greater curvature: begins at the left border of the cardiac orifice. At first it ascends upwards, backwards and to the left to form the fundus of the stomach, then it descends downwards forwards and to the right. It is convex to the left. Opposite the angular notch of the lesser curvature, it presents a dilatation or bulge. It gives attachment to three peritoneal ligaments:
 - a- The Gastrophrenic lig. attached to its upper part.
 - b- The gastrosplenic lig. attached to its middle part. The short gastric vessels run in this ligament.
 - c- The greater omentum attached to its lower part. The Lt. & Rt. gastroepiploic vessels run in it.

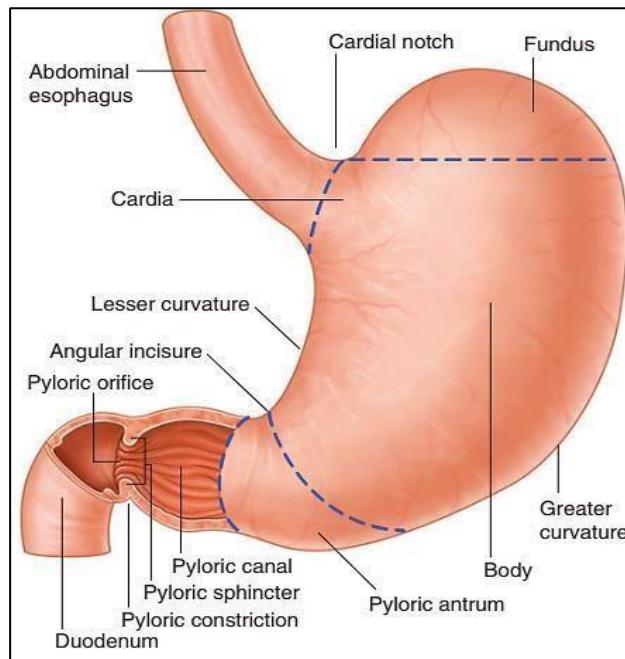
Parts of the stomach:

- It is divided by two lines into four parts.
The first line is drawn horizontally from the lower part of the left border of the cardiac orifice to the greater curvature. The second line is drawn from the angular notch of the lesser curvature to the beginning (left end) of the dilatation on the greater curvature.

- The parts are:

1. Fundus: above the first line.
2. Body: the part between the two lines.
3. Pylorus: the part distal to the second line. It is subdivided into:

- a. Pyloric antrum: the dilated left part of the pylorus.
- b. Pyloric canal: the narrow middle part.
- c. Pyloric sphincter: the junction of the stomach with the duodenum. It is characterized by presence of a constriction on its outer surface due to the presence of circular muscle fibers. The wall is thick compared to that of the stomach, other parts of the pylorus or the duodenum. Presence of the prepyloric vein (vein of Mayo): a small but constant vein which runs in front of the pylorus connecting the Rt. gastric v. with the Rt. gastroepiploic v.



Parts of the stomach

Peritoneal covering and ligaments of the stomach:

- The stomach is completely covered by peritoneum except a small area on its posterior surface near the cardiac orifice. This area called bare area of the stomach & related to the Lt. crus of the diaphragm.
- The peritoneum covering the anterior and the posterior surfaces of the stomach meet at the lesser curvature to form the lesser omentum. The two layers of peritoneum meet at the greater curvature to form greater omentum, gastrophrenic & gastrosplenic ligaments.

Surfaces:

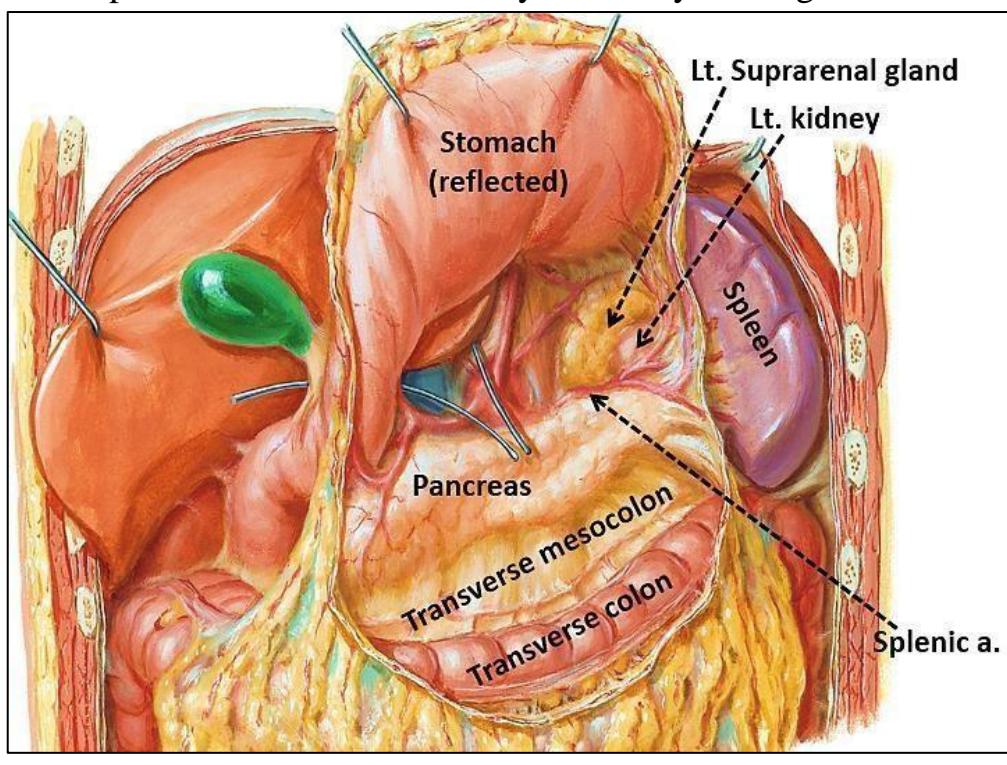
1- Anterior surface: It is directed antero-superiorly. It is related to:

- a. Lt. lobe of liver in front of the fundus.
- b. Anterior abdominal wall.
- c. Diaphragm separating the stomach from the left 6th to the left 9th ribs.
- d. Quadrate lobe of the liver related to the pylorus.
- e. The anterior surface of the stomach is separated from these structures by the cavity of the greater sac.

2- Posterior surface (stomach bed): directed postero-inferiorly and related to several structures known as stomach bed. These structures from below upwards are:

- a- Transverse colon and transverse mesocolon containing the middle colic vessels.
- b- Splenic artery running in a tortuous course along its upper border.
- c- Body of pancreas
- d- Front of left kidney
- e- Left suprarenal gland.
- f- Left crus of the diaphragm.
- g- The spleen.

The stomach is separated from these structures by the cavity of the lesser sac except the spleen which is separated from the stomach by the cavity of the greater sac.



Surface anatomy of the stomach:

1. Cardiac orifice: represented by two vertical lines one cm each drawn at the level of the 7th costal cartilage one inch below and to the left of the xiphio-sternal junction.
2. Pyloric orifice: represented by two horizontal lines one cm each drawn at the level of the transpyloric plane one inch to the right of the median plane.
3. Lesser curvature: represented by a line concave to the right side from the lower end of the right vertical line to upper horizontal line.
4. Greater curvature: represented by a line from the lower end of the left vertical line. At first this line passes upwards, backwards and to the left to reach the left 5th intercostal space at the midclavicular line to define the fundus. Then this line passes downwards, forwards and to the right to pass at the level of left 10th costal cartilage. Then it continues to join lower horizontal line. This line is convex downwards and to the left.

Blood supply of the stomach:

- Arterial:

1. Lt. gastric a.: branch from celiac trunk.
2. Right gastric a.: branch from hepatic a.
Both Rt. & Lt. gastric arteries anastomose with each other on the lesser curvature.
3. Short gastric arteries: these are six branches from the splenic artery. They pass in the gastrosplenic ligament to supply the fundus of the stomach.
4. Left gastroepiploic artery: branch from the splenic artery. It runs on the greater curvature
5. Right gastroepiploic artery: branch from the gastroduodenal artery branch of hepatic artery. It runs on the greater curvature of the stomach.

- Venous drainage:

the veins of the stomach accompany its arteries and they end either in the portal vein or one of its tributaries. These veins are:

1. Left and right gastric veins end in the portal vein.
2. Short gastric veins and the left gastroepiploic vein end in the splenic vein.
3. Right gastroepiploic vein ends in the superior mesenteric vein.

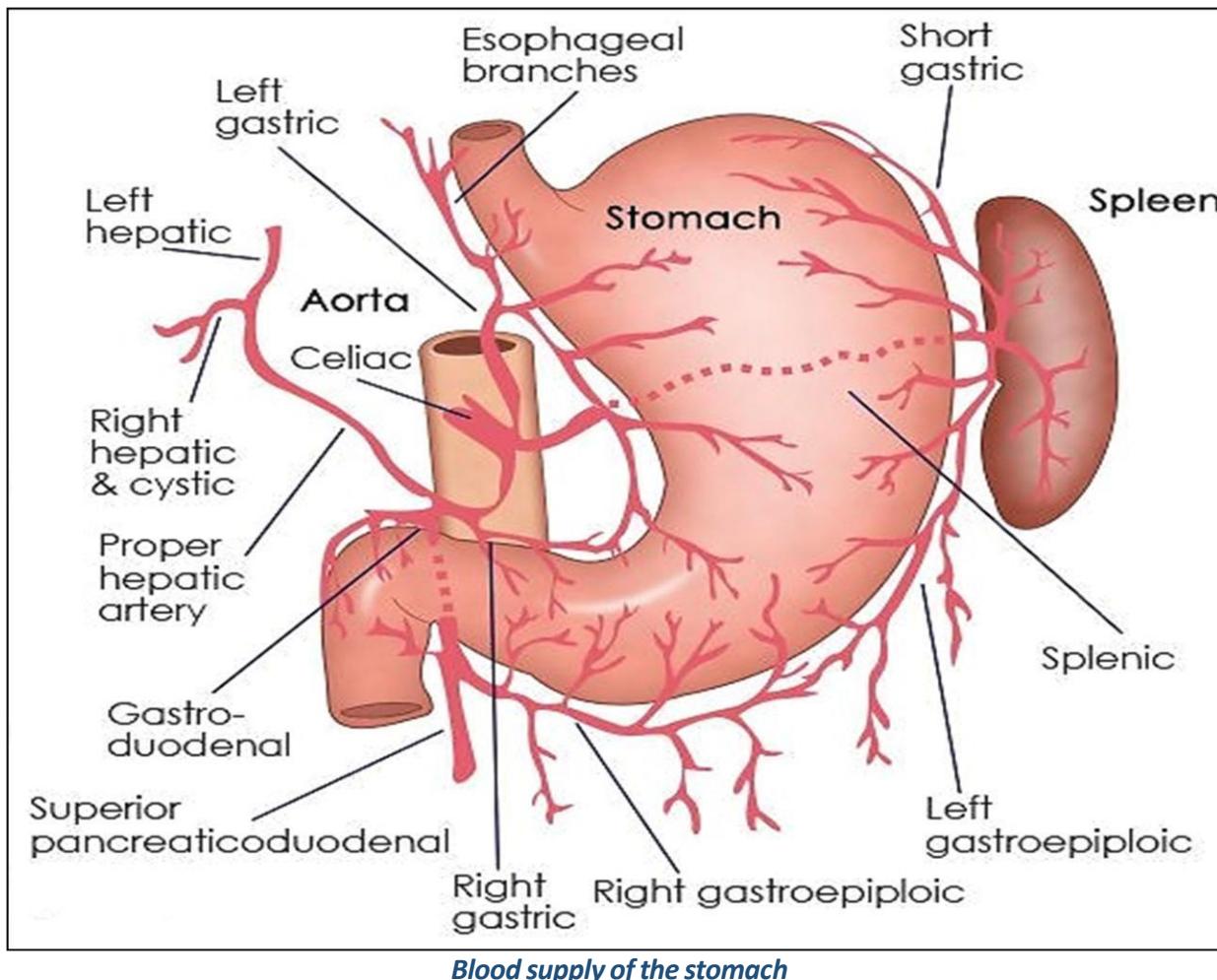
Nerve supply of the stomach:

- a) Sympathetic: from the celiac plexus around the celiac trunk.
- b) Parasympathetic: from both vagus nerves through the anterior & posterior gastric nerves.

Lymphatic drainage of the stomach: The lymph vessels of the stomach also accompany its arteries and they end in one of these lymph nodes groups:

1. Paracardial.
2. Left gastric.
3. Pyloric.
4. Hepatic.
5. Right gastroduodenal.
6. Pancreatico-splenic.

From these lymph nodes efferent vessels drain into the celiac group of lymph nodes



Chapter IV: Intestine and pancreas

Anatomy of duodenum

Is the widest, and most fixed part of small intestine.

Site: above the level of the umbilicus opposite to the L1, L2, L3 vertebrae.

Shape: it is C-shaped. Its concavity is directed upwards and to the left where it surrounds the head of the pancreas. It is formed from **4** parts:

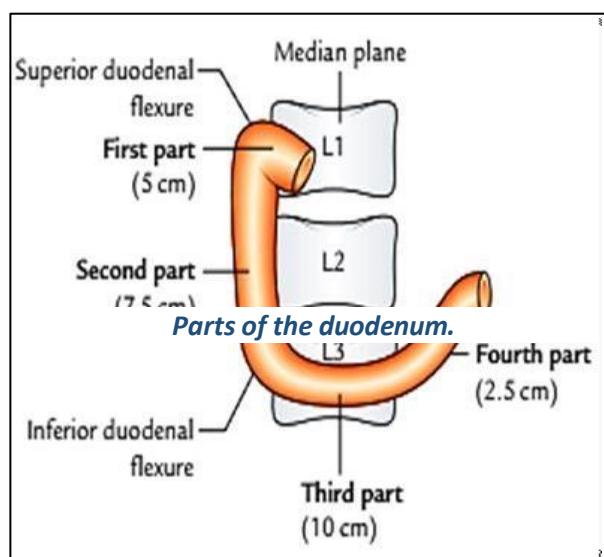
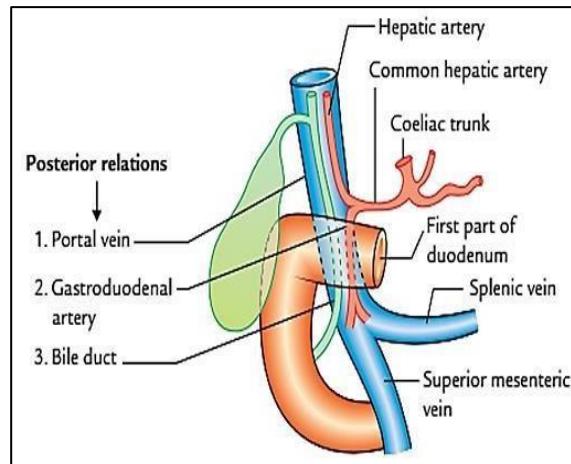
- **1st part:** passes horizontally to the right side at the level of transpyloric plane (L1).
- **2nd part:** It descends vertically from the level of (L1) to the level of (L3).
- **3rd part:** passes horizontally from the Rt. to Lt. at the level of subcostal plane (L3).
- **4th part:** It passes upwards and to the left from the level of L3 to end at level of L2 at duodenojejunal flexure.

Peritoneal covering: It is retroperitoneal

except for its beginning, which is connected to the liver by the hepatoduodenal ligament, a part of the lesser omentum.

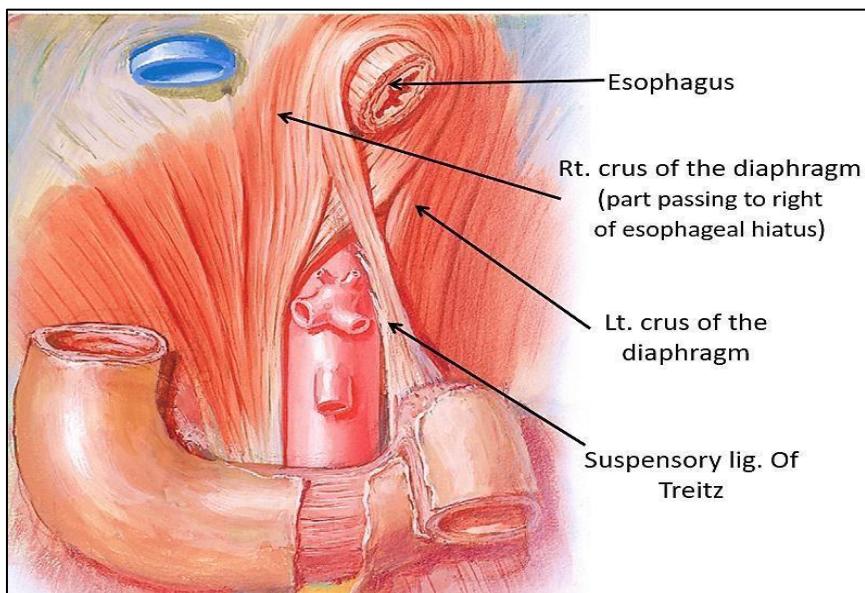
Important relations:

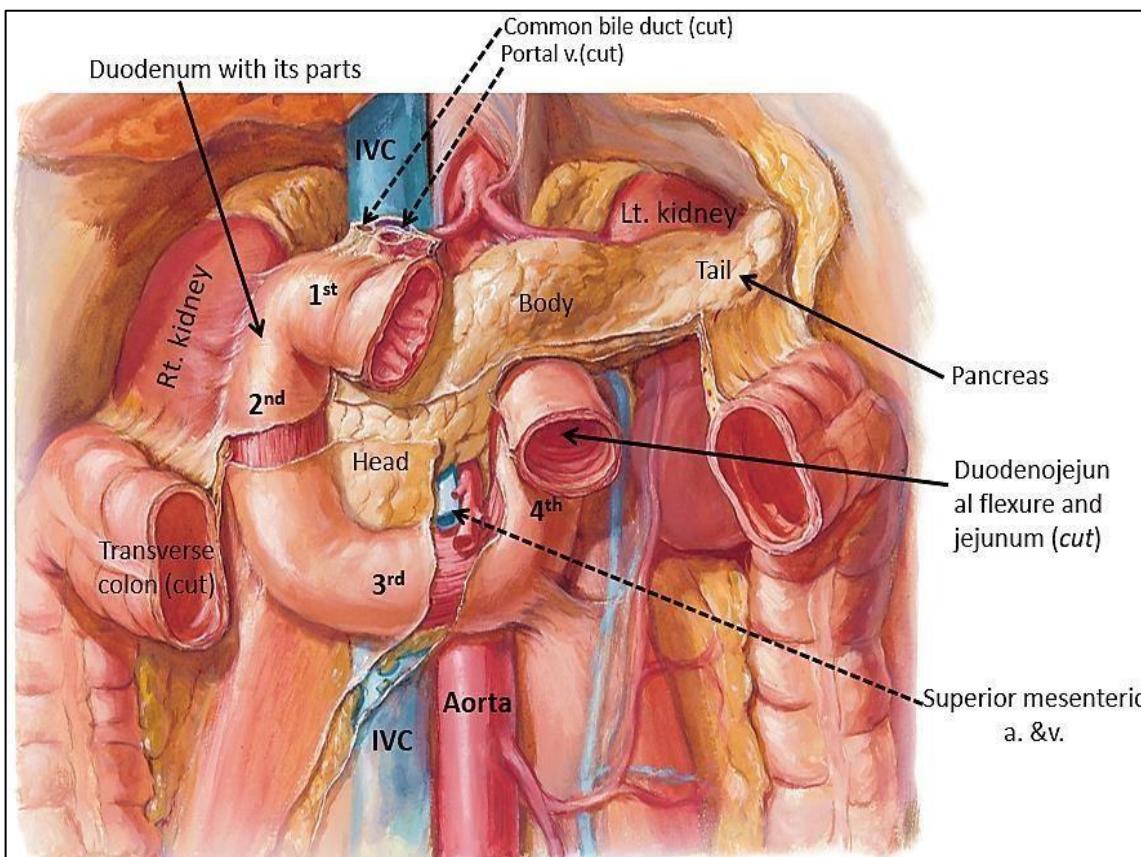
- a) The **1st part:** extends from the pyloric orifice of the stomach to the neck of the gallbladder and passes anteriorly to the bile duct, gastroduodenal artery, portal vein, and IVC. Clinically, the beginning of this part of duodenum is referred to as



the ampulla or duodenal cap & most duodenal ulcers occur in this part of duodenum.

- b) The **2nd part** Its anterior surface is crossed by the transverse colon, posterior to it is the right kidney, and medial to it is the head of pancreas.
 - This part of the duodenum contains *Posterior relation of 1st part of duodenum* the **major duodenal papilla**, where the common hepatopancreatic duct opens on its summit, and the **minor duodenal papilla** above it, which receives opening of the accessory pancreatic duct (*for illustrating image see pancreas*).
 - The junction of the foregut & midgut occurs just below major duodenal papilla.
- c) The **3rd part:** is the longest section, crossing the inferior vena cava, the aorta, and the vertebral column. It is crossed anteriorly by the superior mesenteric a. & v.
- d) The **4th part:** of the duodenum passes upward on (or to the left of), the aorta to approximately the upper border of L2 and terminates at **duodenojejunal flexure**.
 - This duodenojejunal flexure is surrounded by a fold of peritoneum containing muscle fibers called the **suspensory muscle (lig.) of duodenum (lig. of Treitz)**.





Relations of the duodenum

Blood supply of the duodenum:

- Arterial:
 1. Upper half of the duodenum till the middle of the 2nd part is supplied by branches of the celiac trunk (artery of the foregut). These branches are:
 - Supra duodenal artery.
 - Right gastric artery
 - Superior pancreaticoduodenal artery
 2. Lower half of the duodenum distal to the middle of the 2nd part is supplied by the inf. pancreaticoduodenal a. which is a br. from sup. mesenteric a. (artery of the midgut).
- Venous drainage: the veins of the duodenum drain into the portal vein

Anatomy of Pancreas

- It is a mixed endocrine and exocrine gland which is situated transversely across the posterior abdominal wall from the concavity of the duodenum on the right side to the spleen on the left side.
- Its length is 12 – 14 cm.
- The pancreas has head, neck, body, and tail.

A- Head: lies in the concavity of the duodenum. It has a projection from its lower left part called *the uncinate process*. This process is directed upwards and to the left.

Relations:

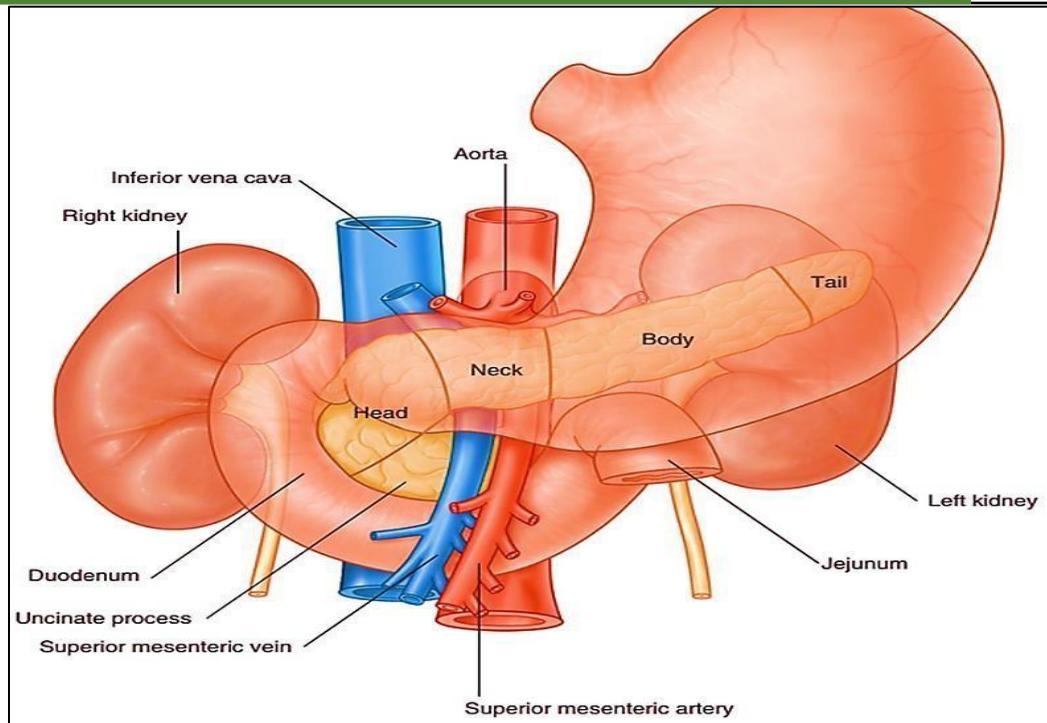
- 1- Anteriorly: transverse colon. The uncinate process is related anteriorly to the superior mesenteric vessels
- 2- Posteriorly: the I.V.C. and the terminal parts of the renal veins. The common bile duct lies in front of the I.V.C. and is embedded in the posterior surface of the head.
- 3- Above: *first* part of the duodenum.
- 4- Right side (laterally): the *second* part of the duodenum separated from it by the superior and inferior pancreaticoduodenal vessels.
- 5- Below: the *third* part of the duodenum.

B- Neck of the pancreas: It is a constriction of about 2 cm in length. It lies in the median plane at the level of the transpyloric plane (L1).

Relations:

Anteriorly: related to the first inch of first part of the duodenum separated from it by the cavity of the lesser sac.

Posteriorly: related to the beginning of the portal vein by the union of the splenic & superior mesenteric veins (very important anatomical & surgical landmark).



Relations & parts of pancreas

C- Body: triangular in cross section. It has three borders: anterior, inferior, and superior, and three surfaces, anterior, posterior, and inferior. Relations of the surfaces:

- 1- **Anterior:** related to the posterior surface of the stomach separated from it by the cavity of the lesser sac.
- 2- **Posterior:** It is related to the following structures from right to left:
 1. Abdominal aorta and the origin of the superior mesenteric artery.
 2. The splenic vein in front of the abdominal aorta and above the origin of the superior mesenteric artery.
 3. *Left* renal vein below the origin of the superior mesenteric artery and it separates the superior mesenteric artery from the abdominal aorta.
 4. Front of the lower part of the *left suprarenal gland*.
 5. Front of the *left kidney*.
 6. *Left* sympathetic chain.
 7. *Left* psoas major muscle.
 8. *Left* crus of the diaphragm.
- 3- **Inferior:** from right to left it is related to:
 - a- Duodenojejunal flexure. b- Loops of small intestine.
 - c- Left colic flexure.

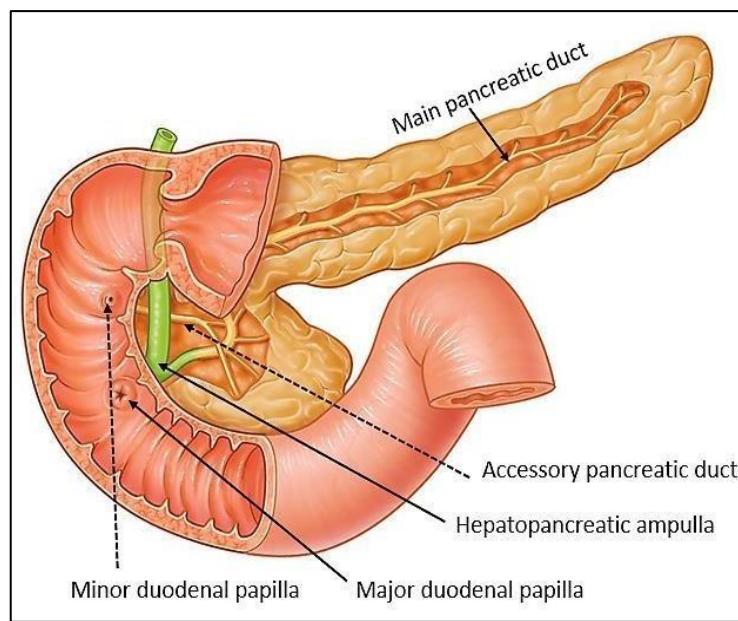
- **Borders of the pancreas:**

- 1- Superior border: It intervenes between the anterior and the posterior surfaces. At its beginning it has an elevation called tuber omental or omental tuberosity of the pancreas. This tubercle projects beyond the lesser curvature of stomach & comes in relation to the celiac trunk & the lesser omentum hence the name *omental tuberosity*.
The splenic artery runs in a tortuous course along the upper border of the pancreas.
- 2- Anterior border: It intervenes between the anterior and the inferior surfaces. It gives attachment to the two layers of the transverse mesocolon which diverge; the anterior of which passes on the anterior surface and the posterior layer passes on the inferior surface of the pancreas.
- 3- Inferior border: It intervenes between the inferior and posterior surfaces of pancreas.

D- Tail of the pancreas: It is a tapering part, and it passes in the lienorenal ligament to the spleen where it is related to its visceral surface below and lateral to its hilum.

- **Ducts of the pancreas:**

- 1- Main pancreatic duct: It begins at the tail of the pancreas and passes to the right side within the body till it reaches the neck. At the neck it inclines downwards and to the right side within the head. It unites with the common bile duct to form the common hepatopancreatic duct (ampulla of Vater).
- 2- Accessory pancreatic duct: It begins at the lower part of the head near the uncinate process. It ascends upwards and to the right side passing in front of the main pancreatic duct. It opens in the posteromedial wall of the second part of the duodenum on the top of the minor duodenal papilla situated 2 cm above major duodenal papilla.



Ducts of pancreas.

Peritoneal covering:

The body: its anterior and inferior surfaces are covered by peritoneum while its posterior surface is devoid of peritoneal covering. So, the body of pancreas is fixed to the post. abdominal wall.

The tail: is completely covered by peritoneum as it lies within the lienorenal lig.

- Blood supply of the pancreas:**A) Arterial:**

- 1- Pancreatic branches of the splenic artery: these are 20 small arteries which arise from splenic a. as it runs its tortuous course along the upper border of pancreas.
- 2- Superior pancreaticoduodenal artery: branch from the gastroduodenal artery which is a branch from the hepatic artery.
- 3- Inferior pancreaticoduodenal artery: branch from the superior mesenteric artery.

B) Venous drainage: the veins of the pancreas drain into the splenic vein, and the superior mesenteric vein. These veins finally drain into the portal vein.

- Lymphatic drainage: into pancreatico-splenic & pancreatico-duodenal lymph nodes.

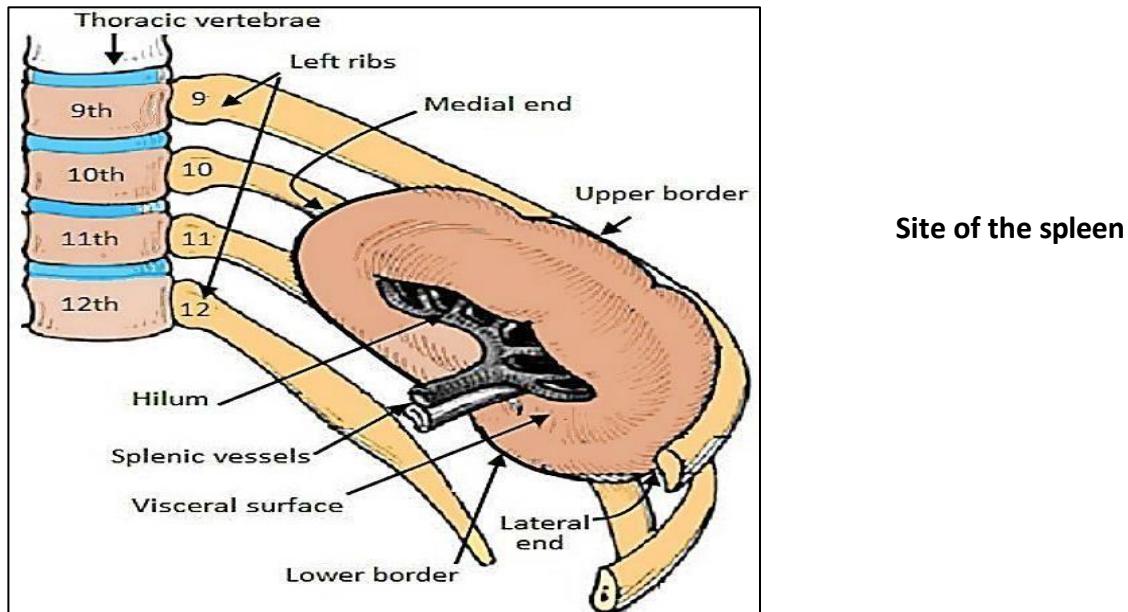
- Surface anatomy of the pancreas: It is represented by three points and a small line:

- 1- Point A & point B are present where the transpyloric plane crosses the midline and the left midclavicular line respectively.
- 2- Point C present at the crossing of the subcostal plane with the midline.
- 3- A small line is drawn 2 inches to the right of the median plane parallel to a line between the points A and C.
 - a- The head lies in the interval between the line & a line between the points A & C.
 - b- The body lies in the triangle between the three points, A, B and C.
 - c- The tail lies at the point B.

Anatomy of the spleen

The spleen is the largest lymphoid organ in the body

Site: The spleen lies in the lt. hypochondrium between fundus of the stomach and the diaphragm, behind the midaxillary line opposite the 9th, 10th, and 11th ribs. Its long axis lies parallel to the long axis of the 10th rib.



Shape, and Colour: The spleen is a wedge-shaped soft organ with purple colour.

Size: it is usually 3–4 cm thick, 7 cm broad, and 12 cm long (1" x 3" x 5")

Weight : 150-200 gm

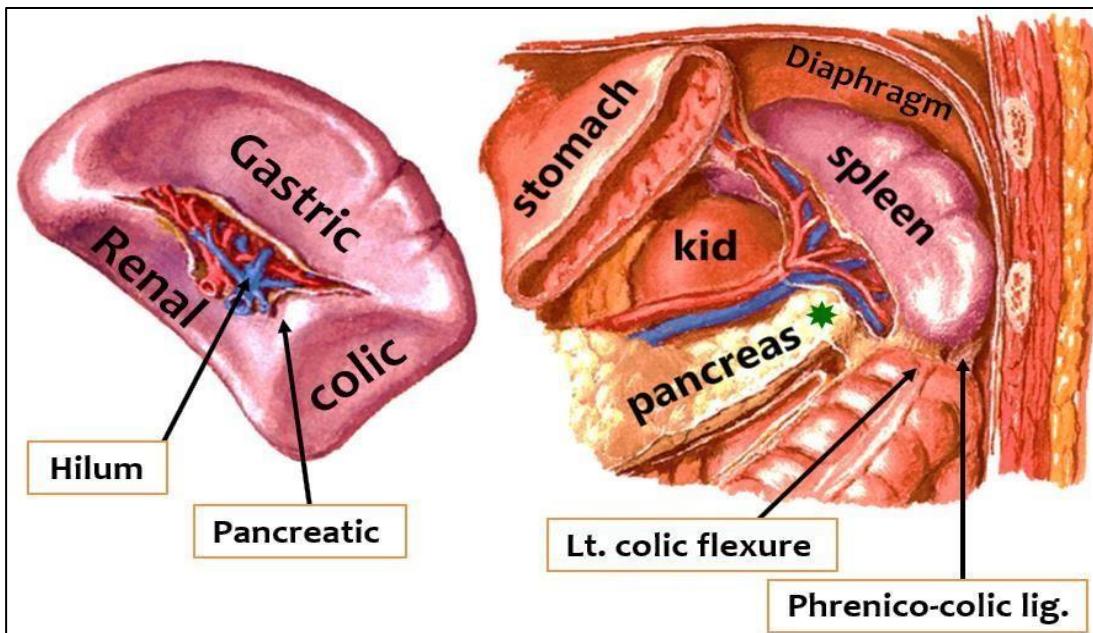
External features: the spleen has:

1. **Two ends:** anterior and posterior.
 - a) The anterior end (lateral end/lower pole) is broad and is more like a border. It is directed downward, forward, and to the left. It rests on the phrenico colic ligament below.
 - b) The posterior end (medial end/upper pole) is rounded. It is directed upward, backward, and medially towards the vertebral column.
2. **Three borders:** superior, inferior, and intermediate.

- a) **Superior Border:** it's a thin and convex border. It characteristically presents 1-2 notches near its anterior end. These notches indicate that the spleen develops by the fusion of separate masses of lymphoid tissue (lobulated development). It ends laterally by an angle.
- b) **Inferior Border:** a rounded, thick and smooth with no notches.

3. Two surfaces: diaphragmatic and visceral.

- a) The diaphragmatic surface is smooth, convex, and related to the diaphragm
- b) The Visceral surface: concave and irregular. It presents four impressions: gastric, renal, colic, and pancreatic
- The gastric impression is produced by the fundus of the stomach. It is the largest impression and lies above the hilum of spleen.
 - The renal impression is produced by the left kidney and lies between the hilum and the inferior border.
 - The colic impression is produced by the left colic flexure. It is ▲ in shape and situated close to the lateral end.
 - The pancreatic impression is produced by the tail of the pancreas. It is located between the hilum and the colic impression (below the lateral end of the hilum).



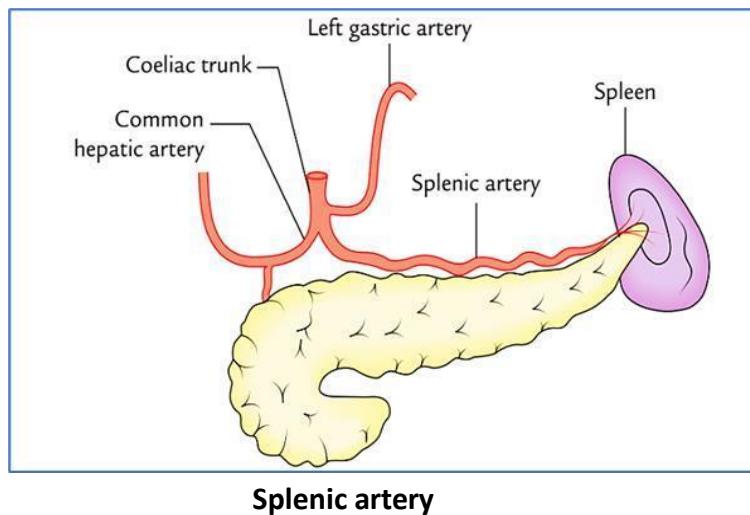
Relations of the visceral surface & impressions

Peritoneal covering: The spleen is completely enclosed in the peritoneum except at its hilum, from where two peritoneal folds extend — one to the stomach and one to the left kidney, called gastrosplenic and lienorenal ligaments, respectively

1. Gastro-splenic lig. extends from the hilum of the spleen to the upper one-third of the greater curvature of the stomach. It contains short gastric vessels.
2. Lieno-renal lig. extends from the hilum of the spleen to the anterior surface of the left kidney. It contains (a) tail of the pancreas, (b) splenic vessels, and (c) pancreatico splenic lymph nodes.
3. Phrenico-colic lig.: It is a triangular fold of the peritoneum which extends from the left colic flexure to the diaphragm opposite to the 10th rib.

Blood supply:

- **Arterial Supply:** by the splenic artery (branch from the coeliac trunk)
- **Venous drainage:** the splenic vein that joins the superior mesenteric vein to form the portal vein



The caecum

- **The caecum:** a blind pouch lying in the right iliac fossa.
- Its average length is 6 cm and its breadth 7.5 cm.
- It continues proximally with the ileum and distally with the ascending colon.

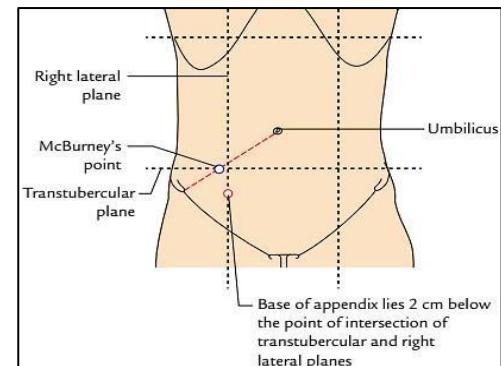
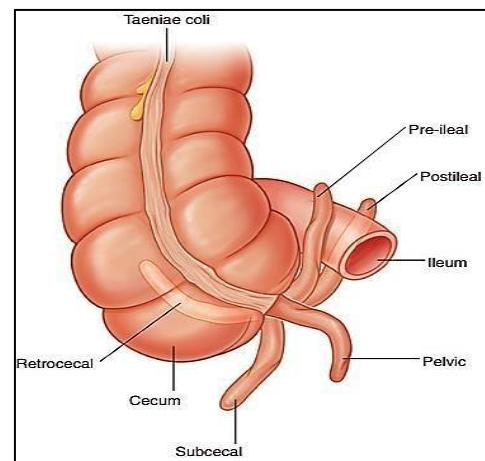
Relations:

- **Posteriorly:** right iliacus and psoas major muscles and the lateral cutaneous nerve of the thigh.
- **Anteriorly:** completely covered by peritoneum and related to loops of the small intestine, the greater omentum and the anterior abdominal wall.

The vermiform appendix

It is a narrow, vermiform (worm-like) tube about 2 cm long. It emerges from the posteromedial wall of caecum below the ileocecal valve.

- It is suspended from the terminal ileum by the mesoappendix, which contains the appendicular vessels.
- Its point of attachment to the cecum is consistent with the highly visible free taeniae leading directly to the base of the appendix, but the location of the rest of the appendix varies considerably.
- **It has several positions:**
 1. Retrocaecal (behind caecum) most common.
 2. Pelvic, or descending (when appendix hangs dependently over the pelvic brim, in close relation to the Rt. uterine tube & ovary in ♀).
 3. Sub-caecal (below caecum).
 4. Pre- or post-ileal (anterior or posterior to the terminal ileum respectively), are occasionally seen, especially when there is a long appendicular mesentery which allows greater mobility.
- **McBurney's point** is located one third of the distance from the right anterior superior iliac spine to the umbilicus (navel). This point roughly corresponds to the most common location of the root of the appendix, where it is attached to the caecum.



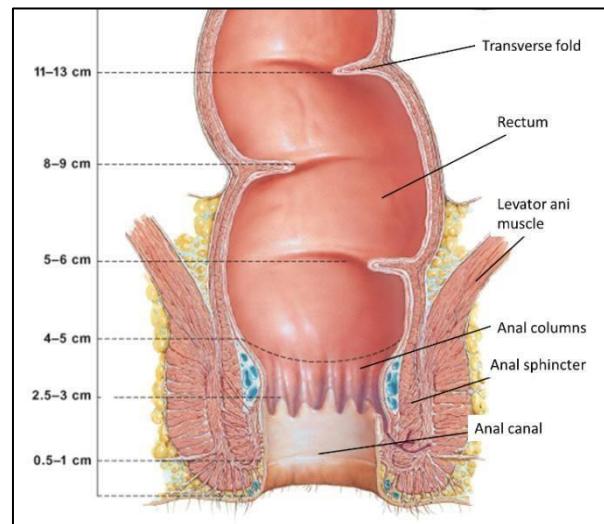
Anatomy of rectum

- The **rectum** is the terminal part of the large intestine.
- It is about 13 cm. (5 inches) long.
- It begins at the level of the S3 as a continuation of the sigmoid colon and ends at the anorectal junction one inch in front of and below the tip of coccyx where it continues as the anal canal .
- It is about 4 cm wide at its beginning (similar to that of the sigmoid colon) but it is dilated near its end to form the rectal ampulla.
- Unlike other portions of colon, **the rectum does not have taeniae coli or sacculations.**

Peritoneal coverings:

1. The upper 1/3 is covered by peritoneum on front and sides
2. The middle 1/3 is covered by peritoneum in front only.
3. The lower third has no peritoneal coverings.

Flexures of the rectum:



1- Anteroposterior flexures

- a. **Sacral flexure** (upper curve): concave forwards. It follows concavity of sacrum.
- b. **Perineal or recto-anal flexure** (Lower curve): convex forwards. The rectum bents backwards at the anorectal junction to form an acute angle of 80 degree. The rectum pierces the pelvic diaphragm to continue as the anal canal.

2- Lateral flexures: the rectum has three lateral flexures (curves). The upper &lower are convex to the right. The middle is the most prominent & convex to the left.

The mucosa of the rectum:

- It has longitudinal folds.
- There are 3 large transverse folds called rectal folds or shelves: known as **Houston's valves**. One-fold lies opposite the concave side of the 3 lateral flexures.
- These folds are about 12 mm. in width
- They contain circular muscle fibers to support the weight of fecal matter to prevent its descent toward the anal canal as its presence always excites a sensation demanding its discharge. In the empty state of the intestine these folds overlap each other.

Relations: see practical

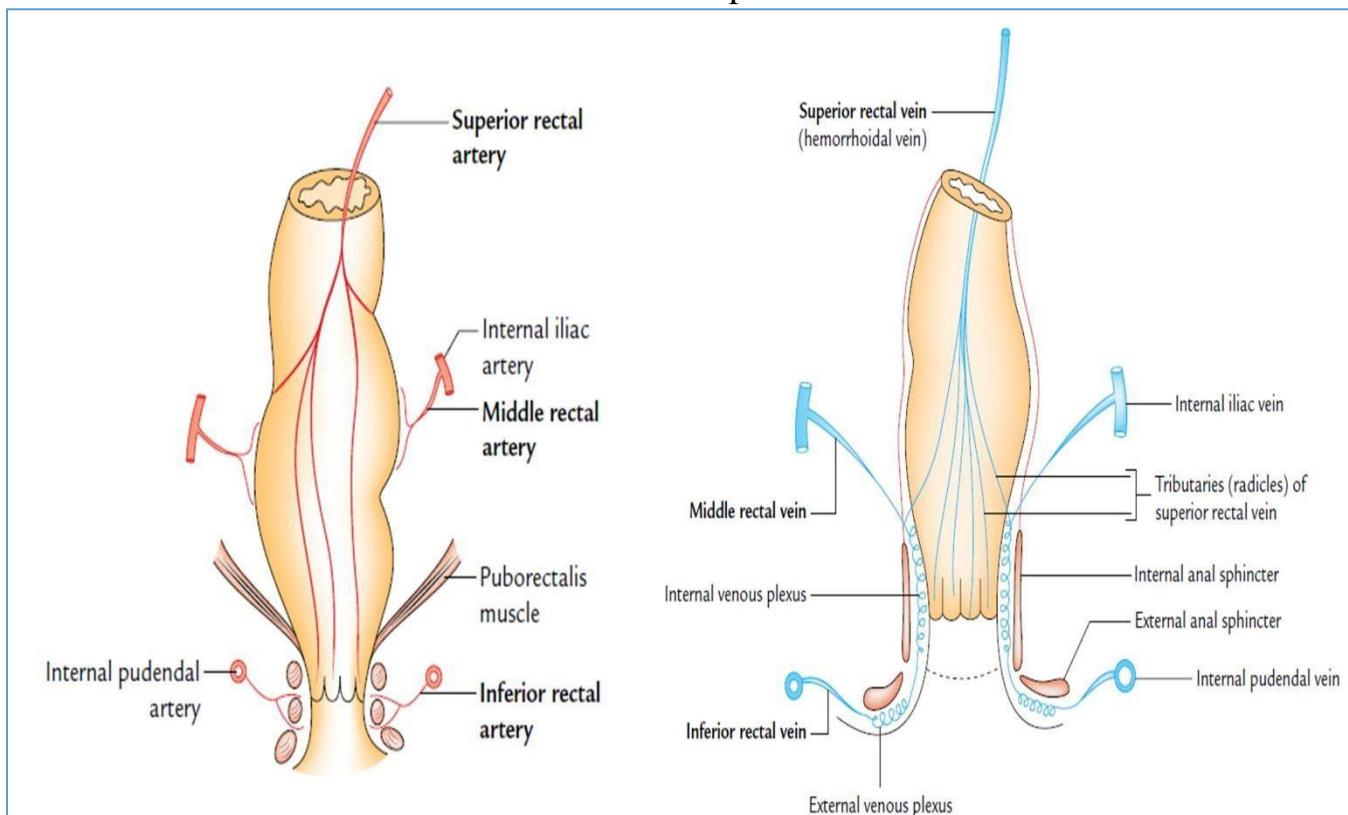
Arterial blood supply of rectum & anal canal:

1. Superior rectal artery: continuation of the inferior mesenteric artery.
2. Middle rectal artery: branch from the anterior division of the internal iliac artery.
3. Inferior rectal artery: branch from the internal pudendal artery, in the perineum, its anastomosis with the middle rectal a. at anorectal junction.

Venous drainage of the rectum and anal canal:

correspond to their arteries.

1. Superior rectal vein ends in the inferior mesenteric vein.
2. Middle rectal vein drains into internal iliac vein.
3. Inferior rectal vein: drain into the internal pudendal vein.



Anatomy of anal canal

- It is the terminal part of the large intestine, it is about 2.5 to 4 cm.
- It begins at the anorectal junction one inch below and in front tip of coccyx.
- It extends in the anal triangle downwards and backwards between the ischiorectal fossae to end at the anal orifice. It forms a posterior acute angle about 80 degrees with the lower part of the rectum.
- It has no peritoneal covering.

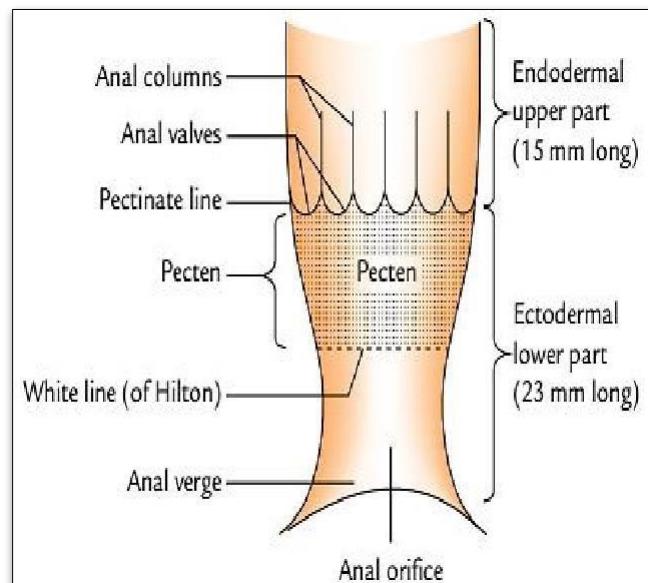
Relations: see practical

The internal features of anal canal:

- The anal canal is divided into upper & lower parts by the pectinate line.
- The pectinate line represents the embryological site of attachment of anal membrane.
- The upper part extends from the anorectal junction to the pectinate line, while the lower part extends from the pectinate line to the anal verge.
- The upper and lower parts of the anal canal are different in development, blood and nerve supply and lymphatic drainage.

Features in the upper part of anal canal: The upper part of the anal canal (15 mm long) presents the following features:

1. **Anal columns (columns of Morgagni):** These are permanent longitudinal mucous folds numbering 6 to 10. They contain radicles of the superior rectal vein.
2. **Anal valves (valves of Morgagni):** These are crescentic folds of the mucous membrane which connect the lower ends of adjacent anal columns. The free margins of these valves are directed upward. The position of these valves is indicated by the wavy pectinate line (also called dentate line).
3. **Anal sinuses:** These are vertical recesses between the anal columns and above the anal valves. The ducts of tubular anal glands present in the submucosa open in the floor of anal sinuses.



Interior of the anal canal

Features in the lower part of anal canal: The lower anal canal is further divided into two regions: upper and lower.

- a) Upper region (often called pecten): It is 15 mm long and extends from the pectinate line to Hilton's line. It is lined by the non-keratinized stratified squamous epithelium. The mucous lining in this region appears bluish in colour due to underlying dense venous plexus and is adherent to the underlying structures.
- b) Lower region of lower anal canal: It is about 8 mm in extent and lined by the true skin containing sweat and sebaceous gland. It shows pigmentation. In adult male, coarse hairs are often found around the anal orifice. The junction between keratinized & the non-keratinized parts is indicated by a whitish line called (Hilton's white line).

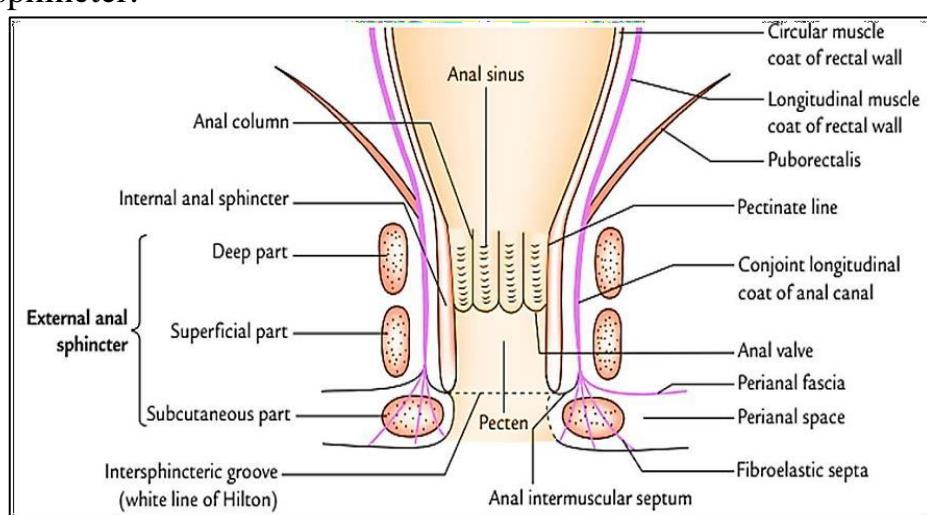
Anal sphincters:

1) The internal anal sphincter

It is a ring of circular smooth muscle fibers which surrounds the upper two thirds of the anal canal. It is continuous with the circular muscle of the gut. Its thickness ranges from 1.5 to 3.5 mm. It is thinner in females. It becomes thicker with age and in chronic constipation.

Nerve supply: by the sympathetic and parasympathetic fibers. Both are distributed via the inferior hypogastric plexus.

- Sympathetic fibers arise from the lower two lumbar segments of the spinal cord. It causes contraction of the sphincter.
- Parasympathetic fibers arise from S2, 3, 4 spinal segments. It causes relaxation of the sphincter.



A coronal section of anal canal showing internal and external anal sphincters

2) **External sphincter:** surrounds the **lower two thirds** of the canal. Thus, it overlaps the internal sphincter in the middle third. It is formed from striated voluntary muscle fibers arranged in three parts:

- a) **Deep part:** It is a thick annular band that forms the true sphincter and has no bony attachment.
- b) **Superficial part:** arises from the tip of coccyx and anococcygeal body and passes forward around the sides of the anus to be inserted into the perineal body.
- c) **Subcutaneous part:** surrounds the anal orifice and has no bony attachment.

Nerve supply: by the inferior rectal nerve and the perineal br. of 4th sacral nerve.

Lymph drainage of anal canal: upper half drains into pararectal lymph nodes and finally into inferior mesenteric L.N. The lower 1/2 drains into superficial inguinal L.N.

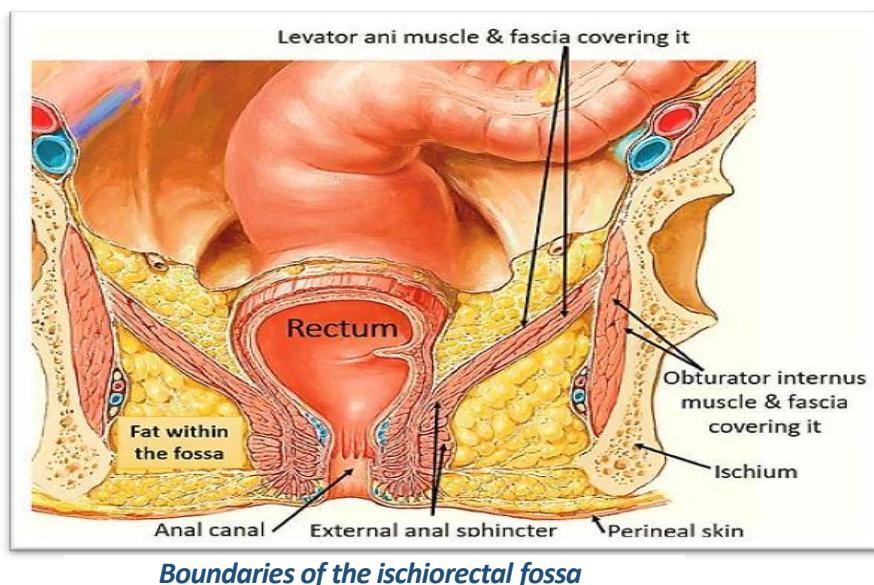
Arterial supply of anal canal: The upper part is supplied by superior rectal a. & the lower part is supplied by inferior rectal a.

Anatomy of Ischiorectal fossa (Ischio-anal fossae)

Site & shape: a wedge-shaped, fat-filled space situated on each side of the anal canal below the levator ani muscles. The 2 fossae communicate with each other behind anal canal.

Functions: They help in dilatation of the anal canal, during defecation.

Measurements: each is 5 cm length x 5 cm width x 5 cm depth



Boundaries:

Lat. wall	* Fascia covering the obturator internus muscle * ischium *sacrotuberous ligament
Med. wall	*Fascia covering the levator ani muscle * external anal sphincter.
superiorly	The medial & lateral walls converge
Anteriorly	continuous with recesses that project into the urogenital triangle superior to the deep perineal pouch.
Post.:	Sacrotuberous ligament & on post. surface of which is gluteus maximus.
Floor:	Perineal skin.

Contents

1. Ischiorectal pad of fat.
2. Inferior rectal nerves and vessels
3. Perineal branch of 4th sacral nerve
4. Posterior scrotal (or labial) nerves and vessels

Chapter V: Liver and biliary system

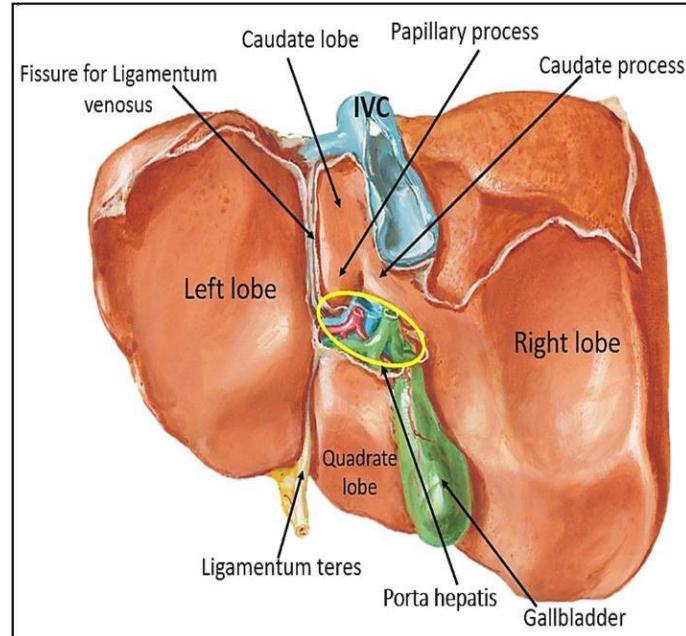
Anatomy of Liver

Site: The liver almost fully occupies the right hypochondrium, upper part of the epigastrium, and part of the left hypochondrium up to the left lateral (midclavicular) line. It lies mostly under cover of the ribs & costal cartilages immediately below the diaphragm.

Shape: wedge-shaped and resembles a four-sided pyramid laid on one side with its base directed towards the right & apex directed towards the left.

Surfaces: Surfaces of the liver include:

- **Diaphragmatic surface:** smooth, dome-shaped, and lies against the inferior surface of the diaphragm in the anterior, superior, right, and posterior (area of bare area proper) directions.



Relation of the posterior and inferior surfaces of the

- **Visceral surface:** relatively flat or concave. It is separated in front from the diaphragmatic surface by the sharp inferior border and lies in the posterior (small part) and inferior directions.

Borders: the borders between surfaces are ill-defined except the inferior border which is:

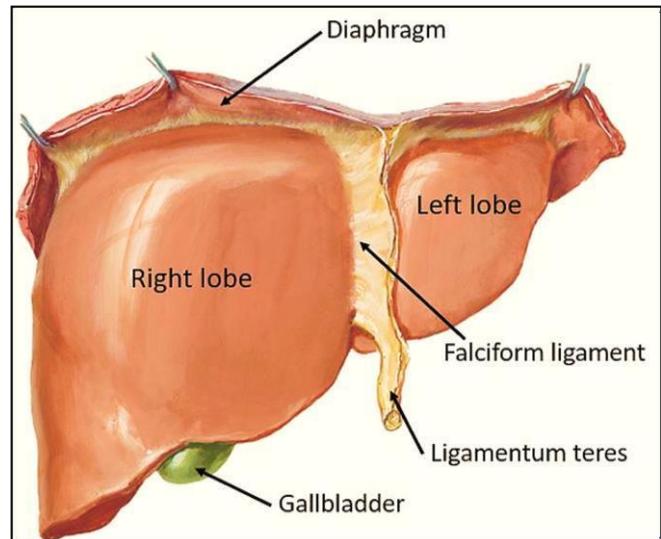
- ✓ rounded laterally where it separates the right lateral from the inferior surfaces.
- ✓ thin and sharp medially where it separates the anterior surface from the inferior surface.
- ✓ It presents two notches:
 - Notch for ligamentum teres: It is located just to the right of median plane.
 - Cystic notch: often corresponds to the fundus of the gallbladder.

Anatomical lobes of the liver:

morphologically, the liver is divided into small Lt. Lobe and larger Rt. Lobe (6 times larger than the Lt. lobe) by:

- The attachment of the falciform ligament on the diaphragmatic surface.
- The fissure for ligamentum venosum on the posterior surface.
- The fissure for ligamentum teres on the inferior surface.

N.B. The Rt. Anatomical lobe shows 2 smaller lobes:



Anatomical lobe of the liver.

1. Caudate lobe: is the part on the post.

surface, lying between groove for IVC to the right, fissure for ligamentum venosum to the left & porta hepatis below.

❖ The caudate lobe has 2 processes: **a papillary process**, which arises from its left side, and **a caudate process** above porta hepatis, which connects it to rest of liver.

2. Quadrata lobe is the part on the inferior surface, lying between: Fossa for gallbladder to right, fissure for ligamentum teres to the left & porta hepatis: above

Ligaments: Ligaments of the liver are of two types: (a) false and (b) true.

a) **False Ligaments:** The false ligaments are peritoneal folds and include:

1. **Falciform ligament:** sickle-shaped fold.
2. **Coronary ligament:** It consists of two layers— upper and lower.
3. **Right triangular ligament:** It encloses the apex of the bare area of liver.
4. **Left triangular ligament:** It is a very-very small \triangle fold.
5. **Lesser omentum**

b) **True Ligaments:** are the remnants of fetal structures and include:

1. **Ligamentum teres hepatitis:** It is the remnant of the obliterated Lt. umbilical v.
2. **Ligamentum venosum:** It is the remnant of the obliterated ductus venosus.

Relations of the liver:

Superior Surface: Related to the diaphragm which separates the liver from:

- Corresponding lung and pleura on either side
- Pericardium and heart in the center

Anterior surface:

- The falciform lig. is attached a little to the right of the median plane.
- It is Related to
 - Xiphoid process and Anterior abdominal wall in the median plane
 - The diaphragm on each side and costal margin

Right lateral surface: with diaphragm intervening, it is related to:

- Rt. Lung and pleura in the upper one-third
- Costo-diaphragmatic recess in the middle one-third
- 10th and 11th ribs in the lower one-third

Posterior surface: This surface presents:

1. **The bare area proper of the liver:**
 - A ▲ area to the right of groove for the IVC between the 2 layers of coronary and Rt. triangular ligaments.
 - It is related to the diaphragm and the Rt. suprarenal gland.
2. **The groove for IVC** as the name indicates lodges the IVC. Its floor is pierced by the hepatic veins.
3. The **caudate lobe** is related to superior recess of lesser sac.
4. **The fissure for ligamentum venosum**
5. **Oesophageal impression:** on the post. surface of Lt. lobe just to the left of the upper part of fissure for lig. venosum & is related to abdominal part of oesophagus.

Visceral surface (inferior surface):

1. **The inf. surface of the Lt. lobe** is related to:
 - a) Stomach (**gastric impression**): related to fundus & body's upper part
 - b) lesser omentum: as the surface comes in contact with the lesser omentum, it presents a slight elevation called **omental tuberosity /tuber omentale**. It lies near the Lt. side of fissure for ligamentum Venosum.
2. **The fissure for ligamentum teres.**
3. The **quadrate lobe** is related to lesser omentum, the pyloric end of the stomach and the first part of the duodenum and transverse colon

4. Inf. surface of Rt. lobe related to: Fossa for gallbladder, Rt. colic flexure, upper part of 2nd part of duodenum (**duodenal impression**) & Rt. kidney (**renal impression**).

Porta hepatis

It is a horizontal fissure on the inferior surface of the liver between the quadrate and caudate lobes. It represents the gateway of the liver and the main structures passing through the porta hepatis (in the order from posterior to anterior [VAD]) are:

- a) portal Vein
- b) right & left branches of hepatic Artery
- c) The right and left hepatic Ducts.

Porta hepatis also contains lymph nodes & nerves of the liver.

Blood supply: It receives blood from two sources:

- 20%: arterial blood (oxygenated) supplied by the hepatic a.
- 80%: venous blood (rich in nutrients) supplied by the portal v.

Venous Drainage: Most of the venous blood from liver is drained by **3** large hepatic veins. They emerge in the groove for IVC and open directly in the IVC.

Lymphatic drainage: it has 2 sets of lymphatics:

- **Superficial lymphatics:** From the **post. aspect** of the liver, they drain into the post. Mediastinal L.N. From the **ant. aspect** of the liver, they drain into 3-4 nodes that lie in the porta hepatis (hepatic nodes).
- **Deep lymphatics:** are lymphatics that accompany the portal triads.

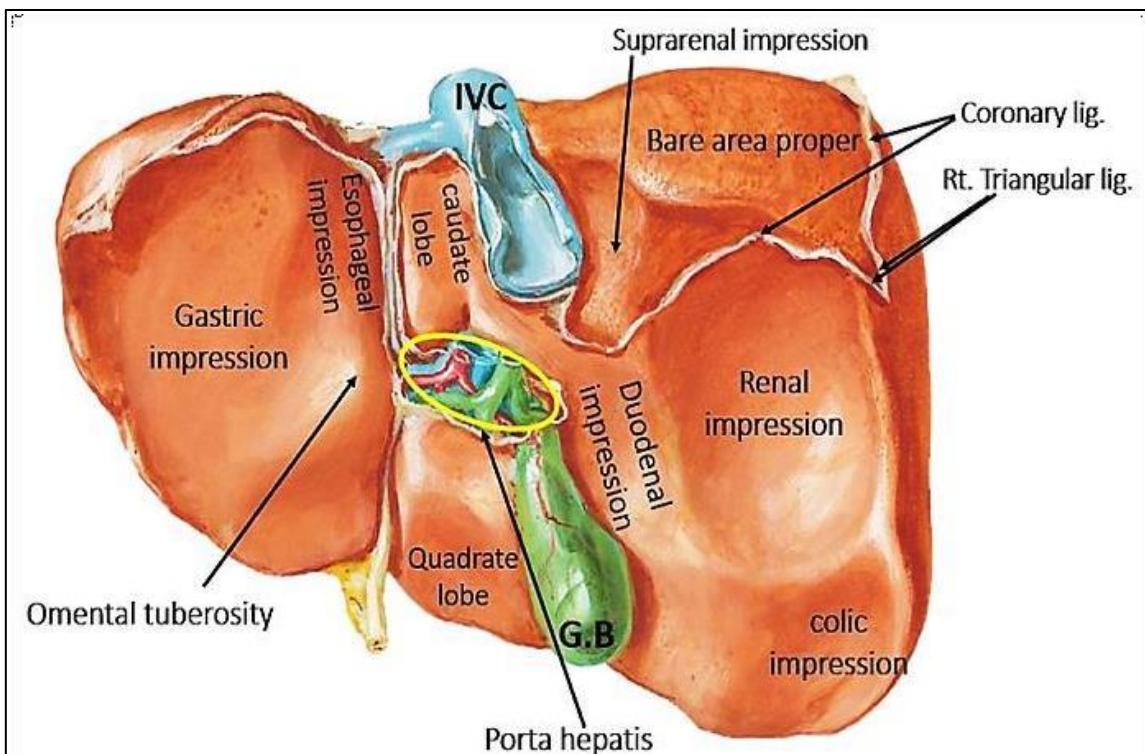
Nerve supply: The liver is supplied by both sympathetic and parasympathetic fibres:

- **Sympathetic fibres:** are derived from the coeliac plexus.
- **Parasympathetic fibres:** are derived from the hepatic branch of anterior vagal trunk

Surface anatomy:

Upper border	Represented by line joining the following points: <ul style="list-style-type: none"> a) A point on the Lt. 5th intercostal space at the Lt. midclavicular line b) A point at the xiphi-sternal junction c) A point on the Rt. 5th rib at the Rt. midclavicular line d) A point on the Rt. 7th rib at the Rt. midaxillary line
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Lower border	Represented by line joining the following points: <ol style="list-style-type: none"> A point on the Lt. 5th intercostal space at the Lt. midclavicular line A point at the Lt. costal margin at the tip of the 8th costal cartilage A point at the transpyloric plane in the middle line (level of L1) A point on the tip of the 9th costal cartilage mid-clavicular line (related to fundus of gallbladder) A point on the Rt. 11th rib at the Rt. midaxillary line
Rt. Border	Represented by line joining the following points: <ol style="list-style-type: none"> A point on the Rt. 7th rib at the Rt. midaxillary line A point on the Rt. 11th rib at the Rt. midaxillary line



Extrahepatic biliary apparatus

It receives the bile from liver, stores and concentrates it in the gallbladder, and transmits it to the second part of the duodenum when required. It consists of **5** components:

1- Rt. & Lt. hepatic ducts: The Rt. & Lt. hepatic ducts drain bile from the Rt. & Lt. lobes of the liver.

2- Common hepatic duct: a 1-inch duct that joins the cystic duct to form the common bile duct (CBD).

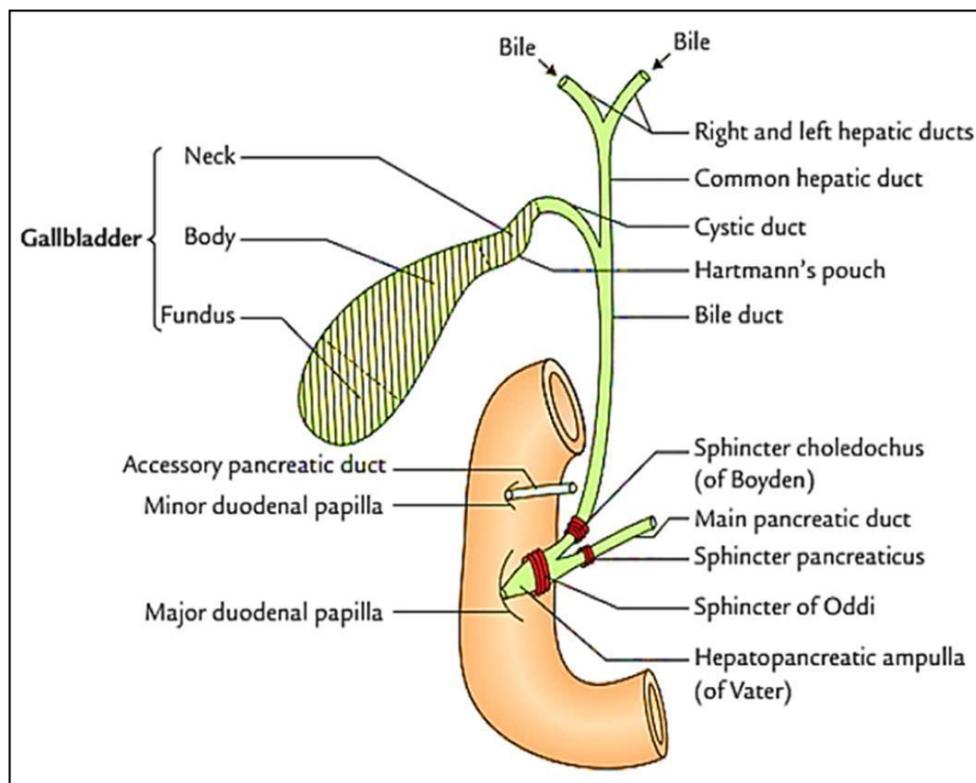
3-Gallbladder.

4-Cystic duct.

5-Bile duct (formerly, common bile duct).

Gallbladder: is an elongated pear-shaped sac of about 30–50 ml capacity. It stores, concentrates the bile & discharges it into duodenum by its muscular contraction.

Location: gallbladder lies in fossa for gallbladder on inferior surface of Rt. lobe of liver.



Dimensions: 10 cm Length and 3 cm Width (at its widest part)

- **Parts and Relations:** The gallbladder is divided into the **3** parts:

1. **Fundus** (expanded lower end that projects below the inferior border of liver):

Related anteriorly to the ant. abdominal wall at the tip of Rt. **9th** costal cartilage. It is completely surrounded by peritoneum.

Body: Its upper surface is related directly to the liver and is devoid

2. of the peritoneum. Its undersurface is covered by the peritoneum and is related to transverse colon and the superior part of the duodenum.

3. **Neck** (narrow end).: It joins the cystic duct and its junction with this duct is marked by a constriction. It is related inferiorly to the **1st** part of the duodenum. The posteromedial wall of the neck shows a pouch-like dilatation (**Hartmann's pouch**). The gall stones lodged in this pouch may cause adhesion with the **1st** part of the duodenum and may perforate it.

Blood supply of gall bladder:

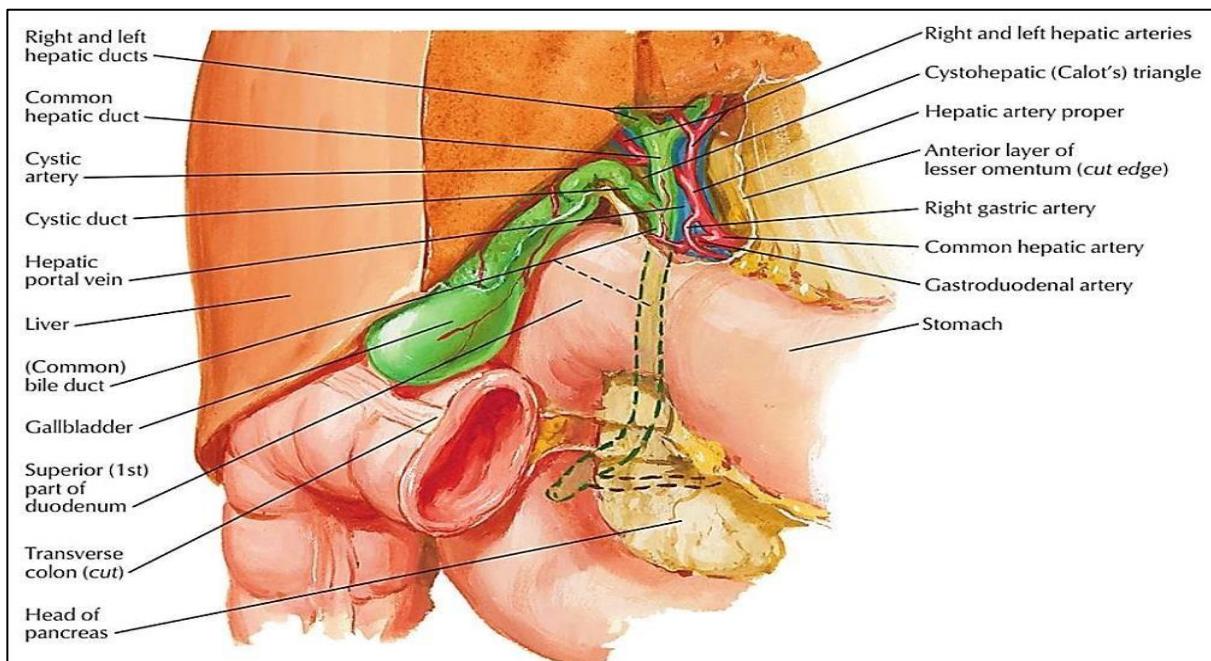
- **Arterial Supply:** the cystic a. (a branch of Rt. hepatic a.).
- **Venous Drainage:** The venous drainage of the gallbladder is dual:
 - by the cystic vein, which drains into the portal vein.
 - by several small veins, which pass directly to the liver.

Lymphatic Drainage: cystic & hepatic L.N.

Nerve Supply

- Sympathetic fibres (T7–T9) via cystic plexus.
- Parasympathetic fibres from the (Rt.& Lt. vagus nerves)
- Sensory: Rt. phrenic n. (thus gallbladder pain is referred to the tip of the Rt. Shoulder)

Cystic duct: It is s-shaped, about 3–5 cm long.



course of the common bile duct.

Bile duct/common bile duct (CBD): It is usually 7.5 cm (3 inches) long and about 6 mm in diameter.

Parts: is divided into 4 parts: -

- Supra-duodenal: It descends in the Rt. free margin of the lesser omentum to the right of the hepatic artery proper and anterior to the portal vein.
- Retro-duodenal: It descends behind the first part of the duodenum.
- Infra-duodenal (or pancreatic): It runs in the groove on the post. Surface of the head of pancreas and is sometimes completely embedded in the pancreatic tissue.
- Intra-duodenal (or Intramural): The terminal part and the main pancreatic duct both enter the posteromedial wall of the 2nd part of duodenum at the same site a little below to its middle. They join each other to form an expansion, the hepatopancreatic ampulla (or **ampulla of Vater**) which open on top of the major duodenal papilla (10 cm distal to the pylorus).

Arterial Supply of the Bile Duct/Common Bile Duct

- The upper part by cystic artery.
- The lower part by superior pancreaticoduodenal artery.

Chapter VI: Blood supply of GIT

Arterial blood supply of the GIT

The abdominal parts of the gastrointestinal system are supplied mainly by the celiac trunk and the superior mesenteric and inferior mesenteric arteries.

1. The celiac trunk supplies the foregut: the lower oesophagus, stomach, superior part of the duodenum, and proximal half of the 2nd part of the duodenum.
2. The superior mesenteric artery supplies the midgut: the rest of the duodenum, the jejunum, the ileum, the ascending colon, and proximal 2/3 of transverse colon.
3. The inferior mesenteric artery supplies the hindgut: the rest of the transverse colon, the descending colon, the sigmoid colon, and most of the rectum.

Celiac trunk (artery of foregut)

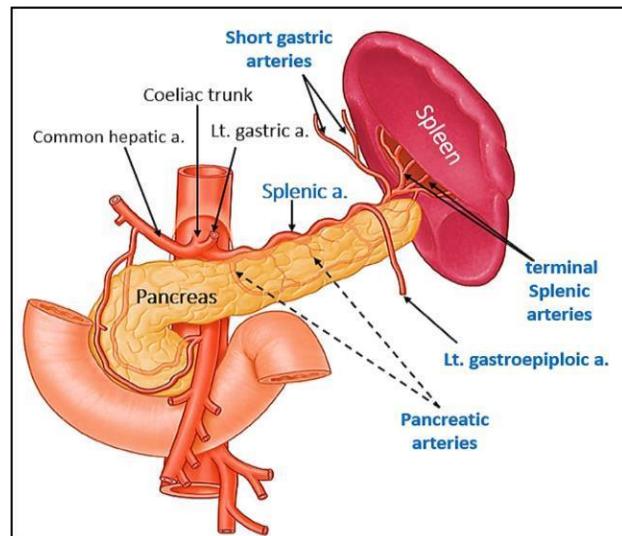
Origin: from the abdominal aorta immediately below the aortic hiatus of the diaphragm, usually at the level of the vertebral body of T12.

Branches: It immediately divides into the left gastric, splenic, and common hepatic arteries.

- **Left gastric artery** is the smallest branch of the celiac trunk. It ascends to the cardio-oesophageal junction then descends along the lesser curvature of stomach and ends by anastomosing with the right gastric a.

Branches:

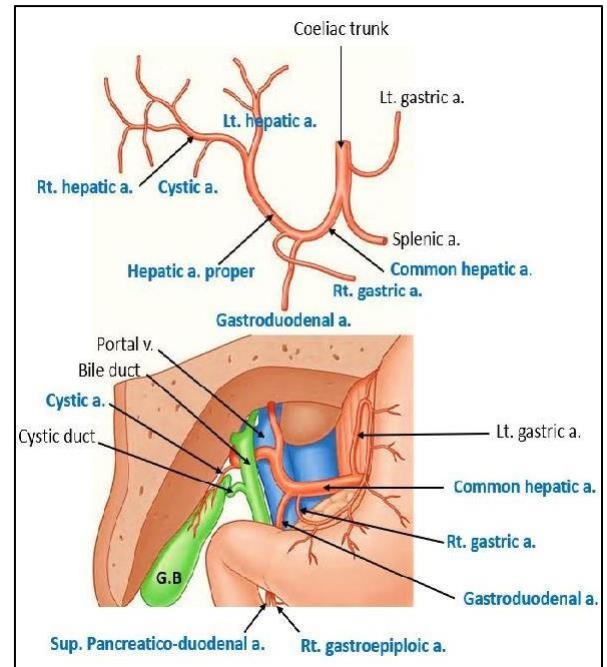
- a. **oesophageal branches** to the abdominal part of the oesophagus.
 - b. **Gastric branches:** to both surfaces of the stomach along the lesser curvature
- **Splenic artery:** the largest branch of the celiac trunk. It takes a tortuous course to the left along the superior border of the pancreas. It enters the lienorenal lig. through which it reaches the hilum of spleen where it divides into five or more segmental branches, which enter the hilum of the spleen to supply it.



Branches of the splenic artery.

Branches:

- Pancreatic branches: numerous small branches, supply whole of the pancreas except the head.
 - Short gastric branches (3–7 in number) pass through the gastrosplenic ligament to stomach's fundus.
 - Lt. gastro-epiploic artery runs along the greater curvature of stomach terminates by anastomosing with the right gastroepiploic artery.
 - Terminal splenic branches
- **Common hepatic artery:** a medium-sized branch that runs to the right and divides into its two terminal branches at the upper border of duodenum, **hepatic artery proper** and **gastrooduodenal artery**.



Branches of the hepatic artery.

1. **The hepatic artery proper** ascends toward the liver in free edge of lesser omentum. On reaching porta hepatis, it terminates by dividing into Rt. & Lt. hepatic arteries.

Branches:

- I. The **right gastric artery**, but it can also arise from the common hepatic artery (**Fig.83**). It passes to the left and ascends along the lesser curvature of the stomach in the lesser omentum, and anastomoses with the left gastric a.

II. Terminal branches: **right** and **left hepatic arteries** near porta hepatis.

III. The right hepatic artery gives off the **cystic artery** to the gallbladder.

2. **The gastrooduodenal artery**, it runs downward behind the duodenum & terminates at its lower border it gives off:

Branches:

- I. The **Sup. pancreaticoduodenal a.** and that supply the head & uncinate process of the pancreas and the duodenum. It divides into Ant. & Post.

branches that eventually anastomose with those of the inf. pancreaticoduodenal artery.

- II. The **Rt. gastroepiploic a.** that passes to the left, along the greater curvature of the stomach, eventually anastomosing with the Lt. gastroepiploic a.

Superior mesenteric artery (artery of midgut)

Origin: from the abdominal aorta immediately below the celiac artery, at the level of the L1 vertebral body.

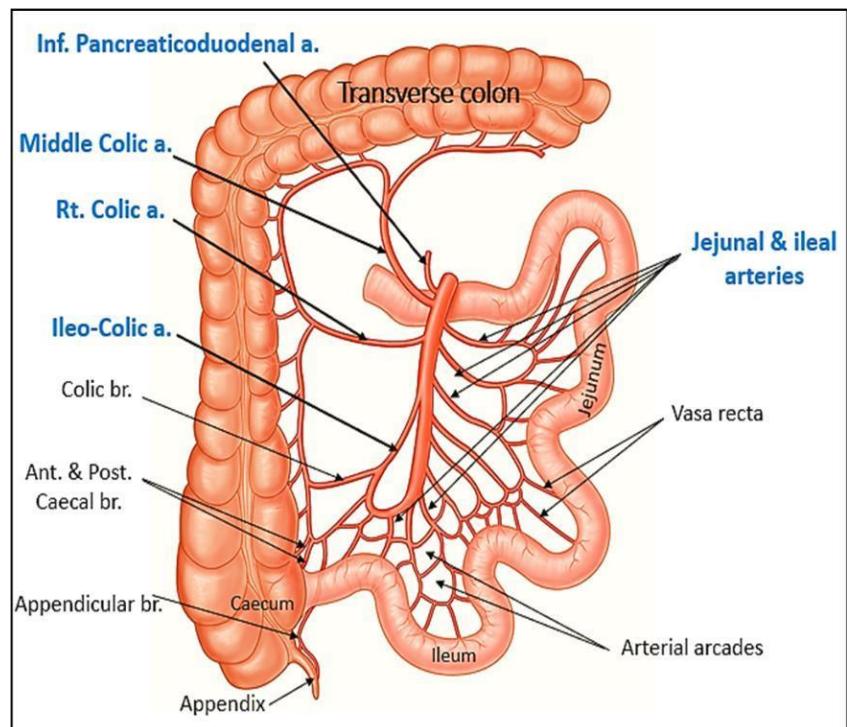
Course: it runs downward and to the right to enter the root of mesentery where it runs between its two layers. Throughout its course, it is accompanied by the sup. mesenteric vein on its right side.

Relations:

Anteriorly it is related to the body of pancreas and splenic vein.

Posteriorly from above downward it is related to the lt. renal vein, uncinate process of the pancreas, 3rd part of the duodenum, IVC, right ureter, and right psoas major (see relations of the 3rd part of duodenum).

End: It terminates in the right iliac fossa by anastomosing with a branch of ileocolic artery—one of its own branches.



Branches: The superior mesenteric artery gives off five sets of branches. All branches arise from its right side except jejunal & ileal branches which arise from its left side as follows:

- 1. Inf. Pancreatico-duodenal a.:** 1st branch arising from the Rt. side and soon divides into Ant. and Post. branches.
- 2. Middle colic a.:** It runs upward and forward to pass between the two layers of transverse mesocolon, where it divides into Rt. and Lt branches.
 - The Rt. branch anastomoses with ascending br. of the Rt. colic a.
 - The Lt. branch anastomoses with ascending br. of the Lt. colic a.
- 3. Rt. colic a.:** It runs to the right behind the peritoneum and divides into ascending and descending branches.
 - The ascending br. anastomoses with Rt. branch of middle colic a.
 - The descending br. anastomoses with the ascending br. of ileocolic a. to form beginning of marginal artery of Drummond.
- 4. Ileocolic a.:** It is the final branch arising from the Rt. side. It passes downward and to the right toward Rt. iliac fossa where it divides into ascending & descending branches.
 - The ascending br. anastomoses with descending br. of Rt. colic a.
 - The descending (inferior) br. anastomoses with the terminal end of sup. mesenteric artery. The descending/inferior branch of the ileocolic artery also gives rise to:
 - a. **Ant. & post. caecal** arteries to the caecum.
 - b. **Appendicular a.** enters the free margin of and supplies mesoappendix & appendix.
 - c. **Ileal branch** to the terminal part of the ileum before anastomosing with the superior mesenteric artery

5. Jejunal & ileal branches:

- about 12–15 in number arising from the convex Lt. side of the artery.
- They supply the jejunum and most of the ileum.
- They pass between two layers of the mesentery, where they branch and anastomose with each other to form a series of arterial arcades from which further branches arise and form the second, third, and even fifth tiers of arterial arcades.

Arterial arcades:

- The number of these arcades increases from the jejunum (1-2 arcades) to ileum.

- vasa recta (straight arteries): Extend from the terminal arcade and provide the final direct vascular supply to the walls of small intestine.

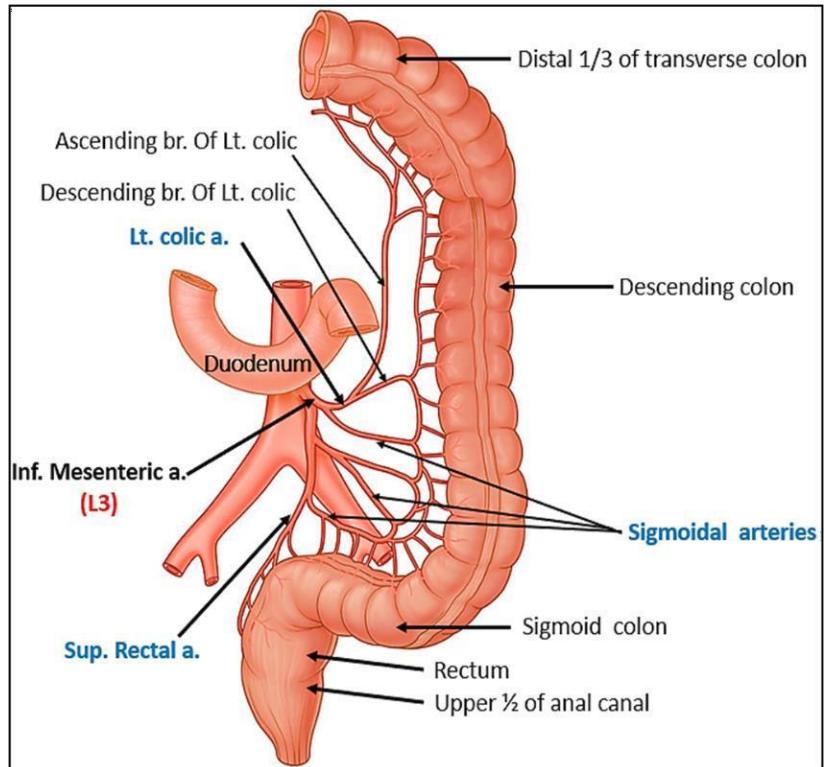
Inferior mesenteric artery (artery of hindgut)

Origin: the smallest of the three anterior branches of the abdominal aorta. It arises anterior to the body of vertebra L3.

Course & End: Initially, the inferior mesenteric artery descends anteriorly to the aorta and then runs downward and to the left to cross the termination of the Lt. common iliac a. (medial to ureter) at which point it becomes superior rectal artery.

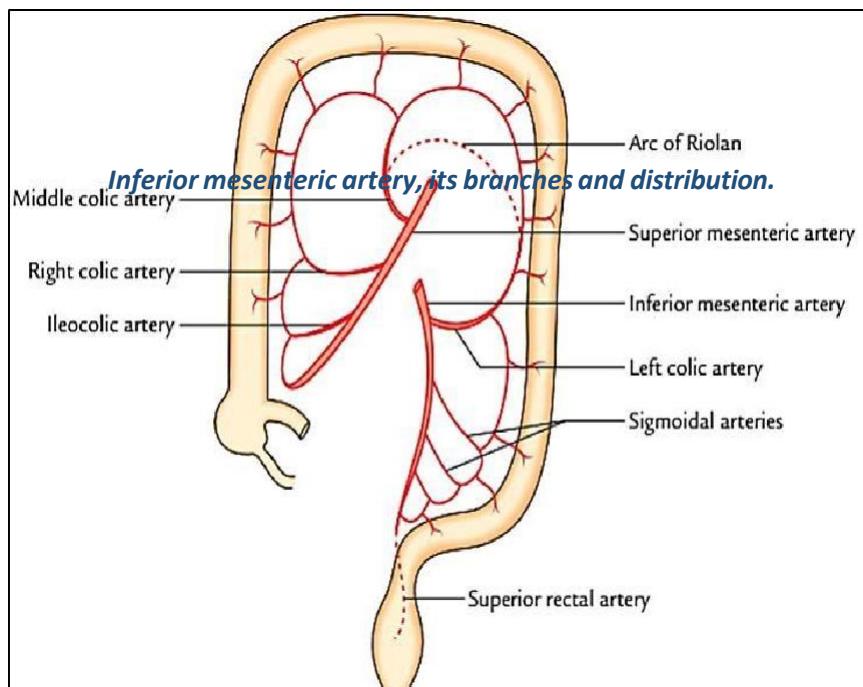
Branches:

- Left colic artery:** It divides into ascending and descending branches:
 - The ascending br.
 - The descending branch anastomoses with the 1st sigmoid a.
- Sigmoidal arteries:** The sigmoid arteries consist of 2-4 branches and descend to the left, in sigmoid mesocolon.
- superior rectal artery:** The continuation of the inferior mesenteric artery. It descends into the pelvic cavity in the sigmoid mesocolon. Opposite vertebra S3, the superior rectal artery divides into 2 terminal branches descend on each side of the rectum. At the level of the internal anal sphincter, end by anastomosing along the way with branches from the middle rectal arteries (from the int. iliac a.) and the inferior rectal arteries (from the int. pudendal a.).



Marginal Artery of Drummond:

- It is a circumferential anastomotic arterial channel extending from the ileocaecal junction to the rectosigmoid junction.
- It is located close (about 3 cm) to inner margin of colon.
- It is formed by the anastomoses between the branches of colic branches of the superior mesenteric artery (i.e., ileocolic, right colic, and middle colic) and colic branches of the inferior mesenteric artery (left colic and sigmoidal). The vasa recta arise from the marginal artery and supply the colon.



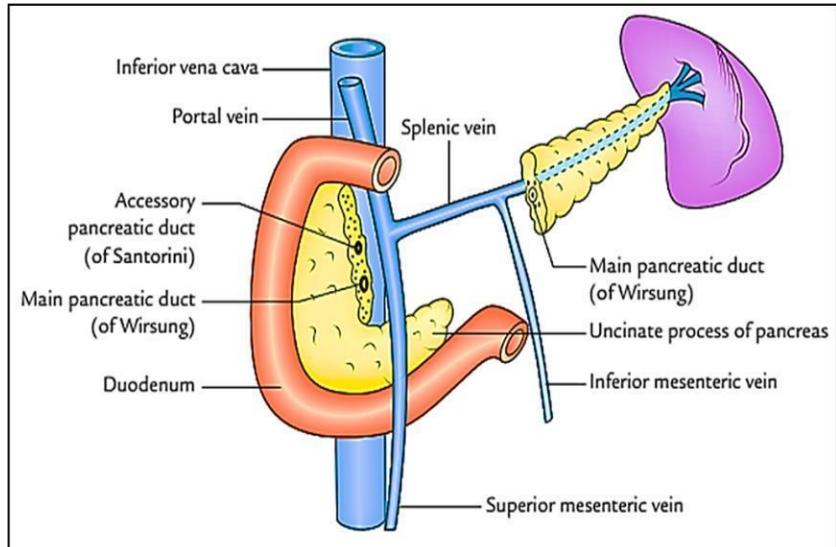
Arterial supply of colon & formation of marginal a. of Drummond.

Portal circulation

Length of portal vein: about 3 inches (7.5 cm) in length

The important features of the portal vein are:

1. It provides about 80% of the blood that flows through liver.
2. Its tributaries & branches contain up to 1/3 of the total volume of blood in the entire body.
3. The portal vein & its tributaries are devoid of valves.



Formation of the portal vein behind the neck of the pancreas

Formation: is formed behind the neck of pancreas by the union of superior mesenteric vein and splenic vein at level of L1.

End: It ends at the right end of porta hepatis by dividing into right & left branches.

Course and parts:

For description, the portal vein is divided into 3 parts in relation to the 1st part of duodenum:

1. **Infra-duodenal part:** behind the Neck of pancreas & in front of IVC.
2. **Retro-duodenal part:** which lies posterior to the 1st part of the duodenum & in front of IVC.
3. **Supra-duodenal part:** which lies in the right free margin of lesser omentum.

N.B. Intrahepatic course: After entering the liver, each branch of the portal vein divides and redivides, like those of the hepatic artery to end ultimately into the hepatic sinusoids. Here the portal venous blood mixes with the hepatic arterial blood. From hepatic sinusoids the blood is drained by hepatic veins into the IVC.

Tributaries:

1. Splenic vein (which receives the inferior mesenteric v.).
2. Superior mesenteric vein.
3. Superior pancreaticoduodenal vein.
4. Left and right gastric veins. The left gastric vein receives a few oesophageal veins from the lower end of oesophagus.
5. Cystic vein joins the right branch of the portal vein before it enters the liver.
6. Paraumbilical veins (of Sappey) are small veins that join the left branch of the portal vein before it enters the left lobe of the liver.

Portocaval (Portosystemic) Anastomoses:

- There are many sites where anastomosis exists between portal and systemic venous systems. These communications form important routes of collateral circulation in cases of portal obstruction.
- The **important sites of portocaval anastomoses** are as follows:

1. Lower third of the oesophagus:

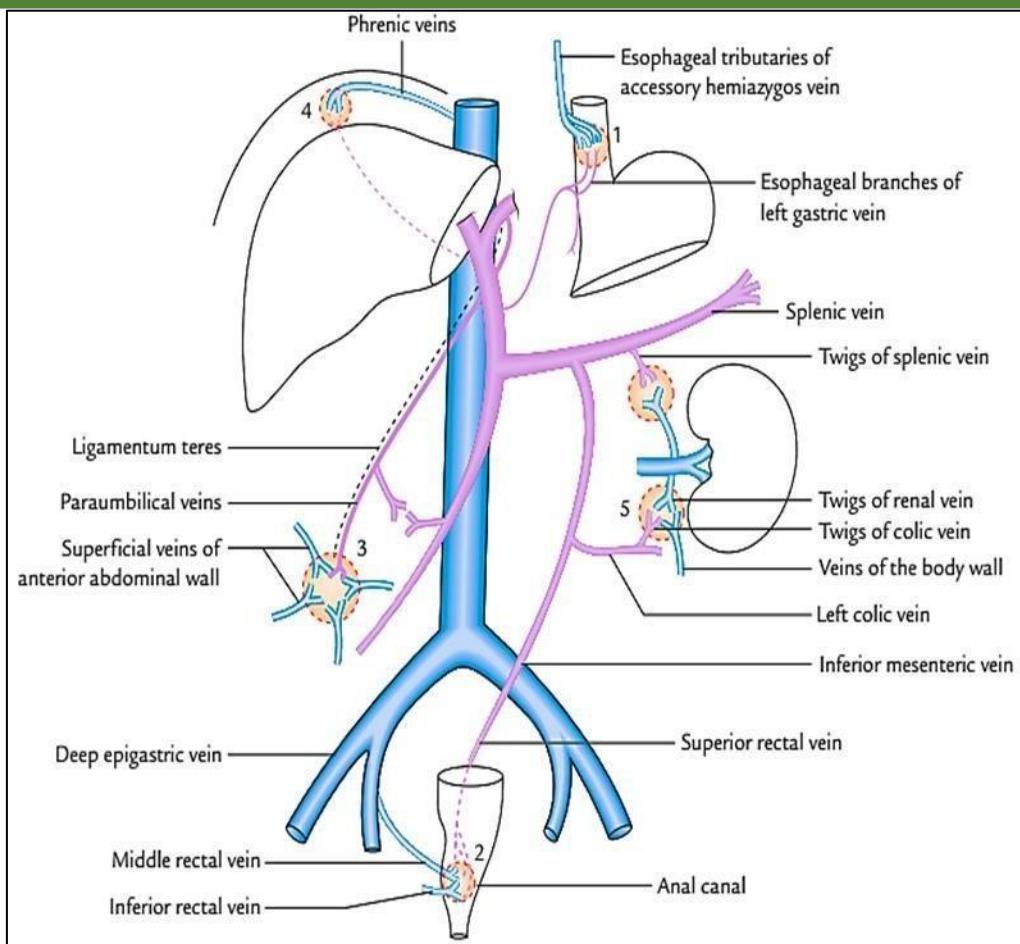
Anastomosis between	Portal: Oesophageal tributaries of left gastric vein Systemic: Oesophageal tributaries of accessory hemiazygos vein
Clinically:	In portal obstruction, these collateral channels become distended and tortuous, forming oesophageal varices.

2. Umbilicus:

Anastomosis between	Portal: Paraumbilical veins Systemic: Superficial veins of anterior abdominal wall
Clinically:	In portal obstruction, the superficial veins around the umbilicus become distended and tortuous (varicosity) (snake like) forming Caput medusae

3. Mid-anal canal

Anastomosis between	Portal: Superior rectal vein Systemic: Middle and inferior rectal veins
Clinically:	The distension and dilatation of these anastomotic channels result in the formation of haemorrhoids or piles which may be responsible for repeated bleeding per annum.



Sites of portosystemic anastomosis: 1=lower end of the esophagus, 2=anal canal, 3= in the region of the umbilicus, 4= at the bare area of the liver, 5=between the colic veins and the renal veins.

Splanchnic Circulation

- The liver and viscera receive about 30% of the cardiac output via celiac, superior mesenteric, and inferior mesenteric arteries.
- The liver receives about 1000mL/min from the portal vein and 500mL/min from the hepatic artery.
- The blood from the intestine, pancreas, and spleen drains via the hepatic portal vein to the liver and from the liver via the hepatic veins to the inferior vena cava.

Intestinal Circulation:

- The intestines are supplied by a series of parallel circulations via branches of the superior and inferior mesenteric arteries.
- The blood flow responds to changes in metabolic activity. Thus, blood flow to the small intestine and hence blood flow in the portal vein doubles after meals and the increase lasts up to 3 hours.
- The intestinal circulation is capable of extensive autoregulation.

Hepatic Circulation:

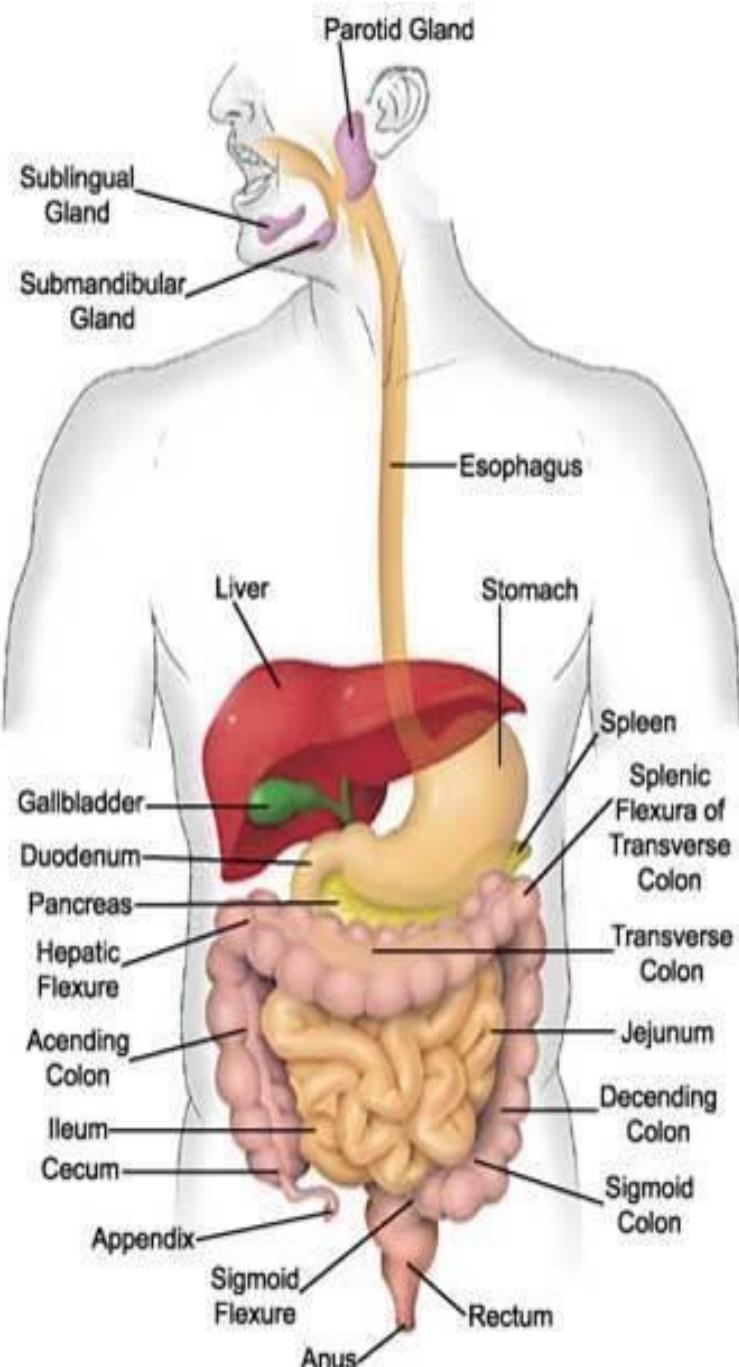
- The functional unit of the liver is the acinus. The human liver contains about 100,000 acini. Each acinus is at the end of a vascular stalk containing terminal branches of portal veins, hepatic arteries, and bile ducts. The hepatic veins drain into the inferior vena cava.
- Portal venous pressure is normally about 10mmHg, the mean pressure in the hepatic artery branches is about 90 mmHg and the hepatic venous pressure is about 5mmHg.

- There is an inverse relationship between hepatic arterial and portal venous blood flow.
- The intrahepatic portal vein radicles have smooth muscle in their walls that is innervated by noradrenergic vasoconstrictor nerve fibers reaching the liver via the third to eleventh thoracic ventral roots and the splanchnic nerves. The vasoconstrictor innervation of the hepatic artery comes from the hepatic sympathetic plexus. There are no known vasodilator fibers reaching the liver. Conversely, when there is diffuse noradrenergic discharge in response to a drop in systemic blood pressure, hepatic blood flow may be reduced to such a degree that there is patchy necrosis of the liver.

Reservoir function of the Splanchnic Circulation:

The reservoir function of the whole visceral circulation is important. For example, 25-30% of the volume of the liver is accounted for by blood and contraction of the capacitance vessels in the viscera can pump a liter of blood into the arterial circulation in less than a minute. During severe exercise, constriction of the vessels in these organs and decreased blood storage in the splanchnic bed, the skin and the lungs may increase the volume of actively circulating blood perfusing the muscles by as much as 30%.

HISTOLOGY OF DIGESTIVE SYSTEM



OBJECTIVES

By the end of this chapter the student should:

- Define the histological structure of different parts of the digestive system.
- Outline the general wall structure of the gastrointestinal tract.
- Recognize histological features of different regions of the gastrointestinal tract.
- The structural adaptations in the gastrointestinal tract that facilitate digestion and absorption.
- Know the glands associating the digestive tract.
- Identify the similarities and differences between these different glands.
- Identify the structural adaptation of these glands to assist digestion and absorption.

The following subjects are going to be discussed in this chapter:

Oral Cavity

- Lip
- Tongue
- Lingual Papillae
- Minor Salivary Glands
- Major Salivary Glands
 - Parotid Gland
 - Submandibular Gland
 - Sublingual Gland

Digestive Tract

- Esophagus
- Stomach (Fundic and Pyloric Regions)
- Small Intestine
 - Intestinal Villi and Crypts
 - Duodenum
 - Jejunum
 - Ileum
- Large intestine
- Appendix
- Anal Canal

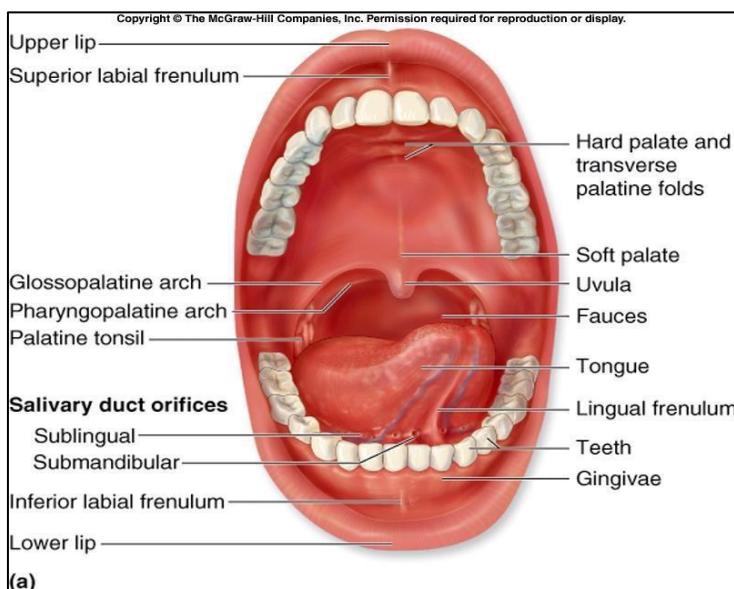
Associated Glands

- Pancreas
- Liver
- Salivary glands

Oral Cavity

- The oral cavity includes the **vestibule** and **oral cavity proper**.
- **Vestibule** is the space between the lips, cheeks, and teeth.
- The oral cavity proper lies behind the teeth bounded by hard and soft palate superiorly, tongue and the floor of the mouth inferiorly (**Fig. 1**).
- It consists of:
 1. Lip.
 2. Teeth.
 3. Tonsils.
 4. Tongue.
 5. Minor & Major salivary glands.
 6. Palate.

Fig.1: General structure of oral cavity



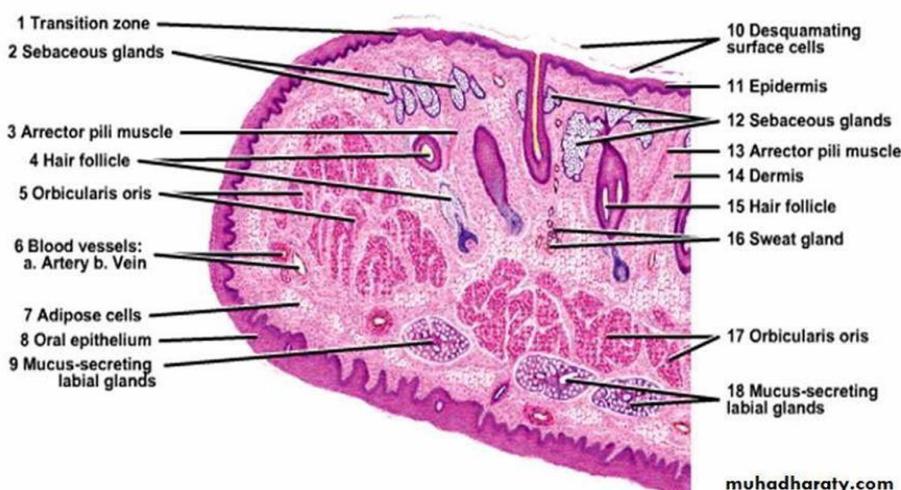
- Oral cavity is lined with stratified squamous epithelium, keratinized or non-keratinized, depending on the region.
- The keratin layer protects the oral mucosa from damage during mastication and it is present mostly in the gingiva (gum) and hard palate.
- Non-keratinized stratified squamous epithelium covers the soft palate, lips, cheeks, and the floor of the mouth.
- The lamina propria (loose connective tissue layer under the epithelium) in these regions rests directly on the bony tissue; it has several papillae, and contains diffuse small salivary glands.

Lip

- The core of the lip is formed of striated muscle fibers (Orbicularis oris muscle), its fibers run in different directions.
- The lip has 2 surfaces and red margin in-between (**Fig. 2**):

 1. **Outer surface:** is covered by **thin skin** containing hair follicles, sebaceous and sweat glands.
 2. **Inner surface:** is covered with a **mucous membrane** formed of thick and transparent non-keratinized stratified squamous epithelium, the underlying lamina propria is formed of loose connective tissue containing blood vessels, lymphatics, nerves and group of salivary mucous acini called labial glands.
 3. The free red margin (**vermillion border**) of the lip is covered by modified stratified squamous epithelium contains no hair follicles, no sebaceous or sweat glands. It contains **richly vascularized** connective tissue papillae (the reflection from these blood vessels gives the red color of the lip).

Fig. 2: The histological structure of lip



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Tongue

- The tongue is a mass of striated muscles covered by a mucous membrane whose structure varies according to the region.
- The muscle fibers are arranged in bundles cross one another in three planes and usually separated by connective tissue.
- Because the connective tissue of the lamina propria penetrates the spaces between the muscular bundles, the mucous membrane is **strongly** adherent to the muscle.
- The lower (ventral) surface** is smooth covered by **a mucous membrane**.
- The dorsal surface** is irregular, covered by partially keratinized stratified squamous epithelium and contains a great number of small eminences called **papillae**.
- The posterior one-third of the dorsal surface of the tongue is separated from the anterior two-thirds by a V-shaped boundary **sulcus terminalis** (**Fig. 3**).

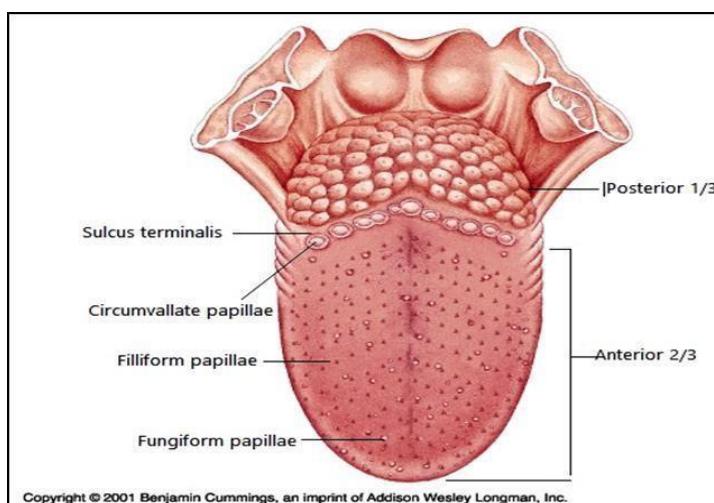


Fig. 3: the general structure of dorsal surface of the tongue

Lingual Papillae:

- They are small projections in the mucous membrane of the dorsal surface of the tongue; each one is formed of a central core of connective tissue covered by stratified squamous epithelium.
- There are 4 types of lingual papillae (**Fig. 4**):
 - Filiform Papillae.
 - Fungiform Papillae.
 - Circumvallate Papillae.
 - Foliate Papillae.

1. Filiform Papillae

- They are **the most numerous**.
- They have an elongated **conical** shape.
- They have **no** taste buds.
- They are covered with **keratinized** stratified squamous epithelium.
- The tip of the papillae is continuously **exfoliated**.

2. Fungiform Papillae

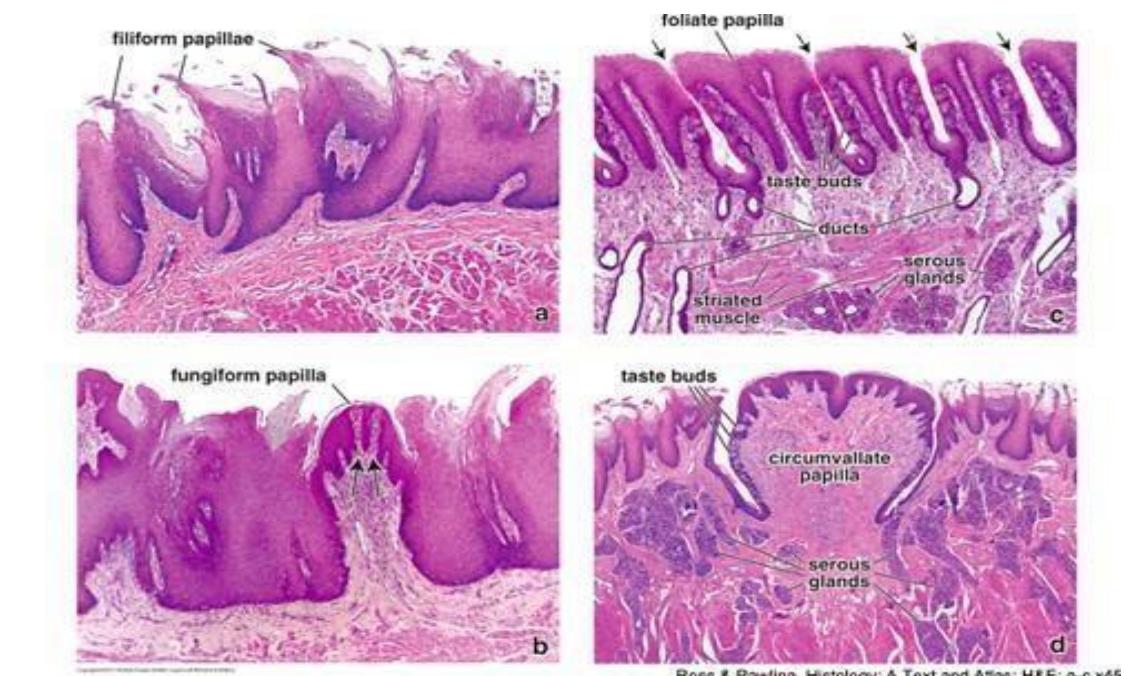
- They are less in number, scattered among filiform papillae especially on the tip of the tongue.
- They resemble **mushrooms** in that they have a narrow stalk and a smooth-surfaced, dilated upper part.
- They contain few scattered **taste** buds on their upper surfaces.
- The covering epithelium is **non keratinized** stratified squamous epithelium.

3. Circumvallate Papillae

- They are the largest papillae. The tongue has **7–12** circumvallate papillae.
- They are distributed in **the V region** in the posterior portion of the tongue.
- They appear as domes extending above the other papillae.
- Each papilla is surrounded by a narrow groove containing underlying C.T with numerous serous (**von Ebner's**) glands drain their secretion.
 - Function of the glands:
 - Secrete watery secretion to dissolve taste materials and to remove food remnant on taste buds. This facilitates recycling of the taste sensation.
 - Secrete lipase enzyme.
- It contains **numerous** taste buds on the lateral wall.

4. Foliate Papillae

- Foliate papillae are poorly developed in human.
- They are found mainly in rabbit tongue.
- Each one consists of two or more parallel ridges and furrows on the dorsolateral surface of the tongue. They contain many taste buds on the lateral wall.



Ross & Pawlina, Histology: A Text and Atlas; H&E; a-c x45

Fig. 4: Different types of lingual Papillae

Taste Buds

- They are oval **neuro-epithelial structures** present in the epithelium covering the dorsum of the tongue, soft palate, pharynx and posterior surface of the epiglottis.
- There are about **3000 taste** buds in the human tongue.
- They occupy the full thickness of the epithelium.
- They are **ovoid pale bodies** in the darker staining lingual epithelium.
- Their apices converge and open in a small opening (**taste pore**) in the superficial layer of the epithelium.
- Each taste bud contain about 50-60 fusiform cells.
- Three cell types are distinguished (**Fig. 5**):

1. Neuroepithelial, sensory cells:

- The most numerous cells.
- They are slender cells situated both at the periphery of the taste bud and its interior.
- They have long microvilli projecting into the taste pore.
- Their apical cytoplasm contains dense secretory granules. They form tight junctions with each other and with supporting cells.

- They receive different taste sensation.
- The turnover time of these cells is about 10 days.

2. Supporting cells:

- Histologically they are similar to the sensory cells but lack secretory granules and appear fainter.
- They are supporting cells.
- The turnover time of these cells is about 10 days.

3. Basal Cells:

- They are small cells found at the base of the taste buds
- They are considered as stem cells for other cell types.

Function: Perception of taste sensation.

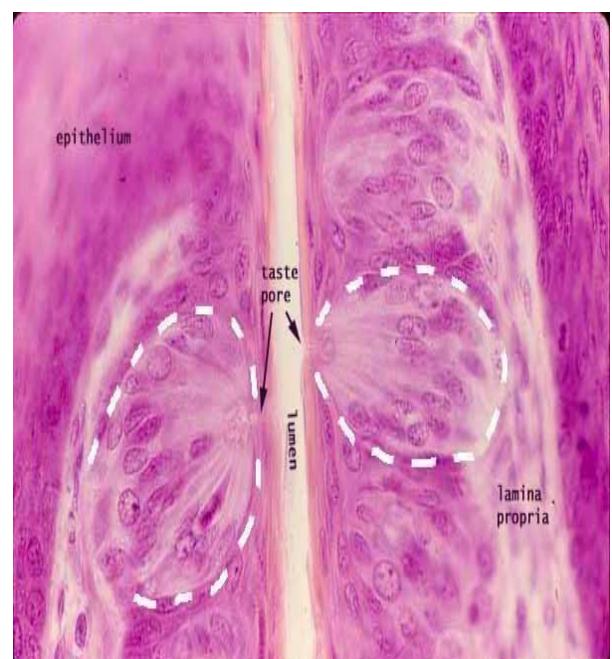
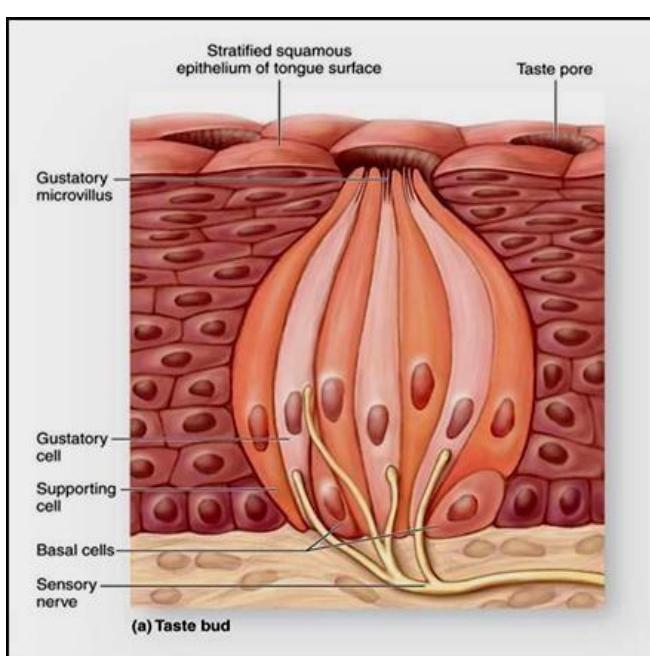


Fig. 5: Structure of taste buds

SALIVARY GLANDS

- They are exocrine glands that produce **saliva** which has digestive, lubricating, immunological functions, and it also allows the process of tasting food.
- They secrete antibacterial agents as lysozymes and lactoferrin.

Types:

I. Minor salivary glands:

- They are simple branched tubulo-alveolar glands which located in the mucosa of the oral cavity.
- They include:
 1. Labial glands in the lip.
 2. Buccal glands in the cheek.
 3. Lingual glands in the tongue.
 4. Palatine glands in the palate.

II. Major salivary glands:

- They are paired compound tubulo-alveolar glands.
- They develop from the lining epithelium of the oral cavity and open into it by ducts.
- They include:
 1. Parotid gland.
 2. Submandibular (submaxillary) gland.
 3. Sublingual gland.

General structure

- Each gland is formed of :
 - a) Stroma or (connective tissue component):
 - i. Capsule.
 - ii. Trabeculae of connective tissue septa which divide the gland into lobes and lobules.
 - iii. Reticular connective tissue forms the background network.
 - b) Parenchyma or (epithelial component) which is formed of:
 - i. Secretory part (serous, mucous or seromucous acini).
 - ii. Duct system.

Serous Acini

- They secrete watery secretion rich in protein and also contain enzymes.

LM: (Fig. 6A).

- They are rounded or ovoid (acinus) in shape, small in size with narrow lumen.
- Their lining cells are pyramidal in shape, with basal rounded nucleus, basal basophilic and apical acidophilic cytoplasm.
- Associated with little number of myoepithelial cells.

EM: (protein secreting cells)

- The serous cell shows abundant rough endoplasmic reticulum mainly in the basal region, prominent supranuclear Golgi apparatus, many ribosomes and mitochondria, apical secretory granules and apical microvilli.
- The cells are joined together by junctional complexes consisting of zonula occludens, zonula adherens and gap junctions.

Mucous Acini

- They secrete mucous secretion.

LM: (Fig. 6B).

- They are tubular in shape.
- They are relatively large with wide lumen.
- The cells are cuboidal in shape, with basal flat nuclei (pressed by mucous).
- The cytoplasm is pale basophilic and has a foamy appearance.

EM:

- The cytoplasm contains Golgi apparatus, few mitochondria, basal rough endoplasmic reticulum and numerous secretory granules containing mucinogen.

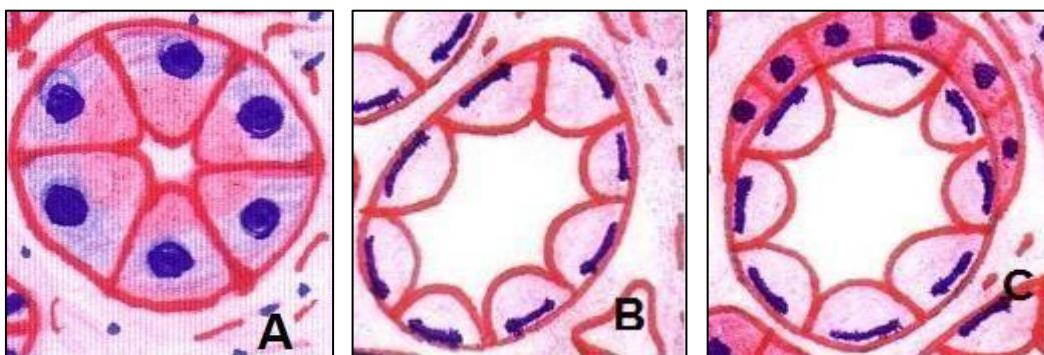


Fig. 6A: Serous acinus

(6B) Mucous acinus.

(6C) Seromucous acinus

Seromucous Acini

- Contain both serous and mucous cells.
- The mucous cells are organized as tubules and form the proximal part of the acini, capped by serous cells and form the distal end and appear as crescent cap of dark cells called serous demilune or **crescent of Gianuzzi** (**Fig. 6C**).
- The secretion of the demilune reaches the lumen through narrow channels present between the mucous cells.

Myoepithelial (Basket) Cells

- They found within the basal lamina of glandular and ductal epithelia of salivary glands.
- They are highly branched cells surround serous acini those associated with mucous acini and intercalated ducts are spindle-shaped and lie parallel to the length of the duct.
- The cytoplasm is rich in **actin and myosin** filaments. Contraction of these cells press on the acini to release their products into the duct system.

Duct System

- The ducts are classified according to their location into: (**Fig 7**).
 - Intercalated ducts:** They are very small ducts arise from the lumen of the acini. They are lined by low cuboidal epithelium.

2. **Intralobular (striated) ducts:** These ducts are found inside the lobules between the secretory acini and lined by cuboidal or low columnar cells. These cells have **basal striation** which is due to basal infolding of the basal cell membrane and parallel mitochondria. This arrangement is characteristic of sites of active transport mechanism. These cells have secretory function.
3. **Interlobular ducts:** They are large ducts found in the connective tissue septa between the lobules. They are lined with columnar cells.
4. **Interlobar ducts:** They are present in the connective tissue septa between the lobes. They are lined with pseudostratified columnar epithelium.
5. **Main ducts:** These ducts open in the oral cavity. They are lined with stratified columnar then stratified squamous near the opening.

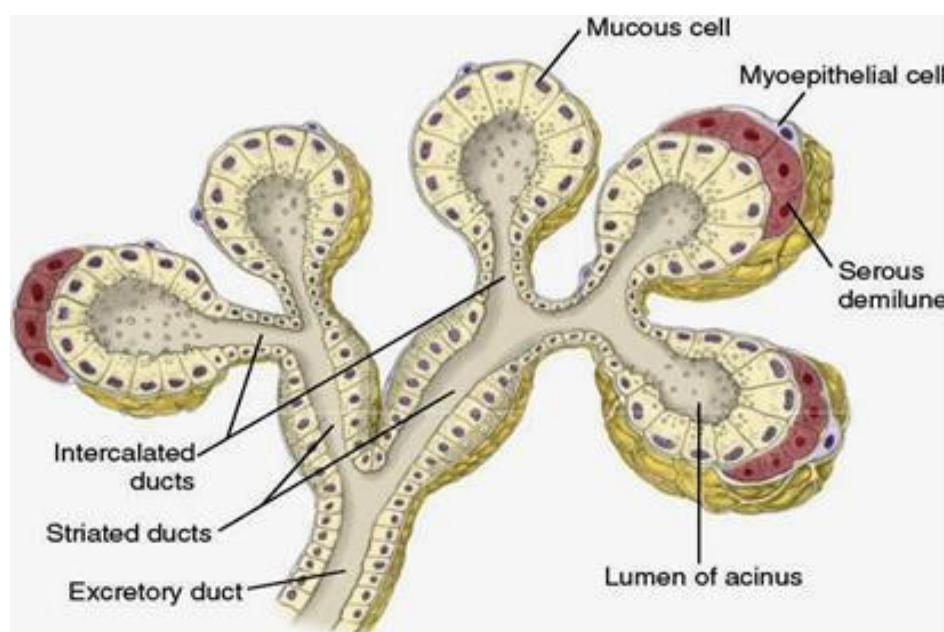


Fig.7: Duct system of salivary glands

PAROTID GLAND

- It is the **largest** major salivary gland.
- It is found in front of the ears.
- It is **purely serous** and produces about 20-30% of the total salivary volume.

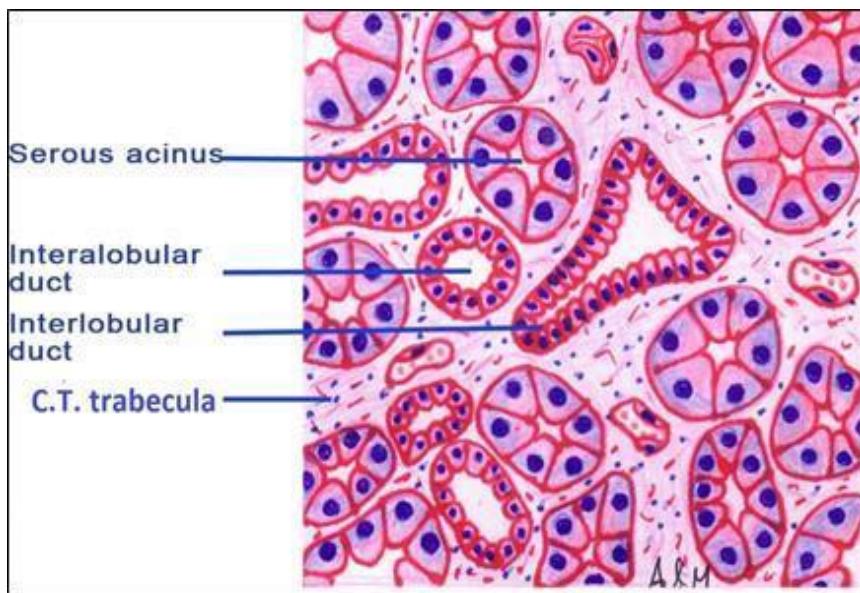
Stroma:

- **Capsule:** well developed connective tissue capsule which contains abundant fat cells and many lymphocytes and plasma cells (secrete IgA).
- **Septa:** Thick septa divided the gland into lobes and lobules.
- **Reticular connective tissue:** Forms the background of the gland

Parenchyma: (Fig. 8).

- It is branched acinar gland.
- The granules in the serous cells are PAS positive (rich in polysaccharide content) and rich in protein (amylase).
- The duct system is well developed.
- The main duct opens in the inner surface of the cheek opposite the second upper molar tooth.

Fig.8: Parotid gland



SUBMANDIBULAR GLAND

- It is present at the inner aspect of the mandible.
- It is a **mixed gland**.
- The serous acini are more numerous than mucous acini.
- It produces about 60-70% of the total volume of saliva

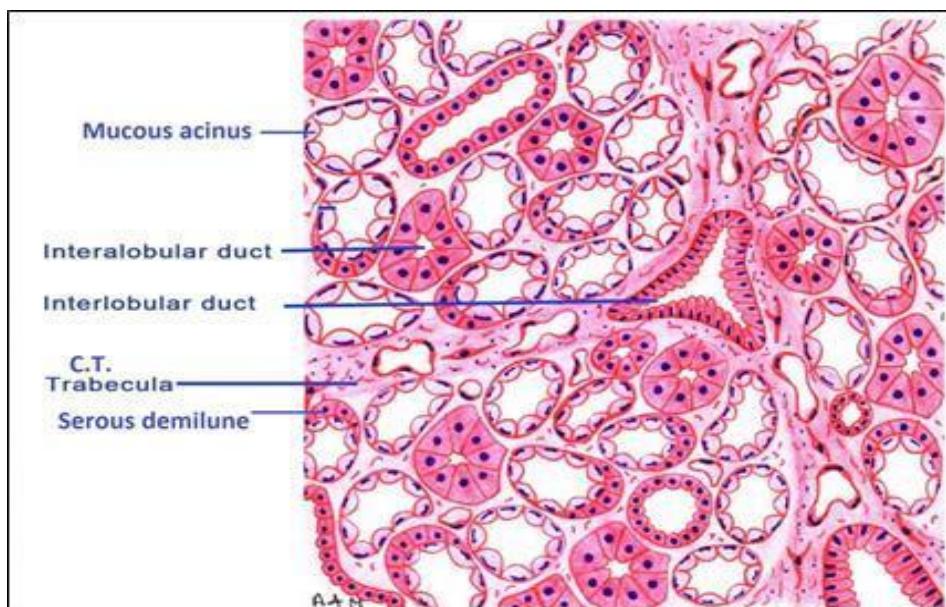
Stroma:

- **Capsule:** It has a well-developed capsule (less fat cells are seen).
- **Septa:** Thick septa divided the gland into lobes and lobules.
- **Reticular connective tissue** forms the back ground of the gland

Parenchyma: (Fig. 9).

- It is a compound tubulo-acinar gland.
- It contains both serous (about 90%) and mucous acini.
- The granules in serous cells are PAS positive because of the presence of carbohydrate and also rich in protein (lysozyme).
- The serous cells that form the **demilunes** secrete the enzyme lysozyme its main activity is to hydrolyze the walls of certain bacteria (bactericidal).
- The **intercalated ducts** are short, while striated ducts are much longer than other glands. Its main duct (**Warton's duct**) opens in the floor of the mouth cavity.

Fig. 9: Submandibular gland



SUBLINGUAL GLAND

- It is a mixed gland.
- It is the smallest of major salivary glands
- Mucous acini are more numerous than serous acini.
- It produces about 5% of the total volume of saliva.

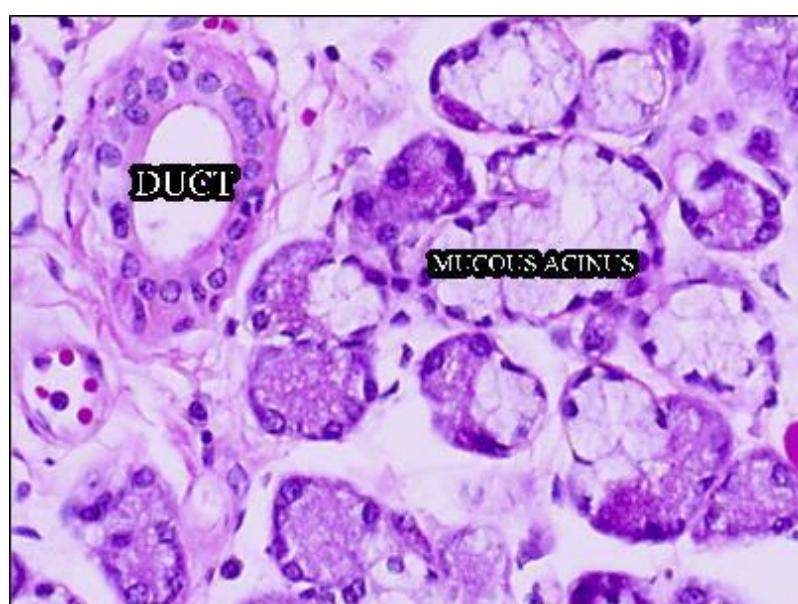
Stroma:

- **Capsule:** thin ill- developed capsule.
- **Septa:** thick septa dividing the gland into lobes and lobules.
- **Reticular connective tissue:** forms the background of the gland.

Parenchyma: (Fig. 10)

- It is a branched tubuloacinar gland.
- It has no pure serous acini.
- The mixed acini with crescents of Gianuzzi represent about 40%.
- Serous cells that form the demilunes form lysozome.
- The gland produces mixed, but mainly mucous saliva.
- The striated ducts are poorly developed.
- There is no main duct; the secretion is released by several ducts into the floor of the mouth or in the main duct of the submandibular gland.

Fig. 10: Sublingual gland



DIGESTIVE TRACT

- The wall of digestive tract is made up of four major layers (**Fig.11**):
 - Mucosa (mucous membrane).
 - Submucosa.
 - Musculosa or muscularis externa.
 - Adventitia or serosa.

1. Mucosa (Mucous Membrane):

- It consists of three components:
 - Epithelium.**
 - Lamina propria.**
 - Muscularis mucosae.**

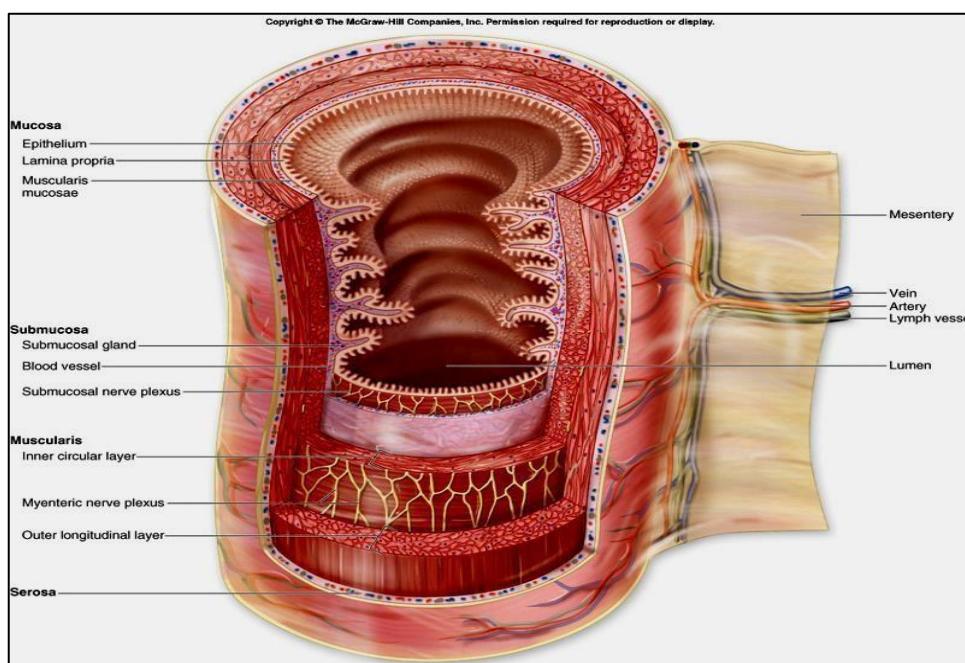


Fig. 11: General histological feature of digestive tract

a) Epithelium:

- The type of epithelium reflects the function of each part of the tract.
 - The esophagus and the anus are protected from abrasion by non-keratinized stratified squamous epithelium.
 - The stomach is lined by simple columnar epithelium that secretes protective mucus.

- The small and large intestines are lined by simple columnar epithelium (absorptive) and mucous-secreting goblet cells.

b) Lamina propria:

- It is a loose connective tissue layer that nourishes and supports the mucosal epithelium and its associated mucosal glands.
- It is richly provided with blood and lymphatic capillaries where various products of digestion pass.
- Diffuse lymphocytes, un-encapsulated lymphoid follicles and plasma cells (secrete antibodies) are commonly found.
- It contains mucous- secreting glands in the esophagus and anal canal.

c) Muscularis mucosa:

- The deepest part of the mucosa.
- It is a thin, layer of smooth muscles usually arranged as inner circular and outer longitudinal.
- Its contractile activity results in an independent local movement and folding of the mucosa that facilitates digestion, absorption and gland secretion.
- In the small intestine, bundles of smooth muscle cells extending from the muscularis mucosa to the tips of villi can regulate villous height.

2. Submucosa:

- A dense irregular connective tissue layer lying between the mucosa and muscularis externa that contains blood vessels, lymphatics, nerve plexuses and glands.
- The submucosa also contains **mucous-secreting glands** in the esophagus and duodenum.
- A plexus of parasympathetic ganglion cells and nerve fibers (**Meissner's plexus**) is present between the submucosa and the muscularis externa.

3. Muscularis externa:

- It consists of two layers of smooth muscle, inner circular and the outer longitudinal.
- It is responsible for rhythmic waves of contraction (peristaltic waves) that move the luminal contents along the tract.
- Between the two layers, Auerbach's (myenteric) parasympathetic nerve plexus is present.
- Contraction of the circular muscle mixes the contents inside the lumen while the longitudinally muscle helps their propagation.

N.B

- The circular smooth muscle layer forms 4 sphincters:
 1. Pharyngoesophageal sphincter.
 2. Pyloric sphincter.
 3. Ileocecal sphincter.
 4. Internal anal sphincter.

4. Adventitia or serosa:

- Adventitia is an outermost layer of loose connective tissue in the retroperitoneal segments of the intestine. It contains major blood vessels, nerves and variable amount of fatty tissue.
- Serosa is an outermost layer of loose connective tissue covered by simple squamous epithelium (visceral peritoneum). It contains major vessels, lymphatics and nerves.

ESOPHAGUS

- A straight long narrow muscular tube (about 25 cm) that conveys chewed food rapidly from the pharynx to the stomach.
- Layers of esophagus are: (**Fig. 12**)

1. Mucosa:

a) Epithelium:

- Non-keratinized stratified squamous epithelium to **overcome abrasion**.
- Langerhans cells are present between the epithelial lining cells.

b) Lamina propria:

- Connective tissue, containing:
 - Simple tubular **mucous glands** both at the upper (to facilitate swallowing) and at the lower end (to neutralize HCl regurgitated from stomach) of the esophagus.

- It contains **diffuse** lymphatic tissue, nodules and other connective tissue cells.
- c) Muscularis mucosa:**

- Is unusual in that it consists only of single layer of longitudinally oriented smooth muscle fibers.

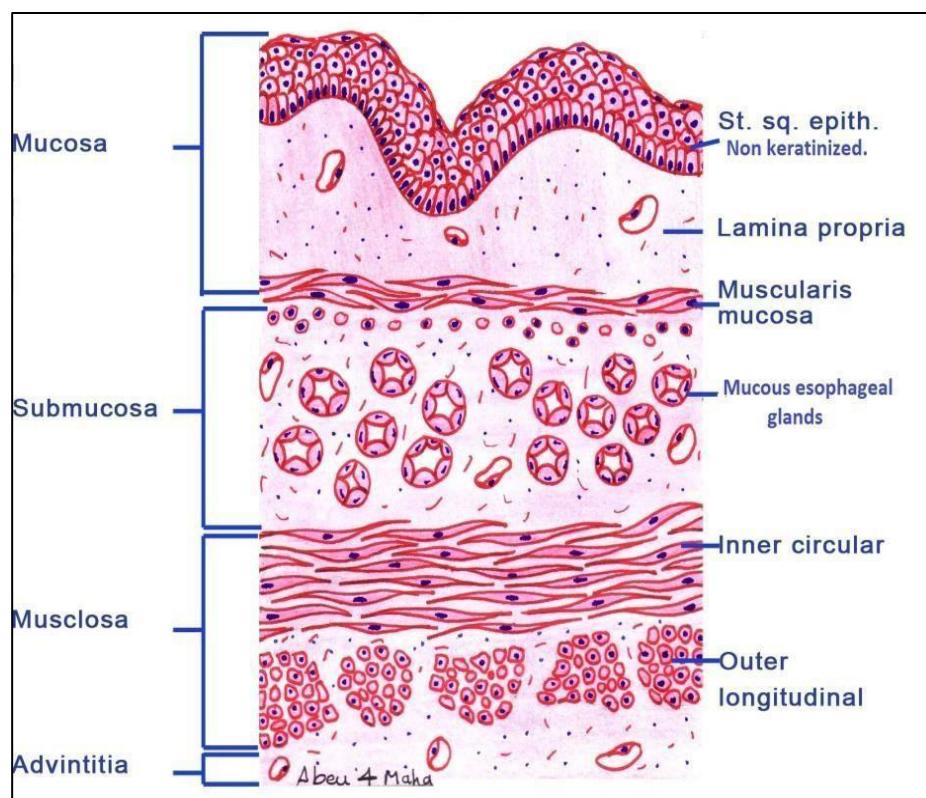


Fig. 12: Layers of esophagus

2. Submucosa:

- Dense connective tissue layer rich in blood vessels, lymphatics, nerves and esophageal glands (mucous glands) which are compound tubulo-alveolar glands.

3. Muscularis externa:

- It is formed of inner circular and outer longitudinal layers.
- It is of striated type in the **upper third**, smooth muscles in the **lower third** and the **middle third** contains both types of muscles.

4. Adventitia and serosa:

The outermost layer of most of the esophagus above diaphragm is an adventitia while the lower abdominal end is covered by serosa.

STOMACH

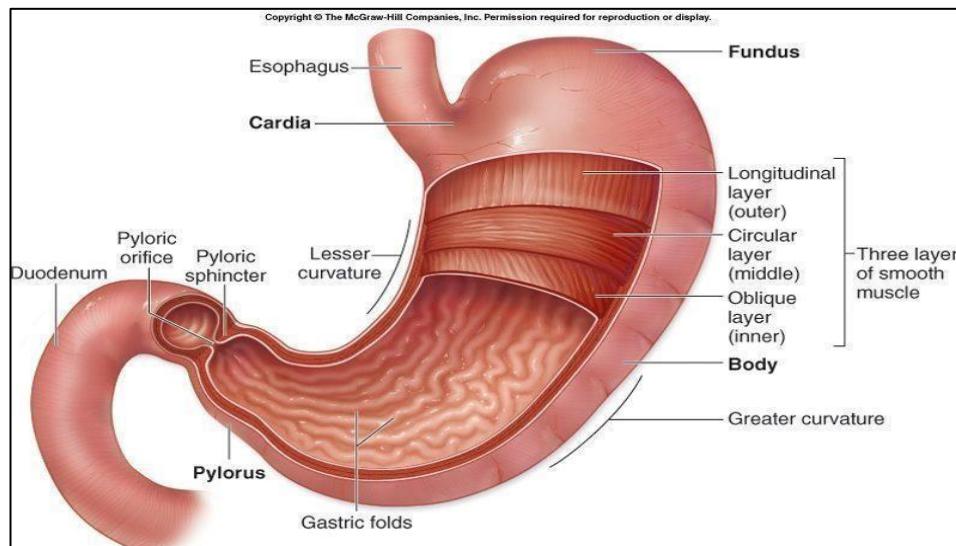


Fig. 13: The anatomical description of the stomach

- It is an expandable muscular reservoir that retains swallowed food for 2 hours or more
- Digestion and absorption (drugs, alcohol, salts, and water) begin in the stomach.
- **Anatomically**, the stomach is made up of (**Fig. 13**):

 1. **Cardiac region**, surrounding the cardiac orifice
 2. **Fundus**, the superior region
 3. **Body**, the main region
 4. **Pyloric antrum, pyloric canal**, and **pylorus**, the distal part.

- **Histologically**, three regions are distinguishable:
 1. **Cardiac region** surrounding the cardiac orifice
 2. **Fundic region**, which includes both the fundus and the body.
 3. **Pyloric region**, which includes the pyloric antrum, pyloric canal, and pylorus.

1. Cardiac Region

- Surrounds the entrance of the esophagus.
- The mucosal glands of the cardiac region (cardiac glands) are small tubular branching and mucous secreting.

2. Fundic Region

1. Mucosa:

- The characteristic feature seen in the gastric mucosa of the empty stomach is that it is raised into longitudinal branching folds termed **rugae** (Latin for wrinkles). These folds and their submucosal cores become flattened out if a substantial meal is ingested.
- Another characteristic feature of the gastric mucosa is the numerous gastric pits dense which represent the distribution of its simple tubular mucosal glands.

a) Epithelium:

- The epithelial lining of the stomach consists of mucous columnar cells (surface mucous cells).
- Gastric pits are little depressions in the stomach lining in which gastric glands open.

b) Lamina Propria:

- Loose connective tissue occupied by most of the fundic glands.

c) Muscularis mucosae:

- Smooth muscle arranged into inner circular and outer longitudinal layers.

2. Submucosa:

- Connective tissue layer containing blood vessels, lymphatics and autonomic Meissner's plexus of nerves.

2. Musculosa (Muscularis externa):

- It is formed of three smooth muscle layers, inner oblique, middle circular and outer longitudinal to facilitate mechanical action in all directions.

- The autonomic Auerbach's plexus is found in between the muscle fibers.
- 3. Serosa:**

- It covers the external surface of the stomach.

Fundic Glands

- They are straight, **simple, branched tubular glands**, divided into **three regions**: (**Fig. 14**).
 - An isthmus.
 - A short neck.
 - Long base or body.
- They open on the surface in the **gastric pit**.
- Gastric glands synthesize and secrete **gastric juice**, which contains:
 1. Hydrochloric acid.
 2. Mucus.
 3. Proteolytic enzyme pepsin (secreted as pepsinogen) and lipolytic enzymes lipase.
 4. Intrinsic factor for vitamin B12 absorption.
 5. Water and electrolytes.
- A variety of cell types is found in fundic glands, depending on the region in which they lie:

<ol style="list-style-type: none"> 1. Undifferentiated stem cells. 2. Surface mucous cells. 3. Mucous neck cells. 	<ol style="list-style-type: none"> 4. Parietal cells. 5. Chief cells. 6. Argentaffin cells.
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1. Undifferentiated Stem Cells

- Present in the **isthmus** and neck regions.
- Columnar cells with basal oval nuclei and basophilic cytoplasm.
- It may show mitotic figure (dividing cell)
- They divide and move upward to differentiate into surface mucous cells or move deeper into the glands and differentiate into the other types of cell.

2. Surface Mucous Cell

LM:

- Columnar cells present in the surface and gastric pits
- Basal oval nuclei.
- Apical mucin granules
- They are pale-staining with H&E owing to their content of mucous-filled secretory granules (stained with PAS).

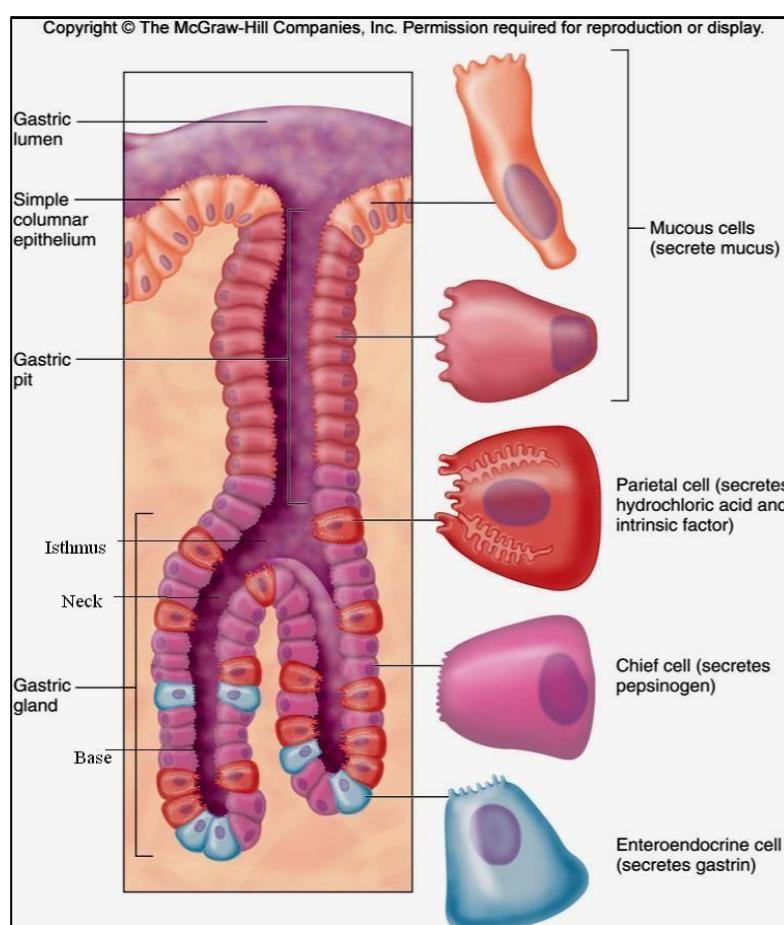


Fig. 14: The fundic glands

EM:

- Electron lucent mucous secretory granules are found in the apical part of the cytoplasm.
- Golgi apparatus below these mucous granules.
- RER in basal region of each cell.

Function:

- It produces a thick coat of neutral mucous that protects the gastric mucosa against digestion by HCl and gastric enzymes in the lumen.

3. Mucous Neck Cells

- Present in the neck of the gland.
- They differ from surface mucous cells in that they secrete a thin acidic mucous.
- Shorter than mucous surface cells with less mucigen and their nuclei are rounded.

4. Parietal (oxytic) Cells

- These cells are distributed along the length of the fundic glands, chiefly in the neck region and in the deeper part between mucous neck cells.

LM

- Large, rounded, or triangular cells with a central spherical nucleus.
- They are rest on the basement membrane, but their apices do not reach the lumen i.e. peripheral in position (**Parietal**).
- Acidophilic (**oxytic**) cytoplasm.

EM

- They are characterized by **intracellular channels (canalliculi)** which are the site of HCl formation. (**Fig. 15**).
- They communicate with the lumen of the gland.
- Numerous **long microvilli** project from its outer surface.
- Tubulovesicular membrane system is present.
- Many **mitochondria** are present on the inner surface of the limiting membrane of these canalliculi and Golgi apparatus is also present.

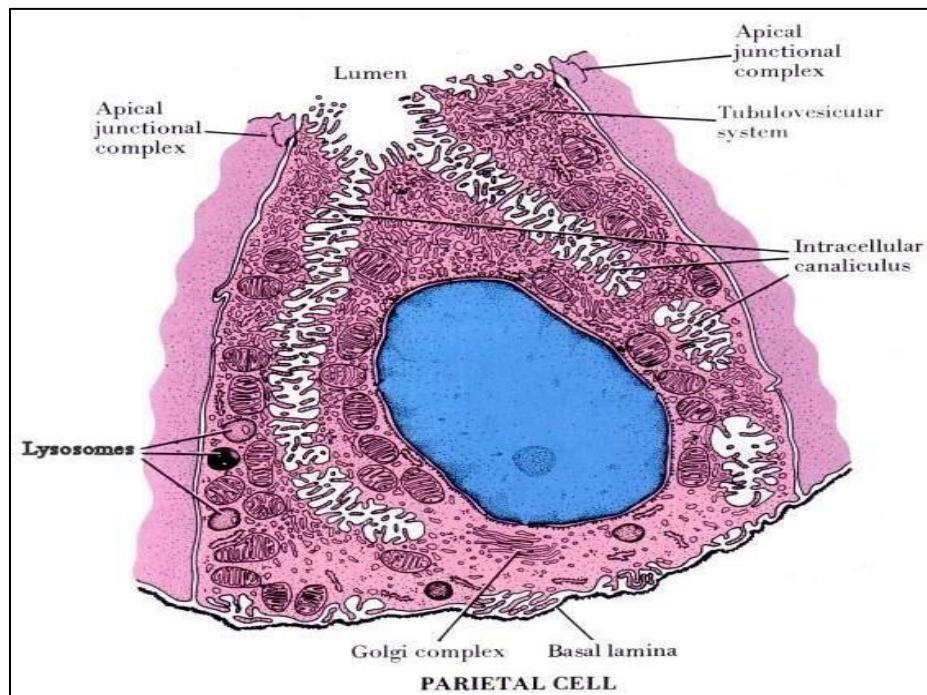


Fig. 15: Diagram showing structure of parietal cell.

Mechanism of HCl secretion

- **Production of hydrogen:** CO_2 passes from blood to the parietal combined with H_2O give H_2CO_3 which dissociates into H^+ and HCO_3^- in the presence of **carbonic anhydrase enzyme**. (**Figs. 16&17**).
- **Transport of H^+ ions:** The canalicular membrane **actively** transports hydrogen ions into the lumen of canaliculi.
- **Transport Cl^- ions:** Cl^- ions is transported passively (counter transport) from blood into the lumen of canaliculi. Cl^- combines with H^+ in the lumen of canaculi to form HCl .
- The gastric mucosa is protected from acidity by:
 1. The local interstitial high concentration of bicarbonate ions **protect** the mucosa from hydrogen ions leaking from the gastric lumen through the epithelium.
 2. The mucous coat of gastric mucosa acts as an important diffusion **barrier** between the mucosal bicarbonate and the luminal hydrogen ions.

Function:

1. Parietal cells form gastric **hydrochloric acid**.
2. They produce **intrinsic factor**, which is essential for absorption of vitamin B12.

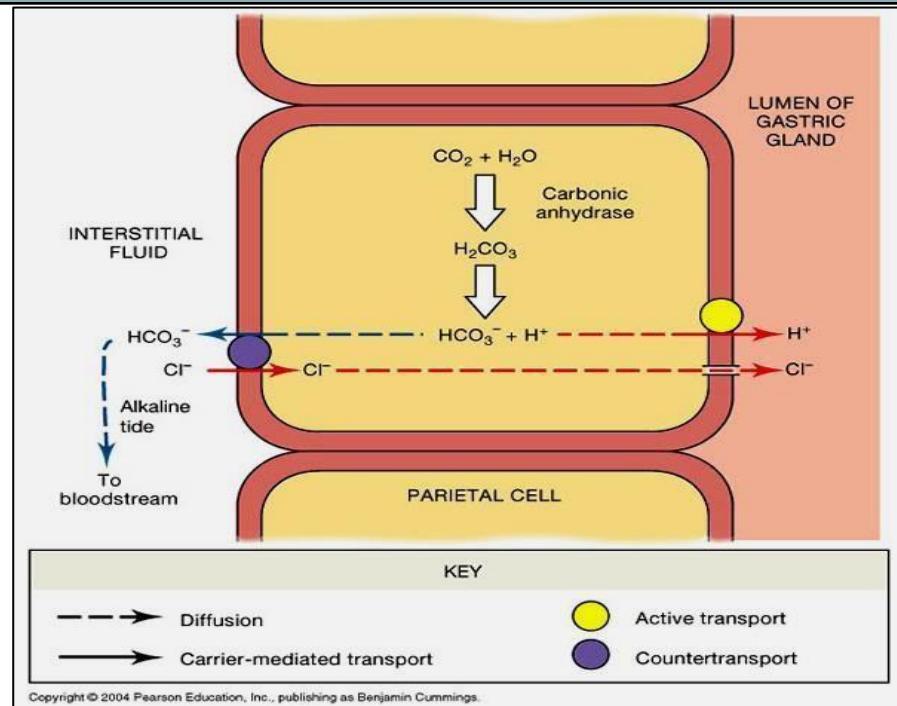


Fig. 16: Mechanism of HCl secretion

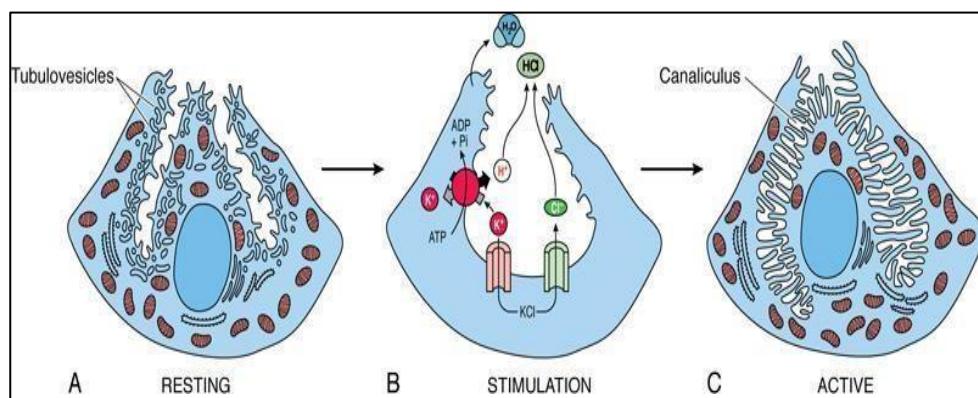


Fig. 17: Parietal cell A, Well-developed tubulovesicular apparatus in the resting cell. B, Mechanism of hydrochloric acid release. C, Numerous microvilli in the active cell.

5. Chief Cells

- Most of the cells at the base of the gland are enzyme secreting chief (zymogenic) cells.
- These cells produce pepsinogen and lipase.

LM:

- Nucleus:
 - Basal and rounded.

- **Cytoplasm**

- Basal basophilic owing to its abundant content of basophilic ribosomes.
- The cells have apical acidophilic enzyme precursor (zymogen) granules.

EM:

- They have all the **ultrastructural features of active protein synthesizing cells** as ribosomes, extensive RER, prominent Golgi complex, and many large secretory granules in the apical part (**Fig. 18**).
- The apical cell membrane contains microvilli.

Function:

- Secretion of pepsinogen (inactive proenzyme or zymogen) and lipase.

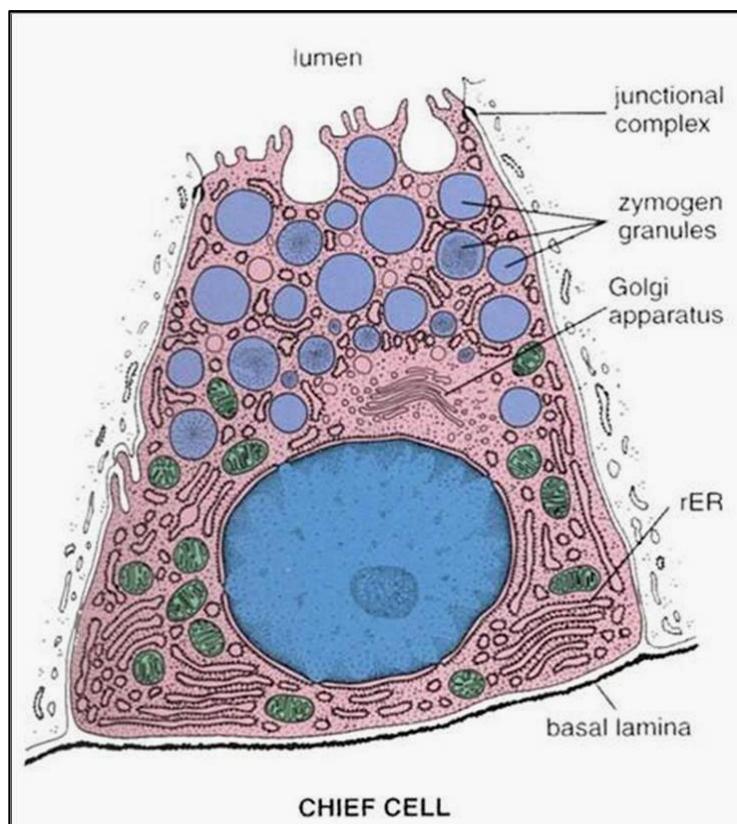


Fig. 18: Chief cell

6. Enteroendocrine Cells (Argentaffin or Enterochromaffin)

- The various gastrointestinal endocrine cells are widely scattered endocrine cells, referred to as **diffuse neuroendocrine system (DNES)** or **amine precursor uptake and decarboxylation (APUD)**.
- They are more abundant among the peptic cells in the basal parts of gastric glands.

LM:

- Small pyramidal cells.
- The nucleus is apical in position.
- The cytoplasm appears clear (unstained) in H&E sections.
- They are stained black with silver so they are called argentaffin cells (Argent = silver), and with bichromate salts so, they also are called enterochromafin cells.

EM:

- They have all the ultrastructure features of amine precursor uptake and decarboxylation (APUD) cells.
- They contain basal small electron dense secretory granules (as they discharge their secretory products into adjacent capillaries of the lamina propria).
- Contain spherical or elongated mitochondria, RER and Golgi apparatus.
- Lipofuscin pigment may be present.
- Two types of cells are identified by EM:
 1. **Open type:** reaches the lumen.
 2. **Closed type:** does not reach the lumen

Function:

- These cells are named according to the substance they produce e.g.:
 1. G cells gastrin → HCl secretion, stimulate stem cells to proliferate.
 2. A cells → glucagon → glycogenesis (liver).
 3. D cells → somatostatin.
 4. EC cells → serotonin

Changes at the Gastro-Esophageal Junction: (Fig. 19).

- The stratified squamous **epithelium changes** into simple columnar epithelium.
- Lamina propria increases** in width to contain fundic glands.
- Esophageal glands** in the submucosa **disappear**.
- Muscularis externa** becomes **thicker** and contains three muscular coats in the stomach.

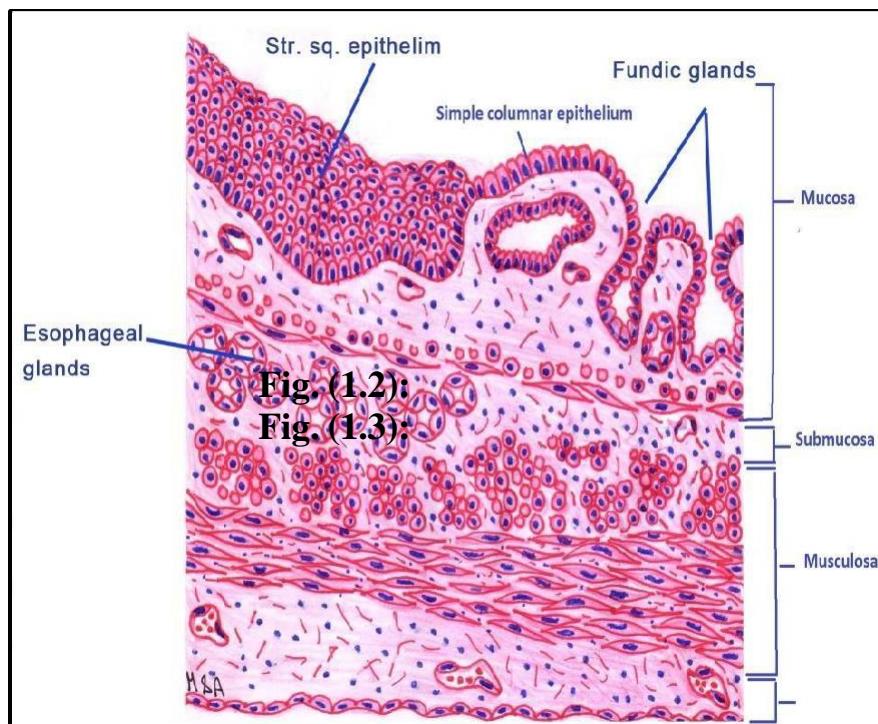


Fig. 19: Gastro-esophageal junction.

3. Pyloric Region

1. Mucosa:

- a) **Epithelium:** Similar to fundus and body.
- b) **Lamina Propria:** Contains pyloric glands.
- c) **Muscularis mucosa:** It is formed of thin inner circular and outer longitudinal layers.

3. Submucosa:

4. Musculosa:

- It is formed of two layers, inner circular and outer longitudinal.
- The circular layer is thickened to form the pyloric sphincter which is a thick ring of smooth muscle that guards the outlet of the stomach. When this sphincter opens, it transmits the semifluid gastric contents to the small intestine.

5. Serosa:

- It is similar to that of the fundus.

Table 1: Comparison between fundic and pyloric glands

Fundic gland	Pyloric gland
Long, simple branched tubular	Short, simple branched tubular.
Gastric pits are narrow and short (1:5).	Wide and deep (1:1)
Very crowded	Not crowded.
Perpendicular to the surface.	Many are coiled and oblique
Lined by mucous, parietal, chief, and enteroendocrine cells.	Lined by mucous and enteroendocrine cells.

Pyloric glands

- The glands are not crowded as fundic glands.
- The gastric pits are wider and deeper than those of the fundus, extending down through half the depth of the mucosa.
- They are highly convoluted and have a wider lumen (**Fig. 20**).
- They are not perpendicular to the surface.
- The glands are lined with:
 - a. Mucous secreting cells secrete mucus and lysozyme.
 - b. Enteroendocrine cells (**G cells**) that secrete serotonin, gastrin (stimulates gastric secretion and motility) and somatostatin (inhibits the release of many other hormones).
 - c. Undifferentiated stem cell.

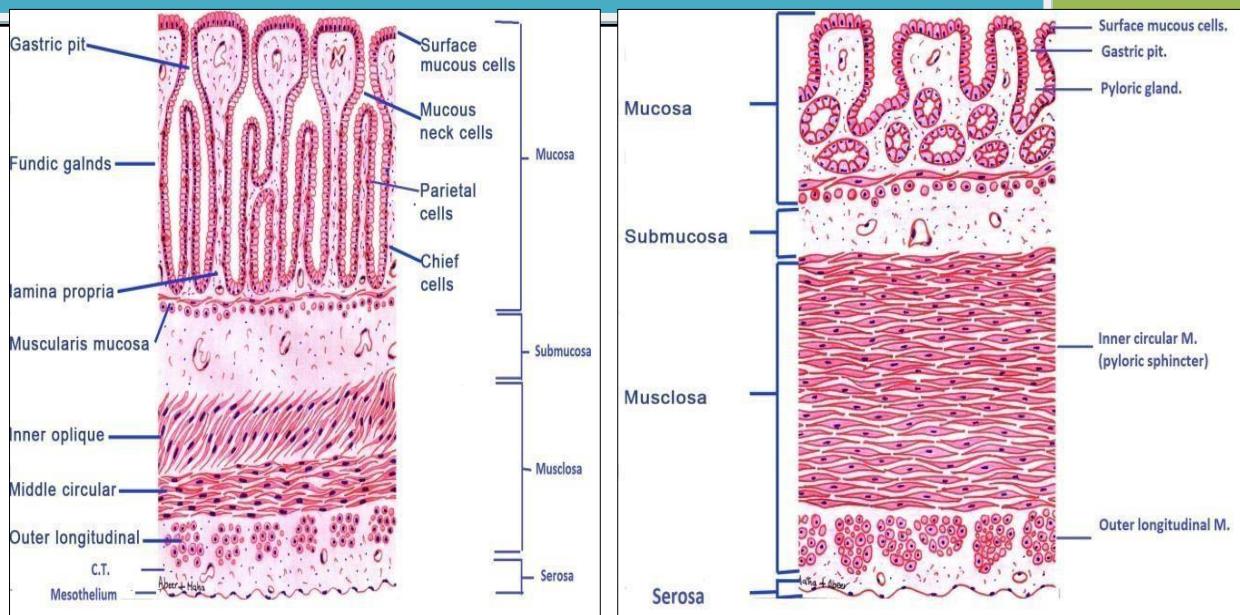


Fig. 20: Comparison between fundus and pyloric regions

SMALL INTESTINE

- The small intestine completes the digestive process, absorbs nutrients, and produces a variety of gastrointestinal hormones.
- It has three parts: duodenum, jejunum and ileum.
- It receives chyme from stomach, bile from liver and digestive enzymes from pancreas.
- Its length is about 6 meters.
- The wall of small intestine is formed of the usual 4 layers: (**Fig. 21**).
 1. Mucosa
 2. Submucosa
 3. Musculosa
 4. Serosa

1. Mucosa:

a) **Epithelium:** The epithelium of the intestinal villi consists of:

- i. Columnar absorptive cells (Enterocytes)
- ii. Abundant goblet cells
- iii. Enteroendocrine cells

b) Lamina propria:

- It is composed of loose connective tissue that forms the core of the villi containing numerous fibroblast, lymphocytes, eosinophils and macrophages.
- It occupies the spaces between the crypts of Lieberkühn.
- It contains strands of smooth muscle cells that extend from muscularis mucosa to the core of the villi.

c) Muscularis mucosa:

- Composed of inner circular and outer longitudinal layers of smooth muscle cells.
- Muscle fibers that extend from the inner circular layer to the villi are responsible for the rhythmic movement of the villi which is important for absorption.

NB. Permanent circular folds of the mucosa and part of the submucosa are seen in the luminal surface (called **plicae circulares** or valves of Kerckring)

2. Submucosa

- Composed of dense irregular connective tissue rich in lymphatic and vascular supply.
- It also contains parasympathetic **Meissner's plexus**.
- The submucosa of the duodenum contains duodenal glands called **Brunner's glands**
- The submucosa of the ileum contains aggregates of lymphocytes called **Peyer's patches**.

Brunner's Glands:

1. Are **branched tubuloalveolar glands**
2. Their ducts open into the base of the crypts of Lieberkühn or into the intervillar space.
3. The cells of the acini showed a well- developed RER, Golgi apparatus, numerous mitochondria and round or flattened nuclei, as well as dense secretory granules.
4. Brunner's glands secrete **alkaline mucous** that protect the duodenal mucosa by neutralizing the acid chyme.

5. The glands also secrete polypeptide hormone called **urogastrone** which inhibits the gastric secretion of HCL and increases the mitotic activity of epithelial cells.

Peyer's Patches:

1. They are aggregates of lymphoid nodules located in the wall of the ileum opposite the attachment of the mesentery.
2. They are present in the lamina propria and penetrate the muscularis mucosa to appear in the submucosa.
3. Each nodule has a large pale germinal center consists of lymphoblast, T and B lymphocytes, macrophages and dendritic cells.
4. The villi over the Peyer's patches are short or absent and the absorptive columnar cells are replaced by M cells.

3. Musculosa:

- It is composed of an inner circular and an outer longitudinal smooth muscle layers.
- Auerbach's myenteric plexus is present between the two layers.
- Muscularis externa is responsible for the peristaltic movement of intestine.

4. Serosa:

- It consists of a thin layer of loose connective tissue covered by a continuous sheet of squamous cells (**mesothelium**).

Intestinal Villi

- They are seen by the light microscope as finger like mucosal projections.
- They consist of cores of lamina propria which contains a central blind end lymphatic (lacteal) and a network of blood capillaries and few smooth muscle fibers.
- They are covered by simple columnar absorptive cells, goblet cells, enteroendocrine cells and stem cells.

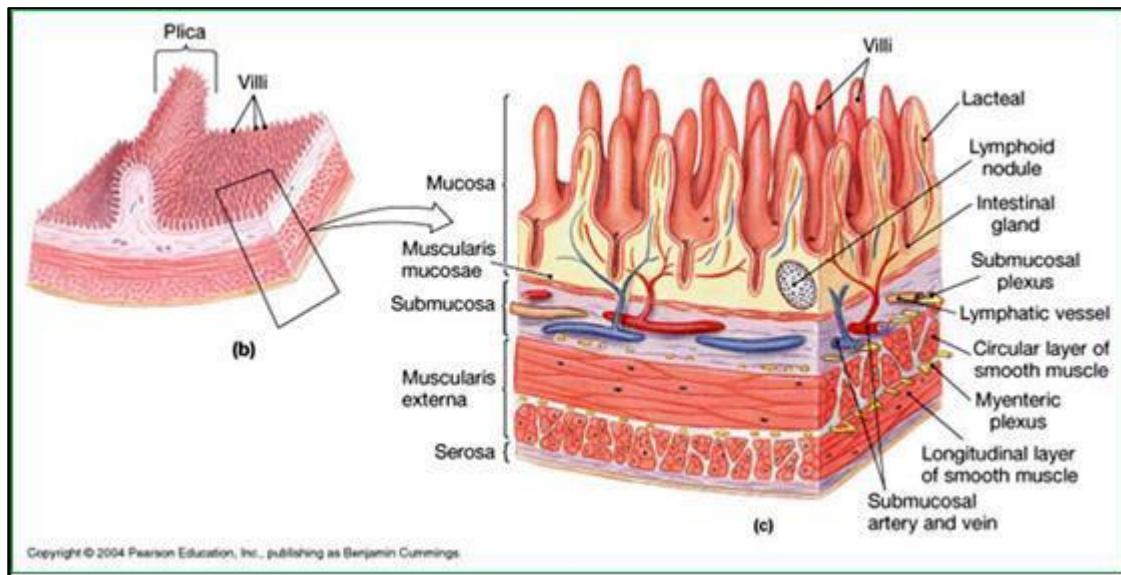


Fig. 21: Small intestinal wall

Crypts of Lieberkühn

- They are **simple tubular glands** below the bases of the villi in the lamina propria (**Fig. 22**).
- They open into intestinal lumen at the microvillar base.
- The epithelial covering the villus continuous with that lining the crypts of Lieberkühn.
- The upper half of the wall of the crypt is lined with columnar absorptive cells and goblet cells.
- Their lower half is lined with stem cells, goblet cells, Paneth cells, enteroendocrine cells, M cells and caveolated cells.

1. Columnar Absorptive Cells (Enterocytes)

LM:

- Tall columnar cells with basal oval nucleus.
- Cover the villi and upper crypts.
- The luminal border is acidophilic and striated (**brush border**) because it has abundant long **microvilli**.

EM:

- The microvilli are abundant on the luminal (apical) surface.

- Its coat contains enzymes to facilitate digestion and absorption.
- The lateral walls show junctional complex that interconnects lining epithelial cells; zonula occludens, zonula adherens and macula adherens (desmosomes).
- The cytoplasm contains elongated mitochondria. Golgi apparatus, SER, rER, lysosomes and centrioles.

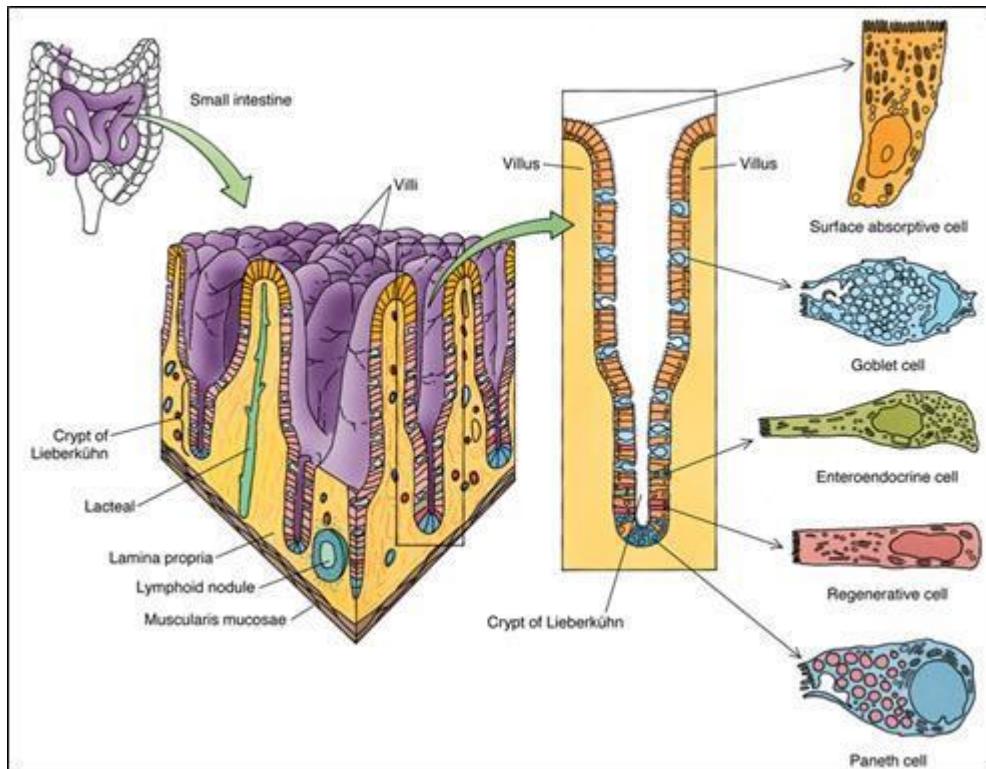


Fig. 22: Intestinal villi and crypts

Microvilli

- They are finger like projections from the apical surface of cell membrane (**Fig.23**).
- In longitudinal sections; they appear as **cylindrical** processes (2 μm long and 80 nm in diameter).
- Its center contains **actin** filaments with tips attached to the covering cell membrane and bases attached to the **terminal web**.
- Also, the actin filaments are attached to each other and to the surrounding cell membrane by the **fimbrin** protein.
- The covering cell membrane has a glycocalyx.
- They increase surface area for absorption by about 30 folds.

Function:

1. **Absorption** of water and nutrients (carbohydrates, fatty acids and Amino acids).
2. Continuous tight junctions **seal off** intercellular spaces from the intestinal lumen and adhering (**anchoring**) junctions keep the cells from pulling apart under tension.
3. They also secrete enzymes.

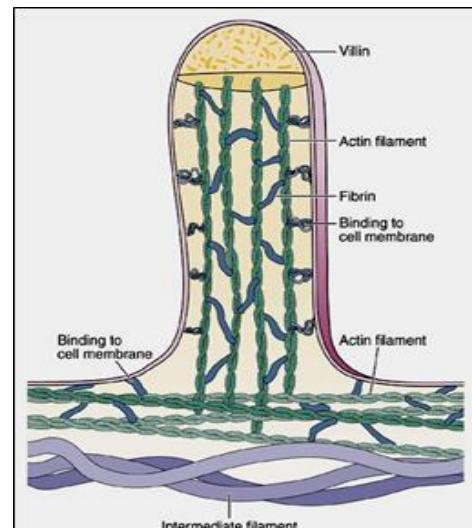


Fig. 23: Molecular structure of microvilli.

2. Goblet Cells

- They are **unicellular** mucous-secreting **glands** and their number increases steadily from the duodenum to the ileum (**Fig. 24**).

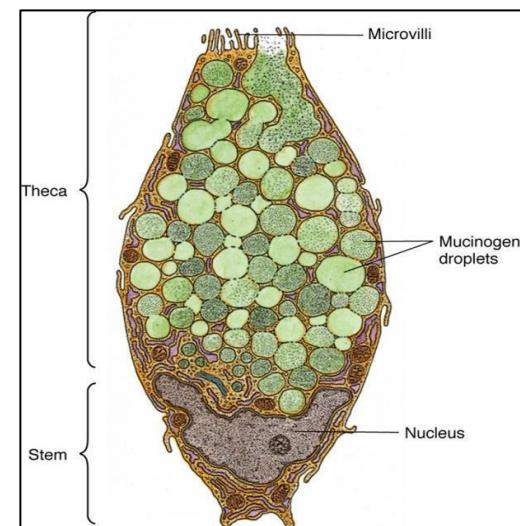
LM:

- Basal flat deeply stained nuclei.
- Expanded **apical pale-stained** part (mucin is dissolve during routine preparation) and narrow basophilic basal part giving the cell flask-shaped appearance.

EM:

- Expanded apical part full of **electron lucent mucinogen** granules.

- Some apical microvilli.
- Basal oval nuclei, RER, Golgi apparatus and free **ribosomes**.

Fig. 24: Diagram showing goblet cell

3. Enteroendocrine Cells

- Present mainly **near crypt bases** and few may be met in the villi.
- They are similar to those of stomach.

LM:

- Appear **clear** in H&E sections.
- In Ag-stained sections, their granules are black .
- Their types are distinguished by **immunohistochemical** stains.

EM:

- These are mainly **peptide hormone secreting cells**
- Their characteristics features are discussed in stomach mucosal cells.
- Examples of these cells: (**Table 2**).

Table 2: Examples of enteroendocrine cells

Cell	Hormone	Action
A	Glucagon (enteroglucagone)	Stimulates glycogenolysis by hepatocytes.
D	Somatostatin	Inhibits release of hormones by DNES cells.
EC	serotonin	Increase peristaltic movement.
G	Gastrin	Stimulates HCl secretion.
I	Cholecystokinin	Stimulates the release of pancreatic enzymes and contraction of gall bladder.
K	GIP (gastric inhibitory peptide).	Inhibits HCl secretion.
Mo	Motilin	Increases intestinal peristalsis

4. Paneth cells

LM:

- These cells are present in the **bases** of the crypts of the small intestine.
- They are large pyramidal or columnar cells.
- Cytoplasm: Have large apical acidophilic **zymogen** granules, while its basal part is basophilic.

EM:

- It has an extensive RER prominent Golgi apparatus and numerous mitochondria and numerous electron dense apical granules (**protein synthesizing cell**).

Function:

1. They are the major source of **lysozyme** (antibacterial enzyme).
2. Secrete a defensive protein (**α - defensin**) and **tumor necrosis factor α** .
3. Regulate the normal bacterial flora in the intestine.

5. Caveolated Cells

- Rare cells present in the intestinal crypts.
- Their bases are wide
- Contain rounded nuclei.
- Their apices are narrow and contain microvilli.
- These cells may be seen in the stomach and large intestine.

6. M-Cells (Microfold cells)

- These are **antigen transporting cells**.
- They are dome shaped.
- Their basal surface contains large basal invaginations enclosing lymphocytes.
- Present between the epithelial cells which overlying large lymphatic nodules e.g. Payer's patches of the ileum. (**Fig. 25**).
- They phagocytose and transport antigens present in the intestinal lumen to the underlying macrophages and lymphocytes to initiate immune response.

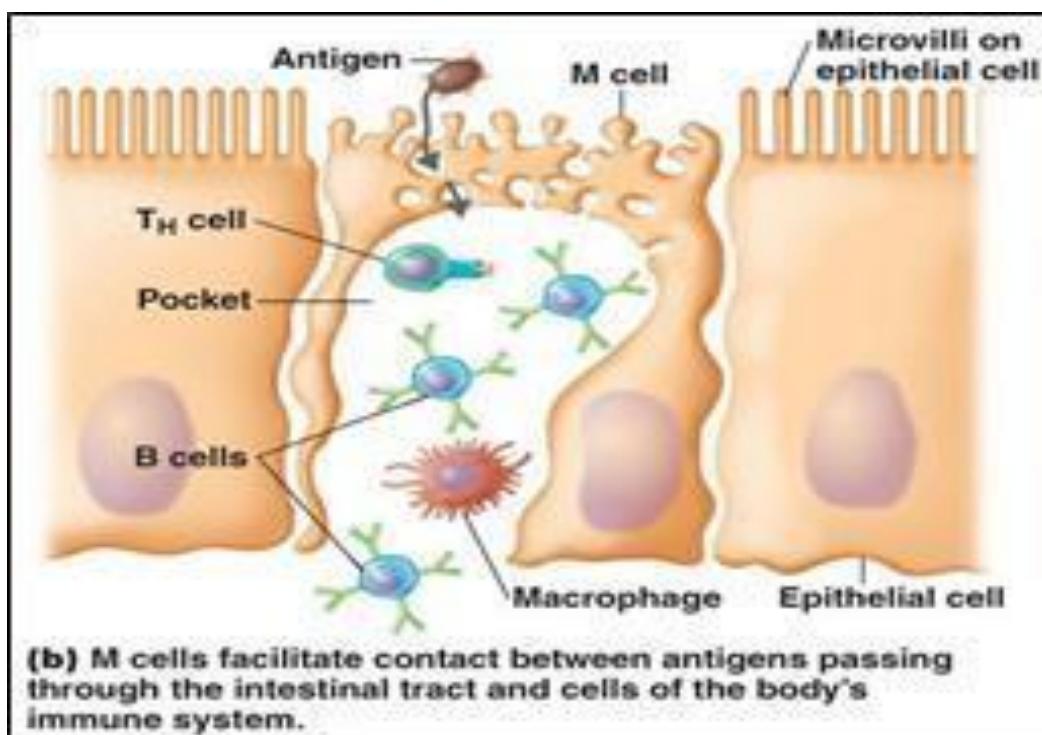


Fig. 25: M cell

Distinctive Regional Specialization of Small Intestine

- The following specializations of the intestinal wall are generally helpful in distinguishing between sections of the different parts of the small intestine (**Table 3**).

Table 3: Differences between duodenum, jejunum and ileum

	Duodenum	Jejunum	Ileum
Villi	Broad, leaf-shaped	Narrow, short, tongue-shape	Fewer and narrow
Goblet Cells	Few	More	Abundant
Submucosa	Brunner's glands	No Brunner's glands. No Peyer's patches	Peyer's patches (antimesenteric border).
Adventitia	In retroperitoneal segment	Serosa.	Serosa.

Functional Features

The following features augment its capacity for digestion and absorption:

1. Enzyme and mucous producing glands

Digestive enzymes and mucus enter the lumen of the small intestine from four sets of glands:

a) Major accessory glands (pancreas & liver)

- Pancreatic juice (alkaline) counteracts gastric acidity. Its digestive enzymes degrade proteins, fats, and carbohydrates.
- Bile, the exocrine secretory product of the liver increases the effectiveness of pancreatic lipase.

b) Mucosal glands i.e. crypts of Lieberkuhn or intestinal crypts produce enzymes, mucus, and hormones.

c) Submucosal glands i.e. Brunner's glands secrete alkaline mucus to protect the duodenal mucosal surface.

d) Goblet cells of the mucosal epithelium also provide mucus.

2. Mucosal folds and projections

- The absorptive surface (20 feet long) of the small intestine is expanded by various orders of luminal projections.
 - i) **Plicae circulares (Valves of Kerckring):** A circular mucosal folds with submucosal cores are numerous in the upper part of the small intestine (increase the surface area **3 folds**).
 - ii) **Intestinal villi:** Countless fingerlike mucosal projections about 1 mm long (increase the surface area **10 folds**).
 - iii) **Microvilli:** A minute finger-like projections of cell membrane (increase the surface area **30 folds**).

LARGE INTESTINE

- Large intestine includes the cecum, colon (ascending, transverse, descending and sigmoid) & rectum and ends in anal canal.
- The large intestine completes absorption and retrieves water and sodium from the luminal contents, which become fecal residue.
- It secretes abundant protective mucus and some gastrointestinal hormones.
- It is formed of the usual 4 layers of the alimentary tract (**Fig. 26**)

1. Mucosa:

- The mucosa is thick.
- It has **no villi** but has deep crypts, which are straight, long and relatively numerous.
- Its whole thickness is occupied by numerous straight intestinal glands

a) Epithelium:

- The crypts are lined with:
 1. **Absorptive columnar cells**,
 2. Numerous **goblet cells** that increase in number from the cecum to the sigmoid colon,
 3. Few **enteroendocrine cells**.
 4. Some basal stem cells.

b) Lamina propria

- Loose connective tissue layer contains simple tubular intestinal glands (crypts).
- Rich in lymphocytes which frequently aggregate to form solitary lymphoid nodules.

d) Muscularis mucosae:

- Outer longitudinal and inner circular layers.

2. Submucosa:

- It resembles those of the small intestine except that it lacks submucosal glands.

3. Muscularis externa (Musculosa):

- The inner circular layer is similar to that of the small intestine.
- The outer longitudinal layer is arranged as three longitudinal bands called **teniae coli**.
- These muscular thickenings maintain bowel tonus and cause the remainder of the wall to sacculate.
- Auerbach's plexus is present between the two layers.

4. Serosa

- Retroperitoneal segment of the colon and rectum are covered by adventitia, and the remainder is covered by a serosa.
- The connective tissue of the serosa is rich in fat cells which may form pouches called “**appendices epiploicae**”.

Function of Large Intestine:

1. Its abundant mucus secretion lubricates the lumen and facilitates compaction and passage of fecal matter i.e. eliminates feces.
2. It helps digestion as it contains digestive enzymes received from the small intestine.
3. Water and electrolyte absorption by the lining columnar cells.
4. Contains bacterial flora that produce riboflavin, thiamin, vitamin B12 and vitamin K.

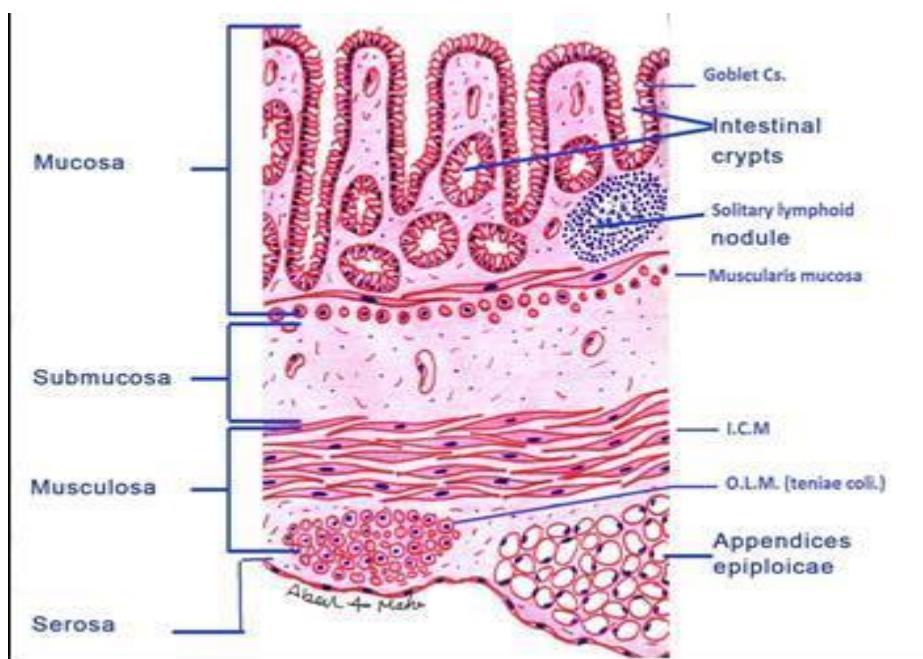


Fig. 26: Structure of large intestine

Appendix

- It is a blind-ending tubular appendage of the cecum.
- Histologically, it resembles other parts of the large intestine but differ in:
 - It is much smaller in diameter.
 - Its lumen is small and irregular.

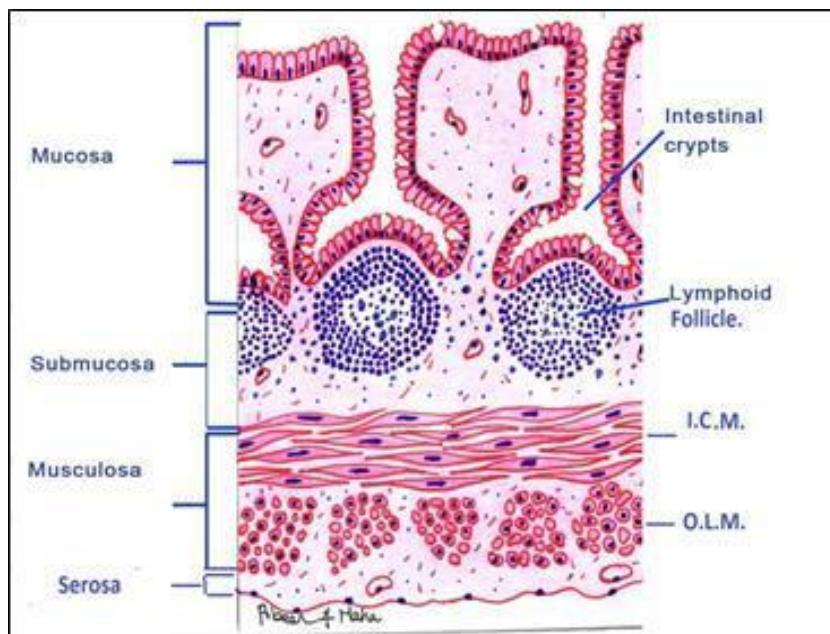


Fig. 27: structure of appendix

Muscularis mucosa layer is ill-defined and may be absent in some areas. (**Fig. 27**).

- Extensive lymphoid follicles in the lamina propria which extend deep into the submucosa. These follicles are large and multiple during the early decades of life, but diminish gradually in subsequent years.
- Special modification of the overlying epithelial cells increases their effective immune responses.
- Contains more DNSE cells in crypts of lieberkuhn.

ANAL CANAL

- It is a tube of 4 cm connects between the rectum and anal opening.
- Contains short few crypts in the proximal parts and no crypts in the distal part.
- The anal canal is lined by simple columnar epithelium The mucosa is thrown into longitudinal folds known as “columns of Morgagny”.
- Each column contains an artery, a vein and some smooth muscles.
- These columns are joined together to form “anal valve”.
- The lamina propria is formed of fibroelastic connective tissue that contains circumanal glands.
- The submucosa is also fibroelastic. It contains internal and external hemorrhoidal plexuses.
- The circular layer of smooth muscle in the muscularis externa is thick and constitutes the internal anal sphincter.
- Along the inferior border of this sphincter, the simple columnar epithelium lining the anal canal changes abruptly, first to a stratified squamous non keratinizing epithelium and then to the epidermis of thin skin. (**Fig. 28**).
- The external anal sphincter is made of skeletal muscle and provides voluntary control of defecation

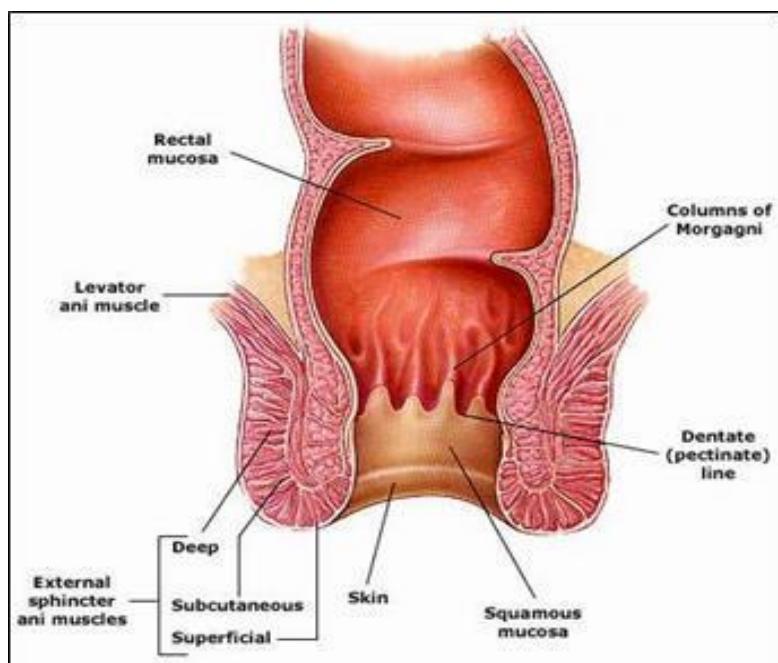


Fig. 28: Anal canal

GLANDS ASSOCIATED WITH THE DIGESTIVE TRACT

- The glands associated with the digestive tract include:
 1. Salivary glands.
 2. Pancreas.
 3. Liver and gallbladder.

PANCREAS

- The pancreas is a mixed exocrine-endocrine gland that produces digestive enzymes and hormones.
- The enzymes are stored and released by cells of the exocrine portion.
- The hormones are synthesized by clusters of cells of the endocrine portion.

Exocrine Portion

Stroma: (Fig.29)

- **Capsule:** poorly developed thin capsule.
- **Septa:** thin septa divided the gland into lobes.
- **Reticular connective tissue:** forms the framework of the gland.

Parenchyma:

- It is formed of compound tubuloacinar **serous gland** with acini and ducts similar to parotid gland.
- The cells of the acini are pyramidal in shape with basal basophilic cytoplasm and basal nuclei.
- The apical cytoplasm is acidophilic due to the presence of zymogen granules.
- The cells show the typical ultrastructural features of protein secreting cells (basal RER, many mitochondria and prominent supranuclear Golgi apparatus).

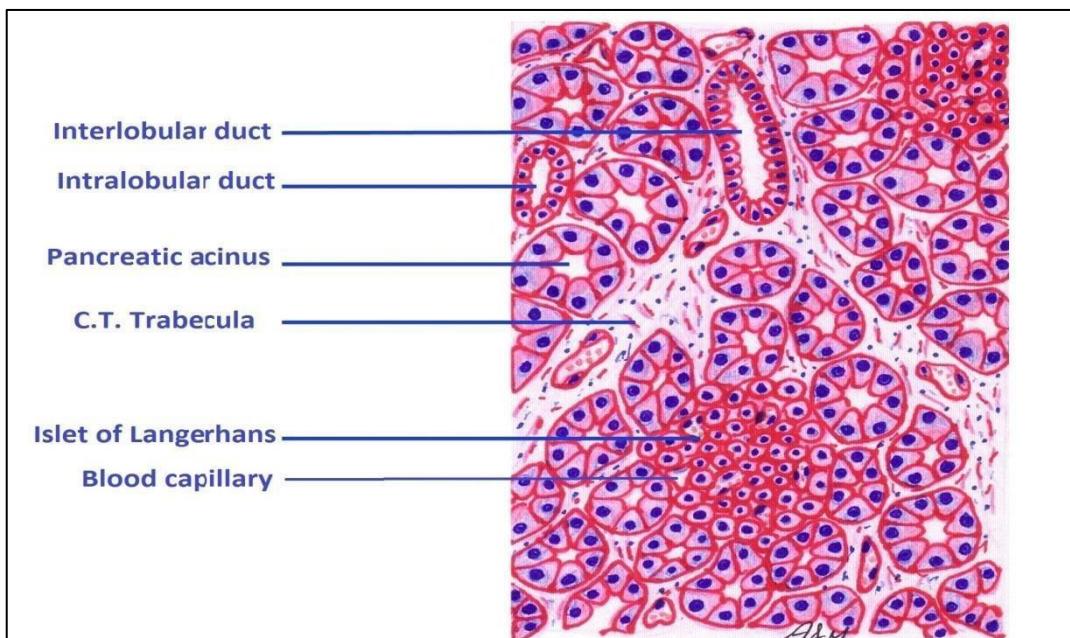


Fig. 29: structure of pancreas

- The lateral borders of the cells are joined by junctional complexes to protect the cells from separation and tight junction prevents the enzymes discharged into lumen from reaching to the intercellular space.

Duct System:

1. **Centroacinar (Centroacinos) cells** are pale squamous or low cuboidal cells that constitute the intra-acinar portion of the intercalated duct. These cells are found only in pancreatic acini.
2. **The intercalated ducts** are lined with low cuboidal cells.
3. **Intralobular ducts** are very small ducts.
4. **Interlobular ducts** are more prominent and lined by simple low columnar epithelium.
5. **Main duct** are lined with simple columnar epithelium. The main duct joins the common bile duct to drain into the duodenum via the **ampulla of Vater** and it is controlled by the sphincter of Oddi.

Functions of Exocrine Portion:

1. Secretion of **alkaline watery** secretion to neutralize the acidic chyme coming from the stomach, so, protects duodenal mucosa.
2. Secretion of **enzymes** and proenzymes as trypsinogen, chemotrypsinogen, lipase, phosphatase, elastase and amylase.

Endocrine Portion (Islets of Langerhans)

- The islets of Langerhans are multi-hormonal endocrine micro organs scattered in the pancreas. They appear as pale cellular clusters embedded within exocrine pancreatic acini more abundant in the tail.
- Each islet is surrounded by a delicate loose connective tissue capsule. In section, they appear as polygonal or rounded cells arranged in cords separated by a network of fenestrated blood capillaries. Both the parenchymal cells and the blood vessels are innervated by autonomic nerve fibers. Using immunocytochemical methods; 7 types of cells; α , β , D, F, G, C and ganglion cells have been located in islets.

1. Alpha Cells (α)

- They located mainly at the periphery representing about 20% of all cells. They are larger than β cells. They contain regular granules with dense core surrounded by a narrow electron-lucent region.

Function:

- They release **glucagon** in response to low blood glucose level that acts upon liver cells to increase the breakdown of glycogen to glucose increasing the blood glucose level.

2. Beta Cells (β)

- The most numerous 70% scattered in the islet but mostly in the center. They have **irregular** granules with dense core surrounded by wide electron-lucent region.

Function:

- The cells synthesis proinsulin in RER and secret it as **insulin** which decrease blood glucose level.

3. Delta Cells

- It constitutes about 5% of all cells.
- They are scattered throughout the islets containing electron-lucent homogeneous granules.

Function:

- Secretion of somatostatin hormones which decrease the rate of secretion of both insulin and glucagon and reduce the intestinal motility.

4. G Cells

- They scattered through the islet and are few in number. They secrete gastrin hormone which stimulate HCL production by parietal cell of the stomach.

5. PP cells or F cells

- They are present in very small number and are scattered in the islet. They secrete pancreatic polypeptide (PP) which inhibits the exocrine secretion of the pancreas.

6. C-Cells

- Very few (3%).
- Contain scanty granules and cell organelles.
- It may act as a reserve cell or may be resting cell (not established yet).

7. Ganglion Cells

- Small aggregations of nerve cells.
- Control the secretory activity of the gland.

LIVER

It is the most important metabolic organ in which the absorbed nutrients are processed and stored for use by other parts of the body. It performs both exocrine (compound tubuloalveolar gland) and endocrine functions by the same cell i.e. the hepatocyte.

Structure**Stroma****1- Capsule**

- It is covered by a thin connective tissue capsule (Gilsson's capsule)

- Thickened at the hilum (porta hepatis) where blood vessels and lymphatics enter and leave the liver.-Gilson's capsule is partially covered by peritoneum.

2- Trabeculae

- Arise from the capsule and divide the liver into lobes and lobules.
- The interlobular connective tissue in human liver is very thin and incomplete → indistinct lobulation, while in pigs, the trabeculae are well developed.

3- Reticular formation:

- Forms a delicate framework to support liver parenchyma

Parenchyma

- The parenchyma of the liver is formed of sheets and plates of liver cells (hepatocytes), blood vessels (arteries, veins and sinusoids) and bile ducts.
- Hepatic artery, portal vein and bile duct run in the portal area in the corners of the hexagonal classic hepatic lobules.

Hepatocytes**LM****Arrangement**

- They form anastomosing cords (plates) of hepatocytes of two cell thickness that radiating from central veins.
- Blood sinusoids are enclosed between cell cords and are mainly lined with endothelial cells and Kupffer cells.

Shape and size: polyhydral with six or more surfaces and have a diameter of 20-30 μm .

Nucleus

- Usually single, rounded, and centrally located.
- About 25% of the cells have two nuclei.
- Mitotic figures can be seen.

Cytoplasm

- Acidophilic due to the large number of mitochondria and smooth endoplasmic reticulum.
- Sections stained with PAS and best's carmine demonstrated glycogen in liver cells.

EM

Nucleus

- It is euchromatic with peripheral clumps of heterochromatin and one or two nucleoli.

Cytoplasm contains:

1. Abundant RER (protein synthesis)
2. Numerous mitochondria
3. Well developed SER (detoxification of drugs).
4. Well developed Golgi complexes.
5. Numerous lysosomes are seen as membrane bounded dense bodies (digest and eliminate undesirable exogenous and cellular waste products).
6. Free ribosomes are scattered in the cytoplasm.
7. Peroxisomes are numerous as they are responsible for H_2O_2 , lipid and alcohol degradation.
8. Intermediate filaments (cytokeratin) and actin filaments.
9. Cell inclusions in the form of lipid droplets and glycogen granules.

Cell membrane (Fig. 30)

- Each hepatocyte surface is either:
 1. In contact with another hepatocytes
 2. In contact with the wall of blood sinusoids through the space of Disse
 3. Sharing in the formation of the wall of a bile canalculus (bile canaliculi run in between hepatocytes and are lined with the cell membrane of two adjacent hepatocytes).
- Junctional complexes fix the adjacent cell membranes around the lumen of the canaliculi.

- Plasma membrane of adjacent hepatocytes shows indentation and projections to assist in holding the cell together.
- The sinusoidal and bile canalicular surfaces of the cell membrane have microvilli while the other surfaces of the cell lack these microvilli.

Space of Disse:

- It is the space which separates endothelial cells lining blood sinusoids from the hepatocytes.
- **It contains**
 1. Blood plasma
 2. Microvilli of hepatocytes.
 3. Reticular fibers which support the sinusoids
 4. Fat storing cells (Ito cells): these cells support the blood sinusoid wall, store vitamin A, and secrete cytokines and growth factors.
 5. Unmyelinated nerve fibers.
 6. Cells with short pseudopodia called pit cells (natural killer cells).
- **Function**
 1. It prevents the collapse of sinusoidal wall and acts as an intermediate compartment between hepatocytes and blood stream.
 2. Helps metabolite exchange.

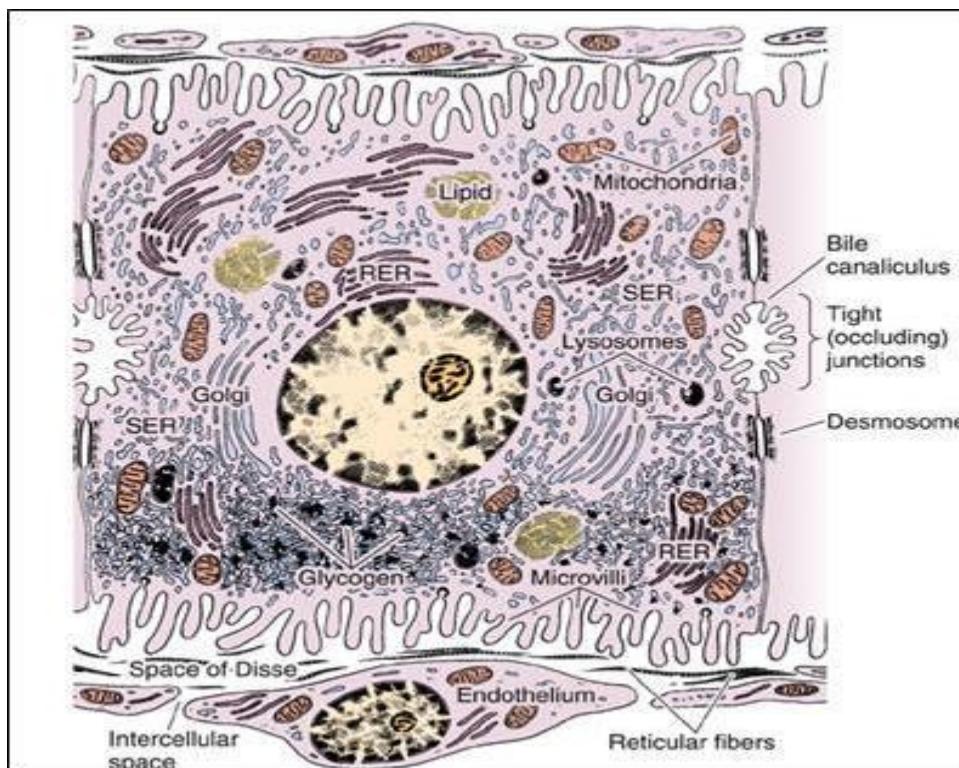


Fig. 30: Hepatocyte

Kupffer Cells

- They are found in the wall of the blood sinusoids in between endothelial cells or on the luminal surface of the endothelial cells.
- It is a phagocytic cell of the mononuclear phagocytic system (typical macrophage).
- It can be demonstrated by using trypan blue stain (vital stain).
- The main functions are to metabolize aged erythrocytes, digest hemoglobin and secrete protein related to immunologic process.

Hepatic Blood Sinusoids

- Sinusoidal capillaries are irregularly dilated vessels present between the plates of liver lobule and drain into the central vein.
- The wall is formed of discontinuous layer of fenestrated endothelial cells and supported by delicate sheath of reticular fibers.
- The sinusoids also contain phagocytic Kupffer cells.

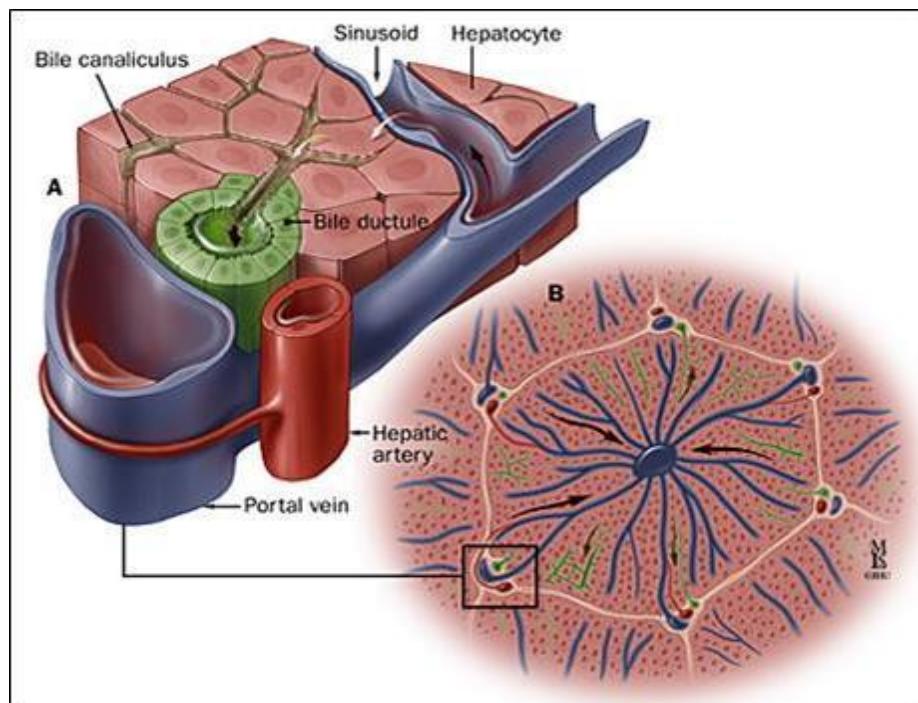


Fig. 31: Portal area

Portal area (Portal tract or canal)

- It is a triangular that demarcated by connective tissue area between corners of three adjacent hepatic lobules (**Fig. 31**).
- It contains bile duct, branch of portal vein, branch of hepatic artery and some nerves with lymphocytes.
- It drains bile to the bile duct present in its center.

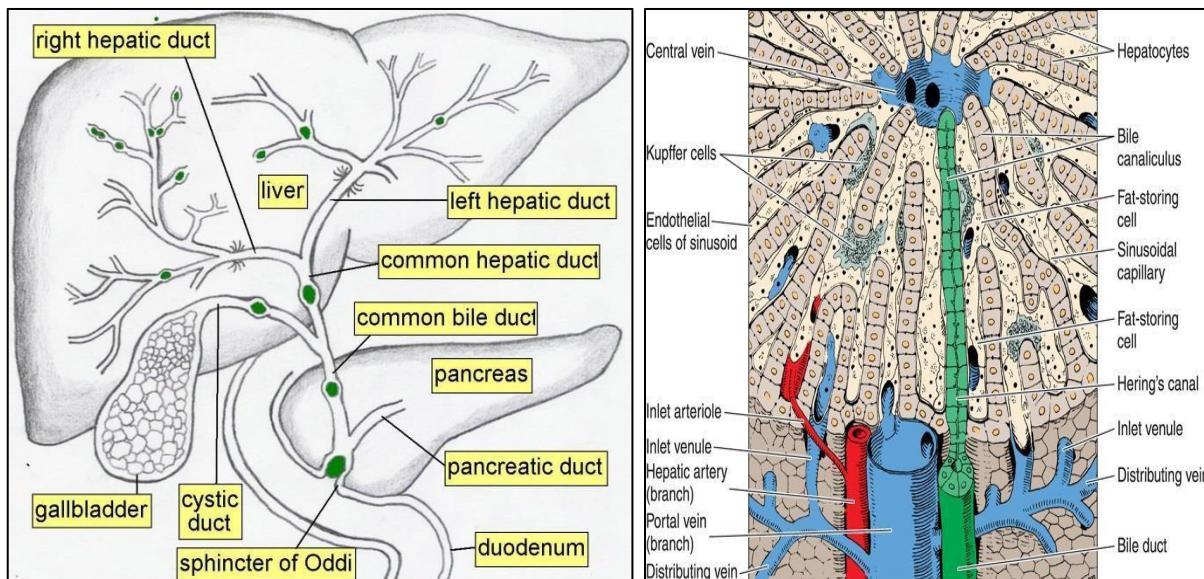
Duct System

- The bile flows in a direction opposite to that of the blood i.e. from the center of classic hepatic lobule to the periphery.

1. Bile canaliculi

- The first portions of the bile duct system are tubules or spaces 1-2 μm in diameter
- It is limited by the plasma membranes of two adjacent hepatocytes and their tight junctions.
- The lateral surface has a small number of microvilli.
- The caliculi form anastomosing network and purists' bile secretion in bile ductules (canals of Herring).

2. **Bile ductule or Herring canals** found at the periphery of the lobule and lined by cuboidal cells.



3. **Bile ducts** in the portal area which lined by cuboidal or columnar cells.

Fig. 32: Bile duct system

4. **Hepatic ducts** (right and left)

- Lined by simple cuboidal epithelium
- Begins inside the liver
- Unite outside the liver to form the common hepatic duct.

5. **Common hepatic duct:** (Fig. 32)

- Lined by simple columnar epithelium
- Surrounded by connective tissue and smooth muscles.

6. **Cystic duct** arising from the gall bladder and joined by common hepatic duct.

7. **Common bile duct** which lined by columnar epithelium which joins the pancreatic duct.

8. Open in the duodenum at **sphincter of Oddi**.

Organization of the Liver

- The liver cells can be organized in three ways,
 - 1- Classic hexagonal hepatic lobule
 - 2- Portal lobule
 - 3- Liver acinus.

1- Classic Liver Lobule

- It is formed of hexagonal or pentagonal mass of hepatocytes.
- The portal tract or portal canal forms the corners of the lobule.
- The central vein located in the center of the lobule.
- The plates of hepatocytes radiate from the central vein
- The radially arranged plates of liver cells are exposed on either side to the blood sinusoids.
- In human, connective tissue septa between adjacent lobules are indistinct.
- The blood flow centripetally in the direction of central vein but the bile flow centrifugally in the direction of the portal tract at the corner.

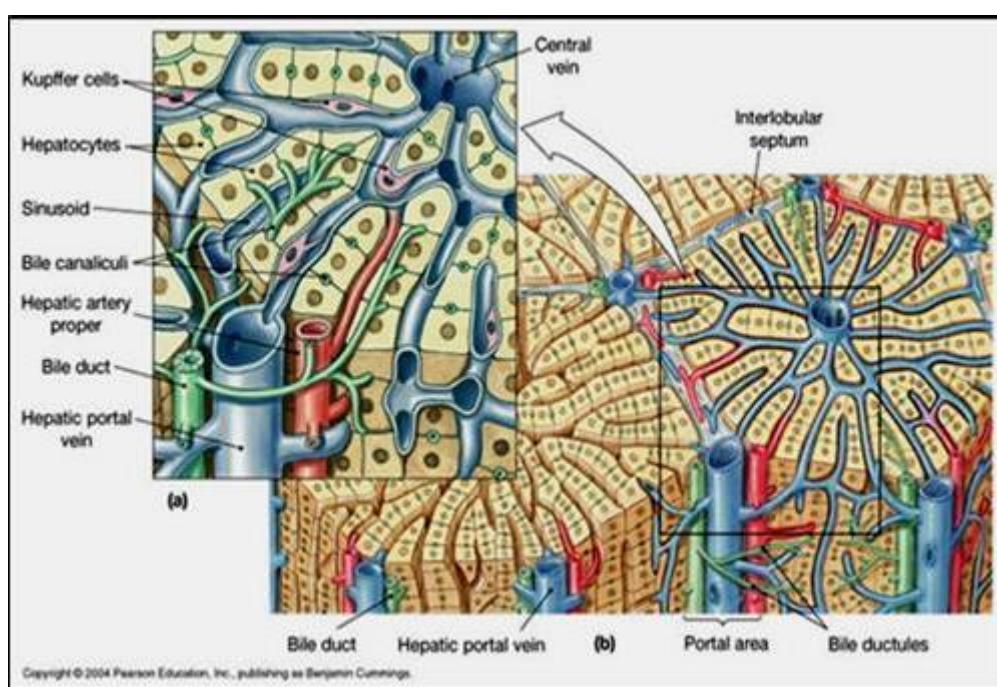


Fig. 33: Classic hepatic lobule

2- Portal Lobule

- It is a triangular mass of hepatocytes (**Fig. 34**).
- It is bounded by imaginary straight lines that connect three central veins.
- The portal tract located at the center of the portal lobule.
- The blood flow centrifugally (out from hepatic artery) but the bile flow centripetally in the direction of the portal tract at the centre.
- This classification considers the liver as an exocrine gland i.e. bile secretion.

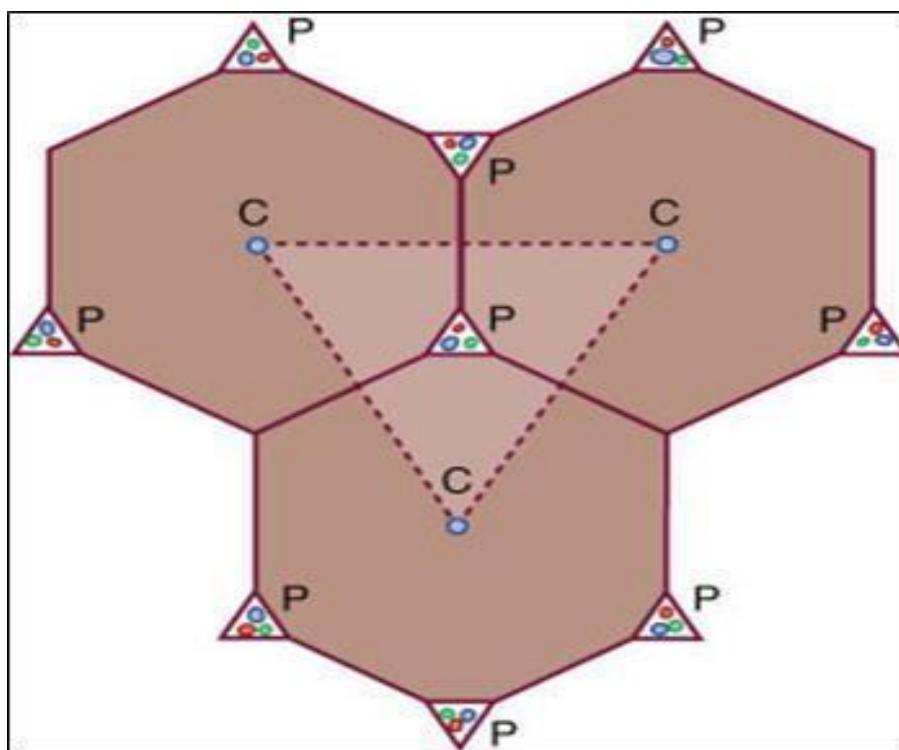


Fig. 34: Portal lobule

3. Hepatic acinus

- This recent classification depends on the blood supply.
- It is a diamond shaped mass of hepatocytes (**Fig. 35**)
- The acinus is formed of parts of two adjacent classical hepatic lobules.
- The terminal branches of the hepatic artery are at the centre.
- This classification considers the blood supply of the liver.
- Hepatic acinus is divided into 3 zones:
 - Zone I-** Lies close to the vascular core and it has rich blood supply and first to receive glucose and oxygen.
 - Zone II-** An intermediate zone which is poorer in blood supply than zone I.
 - Zone III-** The area located toward the periphery of the acinus near the central vein which is the poorest in blood supply and receives fewer amounts of oxygen and glucose.

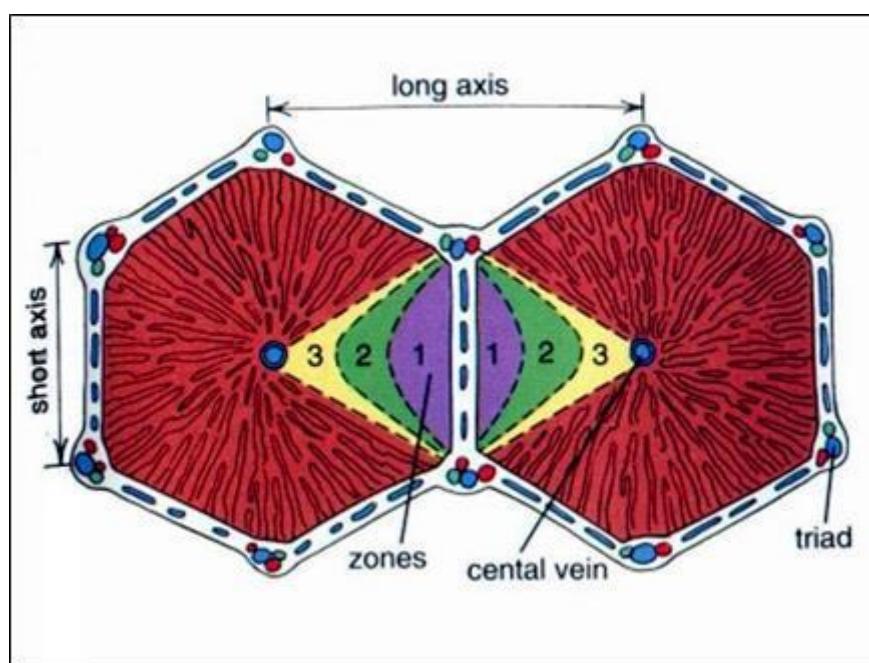


Fig. 35: Hepatic acinus

Functions of the liver:

- The hepatocyte is probably the most versatile cell in the body, as it carries out both endocrine and exocrine functions as well as it performs a significant role in metabolism and detoxification.

1- Protein synthesis :

- Protein synthesis is considered as endocrine functions.
- The hepatocyte produces various plasma proteins, including albumin, prothrombin, fibrinogen and lipoprotein. They do not store protein in the cytoplasm as secretory granules but they continuously release them into the blood stream.
- About 5% of the protein exported by the liver is produced by Kupffer cells; the remainder is synthesized in the hepatocytes.

2- Bile secretion

- Bile secretion is an exocrine function.
- It contains bile salts, conjugated bilirubin, phospholipids, cholesterol, electrolyte and water.
- Bile salts have an important role in emulsifying lipids to facilitate their digestions.
- Bilirubin results from break down of hemoglobin during disposal of worn out erythrocytes.

3- Metabolites storage

- Lipids and carbohydrates are stored in the liver in the form of triglycerides and glycogen respectively.
- This capacity to store metabolites is important, because it supplies the body with energy between meals.
- The liver also serves as the major storage compartment for vitamin especially vitamin A.

4- Metabolic functions

- The hepatocyte is responsible for converting lipids and amino acids into glucose by means of complex enzymatic process called gluconeogenesis.
- It is also the main site of amino acid deamination resulting in the production of urea.
- Urea is transported through the blood to the kidney to be excreted. This is considered as an endocrine function.

5- Detoxification and inactivation

- Toxins are detoxified in the liver, Degradation of hormones as steroids occurs in the hepatocytes.
- Drugs such as barbiturates and antibiotics and toxin are inactivated in the hepatocytes.

6- Immune function

- Hepatocytes secrete complex IgA and release it into bile.

Gall Bladder

- The gall bladder is a hollow pear shaped organ.
- It is attached to the lower surface of the liver.

- It stores bile (about 30-50) ml
- It communicates with the hepatic duct through the cystic duct.
- Histologically, its wall is formed of three layers; mucosa, musculosa and serosa.

1. Mucosa:

- It is highly folded which is more clear in empty bladder (**Fig. 36**).
- **The epithelium** is simple columnar, nuclei are oval and basal. The cytoplasm is acidophilic (rich in mitochondria) with supranuclear secretory granules. The apical surface has microvilli.
- **Lamina propria** is formed of connective tissue rich in blood vessels.
- There are no goblet cells.

2. Muscular layer:

- The muscular layer is thin and formed of longitudinal and oblique bundles of smooth muscle fibers.

3. Serosa:

- It is a thick layer of connective tissue which is covered by the peritoneum except the part which lies on the hepatic surface.

Function of the gall bladder:

It stores and concentrates bile and releases it in response to cholecystokinin.



Fig. 36: Section in the wall of gall bladder

Physiology of the GIT & Nutrition



Physiology Of Oral Cavity And Oropharynx

Regulation of Gastrointestinal tract:

A- Nervous regulation: The smooth muscle activity and the secretion of the digestive glands are regulated by:

1- External autonomic nerves:

-Parasympathetic: (dominant)

- a- Vagus nerve → GIT from oesophagus till the 1st half of large intestine.
- b- Sacral division → the rest of GIT till the anal region.

The effects of parasympathetic stimulation are:

- contraction of the wall. (excitatory).
- Relaxation of sphincters. (inhibitory)
- Evacuation of GIT contents.
- Evacuation of secretion – vasodilatation.

-The preganglionic neurons end on the enteric plexus.

- Sympathetic:

- a- From L.H.C of T5 → L2
- b- The effect is inhibitory to motility and secretion and vasoconstriction.
- c- It also contains some excitatory fibers.
- d- The post ganglionic neurons end either direct on the smooth muscle or 2nd relay on enteric plexus. Some fibers end on postganglionic cholinergic neuron causes decrease in the released Ach via activation of presynaptic alpha 2 receptors.

N.B.: Blood vessels have dual innervation:

- 1- Noradrenergic V.C.
- 2- Enteric nervous VIP & nitric oxide secreting nerves cause VD.

2-Local nerve (enteric) plexus:

- In the wall of the alimentary tract there are two nerve plexuses:

a. The Myenteric (Auerbach's) plexus: -

1. It lies between the longitudinal and circular layers of smooth muscle.
2. Concerned with controlling the motor activity of GIT.
3. Its stimulation →↑ tonic contraction, ↑ intensity and rate of rhythmic contraction and ↑ conduction of excitatory waves.
4. The excitatory fibers are mainly cholinergic (secrete Acetyl choline).
5. Some inhibitory fibers secrete VIP (Vaso active intestinal peptide) or purinergic (secrete ATP).

b. The submucosal (Meissner's) plexus: -

1. It lies in the submucosal layer and supply the glandular epithelium, intestinal endocrine cells and submucosal blood vessels.
 2. Concerned with local secretion of GIT.
 3. Its stimulation →↑ local exocrine and endocrine secretion.
 4. It contains the neurons of the sensory afferent nerves which arise from the mucosal layer.
- The activity of one plexus affects the activity of other plexus, by nervous connection in-between.
 - The axons of both plexuses are extensively branched and contain about 100 million neurons.
 - Many transmitters may be secreted in the enteric plexus according to functions as substance P, enkephalin, somatostatin, Ach Serotonin, Noradrenaline, GABA also polypeptides as CCK, VIP, neuropeptide.

Gastrointestinal reflexes:

Reflexes for nervous regulation are of 3 types.

1- Local enteric reflexes: (short reflex):

1. The receptors are present in the wall of the GIT, stimulated by stretch or food.
2. The afferent are the dendrites of the enteric neurons in submucosa.
3. The center: cell body of enteric neurons.
4. The efferent: is axons of neurons to smooth muscle fibers or secretory glands.
5. The response: in peristalsis →
 - 1- Ring constriction proximal to bolus by contraction of circular ms. & relaxation of longitudinal ms. (via Ach).
 - 2- Relaxation distal to bolus by relaxation of circular ms. & cont. of longitudinal ms. (via NO, VIP).

2- Ganglionic reflexes:

- a. Receptors: in the wall of GIT.
- b. Afferent: sympathetic afferent fibers from submucosal layer.
- c. Center: collateral sympathetic ganglia (coeliac & mesenteric).
- d. Efferent: efferent sympathetic fibers to GIT.
- e. e.g : enterogastric reflex (inhibition of gastric motility and secretion by afferent from intestine) and gastrocolic reflex.

3-Central Nervous system reflexes:

- a. Receptors: in the wall of GIT.
- b. Afferent: usually via afferent parasympathetic submucosal fibers to dorsal root ganglia.
- c. Center: in brain stem (vagal center) and spinal cord as (sacral parasympathetic center- L.H.C).
- d. Efferent: efferent parasympathetic fibers.
- e. e.g.: unconditioned reflexes as peristaltic reflex in upper esophagus (vagovagal reflex) – spinal defecation reflexes.

Gut law:

Distension of the gut produces a peristaltic wave that starts at the point of distension and proceeds anal wards.

B- Hormonal regulation:

- The GIT hormones are polypeptides.
- They are secreted by special mucosal cells which are involved in amine precursors uptake and decarboxylation (APUD).
- They are secreted under different stimuli and pass to blood → general circulation → return to GIT to affect its function.
- They are classified according to similarity in function and structure into:
 - a- Gastrin group: gastrin and cholecystokinin.
 - b- Secretin group: secretin, gastric inhibitory peptide (GIP), glucagons, enteroglucagon and VIP.
 - c- Motilin .
 - d- Somatostatin.
- They are affected by external autonomic nerves and local nerve plexuses.

Physiology of oropharynx

Oral cavity

* Mastication (chewing)

- **Definition:** It is the process of mechanical breakdown of large food particles into smaller ones in the mouth.
- **Its importance:**
 - Stimulation of taste and smell receptors → sense of satiety.
 - Help swallowing by lubrication of food by saliva.
 - Help digestion by break down of indigestive cellulose membrane around the digestive portion of fruits and vegetables also by increasing the exposed surface area to enzymatic effect.
- **It is partly voluntary and partly reflexly by chewing reflex** in which:
Presence of food in mouth → reflex relaxation of chewing muscles → drop of mandible and open the mouth → initiates a stretch reflex of the jaw muscles that leads to muscles contraction, and closure of the mouth and so on. (The mastication muscles are supplied by the motor branch of the trigeminal nerve.)
- **The chewing center** is present in the pons.

* Salivary Secretion

- **Saliva:** Daily secretion average 1L /day, hypotonic, pH is 6-7 which is a favourable for the digestive action of ptyali, but during active secretion becomes more alkaline about 8 due to addition of HCO_3^- .

- **Salivary glands:** three pairs of salivary glands

	Parotid	Submaxillary	sublingual
Secretion %	~ 20 %.	~70%.	~ 5 %.
Type of secretion	Serous secretion (watery & rich in enzymes).	Mixed	Mucus (thick, rich in mucin).
supplied by	Glossopharyngeal N	Facial N	Facial N

N.B : Ebner's glands and buccal glands secrete ~ 5% of saliva.

- **Composition of saliva:**

- a- 99.5 % water.
- b- 0.5 % solids which includes:

1. 0.3 % organic constituents: These are mainly enzymes (amylase, Lipase, Lysozymes) and mucin. In addition to Ig A, lactoferrin and proline-rich proteins

2. 0.2 % inorganic ions:

- Buffers as (H_2CO_3 : Na HCO_3^- & NaH_2PO_4 : Na_2HPO_4).
- Soluble calcium salts: $\text{Ca}(\text{HCO}_3^-)_2$, $\text{Ca}(\text{H}_2\text{PO}_4)_2$ which saturate saliva to prevent decalcification of teeth.
- Some electrolytes as Na^+ , Cl^- , HCO_3^- , and K^+ , they act as coenzymes for salivary enzyme amylase.

- **Functions of saliva:**

- Facilitation** of speech (keeps mouth moist) and deglutition by presence of mucin lubricates food.
- Cleaning (hygiene)** of the mouth by washing and antibacterial effect of lysozymes, thiethianate ions and Immunoglobulins A.
- Buffering function:** by bicarbonate and phosphate systems to keep the pH at about 7.0 → the teeth do not lose their calcium. Also, saliva neutralizes gastric secretion in case of gastroesophageal reflux.

- Digestive function:**

-**Ptyalin (salivary α- amylase):** digest starch (especially cooked) to maltose, maltotriose, alpha limit dextrin in pH 6.9 so it is inhibited in the stomach. It requires Cl^- as a coenzyme activator.

-**Lingual Lipase:** digest triglycerides forming fatty acids and glycerol. It secreted

from Ebner's gland of tongue.

5. **Excretory function:** of lead, mercury, iodides, fluoride and some drugs as morphine and alcohol
6. **Facilitate taste sensation** serves as a *solvent* for the molecules that stimulate the taste receptors.
7. **kallikrein enzyme** produce bradykinin which acts as vasodilator during salivary secretion.
8. Regulation of **water balance** (\downarrow in dehydration and give thirst sensation).
9. Contains **hormones** as somatostatin & glucagon.

- **The Stages of salivary secretion:**

- I) **Salivary acini (Primary)** → saliva similar in composition to plasma= **isotonic** ($\text{Na}^+ = 150 \text{ mmol/L}$, $\text{K}^+ = 10 \text{ mmol/L}$, $\text{Cl}^- = 113 \text{ mmol/L}$, $\text{HCO}_3^- = 23-30 \text{ mmol/L}$).
- II) **Salivary duct (secondary)** due to modification by the duct cells under effect of aldosterone hormone → active reabsorption of Na^+ , & Cl^- and active secretion of K^+ & HCO_3^- . Because ductal cells are relatively water impermeable, water is not absorbed along with the solute, making the final saliva **hypotonic** to plasma.

-So, the final concentration: $\text{Na}^+ = 50 \text{ mmol/L}$, $\text{Cl}^- = 15 \text{ mmol/L}$ $\text{HCO}_3^- = 50-70 \text{ mmol/L}$, $\text{K}^+ = 15 \text{ mmol/L}$.

If the flow of salivary secretion increased → little time for modification → \uparrow Na^+ , Cl^- &, $\downarrow \text{K}^+$ concentration as in parasympathetic stimulation.

- **Innervation of salivary glands:**

A-Parasympathetic stimulation:

It arises from superior salivary nucleus in the pons → chorda tympani as a branch of the facial nerve → submandibular ganglion → submandibular and sublingual glands. Also, inferior salivary nucleus in medulla oblongata → lesser superficial petrosal nerve as a branch of glossopharyngeal nerve → otic ganglion → parotid gland.

- **True secretion:** large in volume watery, rich in ptyalin, Na^+ , Cl^- , HCO_3^- and secretion of salivary lipase.
- Its action via M receptors on duct and acinar cells → increased IP_3 / Ca^{2+}

- V.D by VIP (co-transmitter to Ach)

B- Sympathetic Stimulation:

It arises from lateral horn cells of the upper two thoracic segments and relay in the superior cervical sympathetic ganglia.

- Trophic secretion: little in volume, viscous, and rich in mucin.
- V.C (alpha → V.C).
- Contraction of myoepithelial cells → squeeze saliva → evacuation.
- Its action via cAMP (beta) and ↑ intracellular Ca^{+2} (alpha).

-**Augmented secretion** occurs by stimulation of parasympathetic then sympathetic → large volume rich in mucus and ptyalin.

• Control of salivary secretion:

Nervous **ONLY** via conditioned and unconditioned reflexes.

[I] Unconditioned reflex: Inborn reflex that needs no previous learning.

- Stimuli:** Direct contact of food, chewing & Irritation of GIT.
- Receptor:** Taste receptors & Receptors in GIT wall.
- Afferent:**
 - Chorda tympani: from ant. 2/3 of tongue.
 - Glossopharyngeal: from post. 1/3 of tongue
 - Lingual nerve: movement of tongue.
 - Vagus nerve: from epiglottis.
- Center:** superior & inferior salivary nuclei in M.O.
- Efferent:** chordae tympani & glossopharyngeal.
- Response:** ↑ salivary glands secretion.

[II] Conditioned reflex: Acquired reflexes and need previous learning.

a. Stimuli:

- Sight of food. -Smelling of food.
- Hearing about food. -Thinking of food.

b. Receptors: special sense receptors.

- Afferent:** optic, olfactory & auditory nerves.
- Center:** to cerebral cortex → salivary nuclei.
- Efferent & response** → as unconditioned reflex.

Physiology Of The Pharynx And Oesophagus

Pharynx It is a common pathway for respiratory and digestive system and has swallowing receptor area and the primary peristalsis waves start from it. It is separated from oesophagus by the upper oesophageal sphincter which is normally closed.

Oesophagus

It is a muscular tube has outer longitudinal and inner circular muscle layers which are striated in the upper portion and smooth in the lower portion. So, the peristalsis in the upper portion depends on the vagovagal reflex, however in the lower portion it depends on the local enteric reflex.

Swallowing(Deglutition)

- It is the propelling of food bolus from mouth to stomach.
- It is under control of the swallowing center in the medulla.
- **It is divided into 3 phases:**

1-Buccal phase: (voluntary) elevation and retraction of tongue against the hard palate propels the bolus to the pharynx.

2-Pharyngeal phase (involuntary): It is very rapid (1 second), occur reflexely via:

Swallowing reflex:

- **Receptor:** in oropharynx (tonsillar pillars).
- **Afferent:** glossopharyngeal nerves.
- **Center:** medulla oblongata (swallowing center).
- **Efferent:** motor fibers of cranial nerves V, 1X, X, X11.
- **Response:** Series of reflexes to prevent entry of food into air passages:
 - a- **Elevation of soft palate** → closure of nasal cavity.
 - b- **Approximation of palatopharyngeal folds** → sagittal slit through which small food particles pass and prevent passage of large particles.
 - c- **Closure of glottis** (opening of larynx) by approximation of vocal folds & elevation of larynx and folding of epiglottis

d- **Inhibition of breathing** (swallowing apnea).

- ✓ Relaxation of pharyngoesophageal sphincter and contraction of superior pharyngeal muscle → rapid pharyngeal peristalsis → forces the food into relaxed upper esophagus.

3-Esophageal phase (involuntary):

a- Upper esophageal sphincter: (UES)

The pharyngeo – esophageal junction is normally closed by striated muscle tone to prevent entry of inspired air into stomach. During swallowing the sphincter relaxes reflexely and then reclosed after swallowing.

b- Traveling along the esophagus:

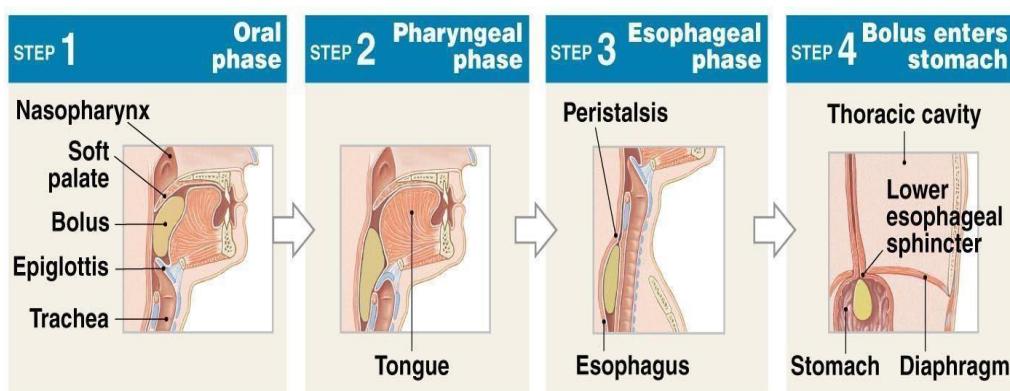
Entry of food bolus into the esophagus initiate peristaltic waves of 2 types:

- **Primary peristaltic waves:**

- a. They start at the upper end of oesophagus.
- b. They are continuation of the pharyngeal peristalsis.
- c. It travels at the rate of 2-4 cm/sec. But gravity may increase velocity of food bolus to about 4cm/sec.

- **Secondary peristaltic waves:**

- a. Presence of bolus in the esophagus initiates peristaltic waves at site of bolus.
- b. These waves repeated until food bolus is driven down the stomach.
- c. Peristaltic movements in the upper half of esophagus are coordinated by vago – vagal reflex (striated ms.), while in lower half is coordinated by local enteric reflex so, bilateral vagotomy → difficult swallowing in the upper half only (In this case the food bolus must be small, soft and well lubricated and by aid of gravity).



c- Lower esophageal sphincter (LES):

- a. It is called the cardiac sphincter.
- b. It is the lower 3-5 cm of the esophagus.
- c. It has high resting tone (**High – pressure zone**) and exert a pressure 15-30 cm H₂O above intra – abdominal pressure to prevent reflux of gastric content into esophagus.
- d. It is relaxed when food bolus reaches it with some delay, so this area is liable to damage or ulceration by cold, hot and spicey food.
- e. ***Its tone is increased by :*** (contracted)
 - Sympathetic alpha adrenergic.
 - Local nerve plexuses (Myenteric).
 - Gastrin hormone (so, drugs which neutralize gastric acidity →↑ gastrin hormone release → contraction of the LES).
- f. ***Its tone is decreased by :*** (Relaxed)
 - Inhibitory vagal via VIP secretion.
 - Local nerve plexus (Myenteric)
 - Some food as fats, chocolate & coffee.

Gastric reflux into esophagus is prevented by:

1. High pressure zone sphincter.
2. The intra-abdominal small part of the esophagus is squeezed by the increased intra-abdominal pressure.
3. The esophagus enters the stomach in acute angle and act as a flap.
4. Gastrin hormone increases the tone in the lower esophagus

Dysphagia: *difficult swallowing.* Its common causes are Lesions of the 9th or 10th cranial nerves (e.g. due to diphtheria). Damage of the deglutition center (e.g. in poliomyelitis). Malfunction of the swallowing muscles (e.g. in myasthenia gravis). Esophageal strictures (narrowing) e.g. due to cancer or scarring.

Achalasia (Cardiospasm)

This is a condition characterized by *increased resting tension in LES.* As a result, food transfer from the esophagus to the stomach is delayed or blocked, so food accumulates in the esophagus and becomes severely dilated. The condition is due to **deficiency of NO &**

VIP because of defective development of the myenteric plexus in the lower part of the esophagus.

Stomach

Functions of the stomach:

1. Storage of food.
2. Slow evacuation of meal to allow good digestion and absorption.
3. Partial digestion of proteins and fats.
4. Sterilization of ingested food by high acidity.
5. Secretion of HCl & intrinsic factor help in RBCS formation.
6. Help defecation by gastrocolic reflex.
7. Absorption of small amounts of water and alcohol.

Gastric secretion

2.5 – 3 L/day of acidic juice (pH may reach 1). It is secreted from gastric glands:

- Stomach mucosa has two important types of tubular glands—oxyntic glands (also called gastric glands) and pyloric glands.
- Simple tubular glands open at the mucosal surface at the gastric pits.
- In these glands, many types of cells are present:
 - 1) Mucous neck cells (Goblet) → Mucus.
 - 2) Chief cells → Pepsinogen & enzymes.
 - 3) Oxyntic (parietal) cells → HCl & intrinsic factor (essential for life for absorption of vit.B12).
 - 4) G. cells → Gastrin H.
 - 5) D. cells → Somatostatin.
 - 6) Enterochromaffin like cells → histamine
- The pyloric canal and cardiac region contain goblet cells only.
- The body & fundus contain all types of cells except G. cells.
- The antrum of pyloric area contains 1, 2, 4& 5 types of cells.

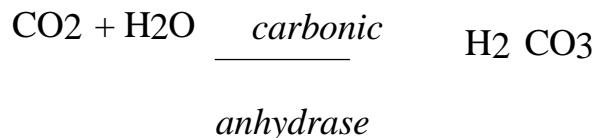
1) HCL secretion:

- Parietal cells secrete an acid solution that contains about 160 mmol/L of hydrochloric acid, which is nearly isotonic with the body fluids.
- The pH of this acid is about 0.8
- Concentration of H⁺ ions in gastric juice is three million times the conc. in

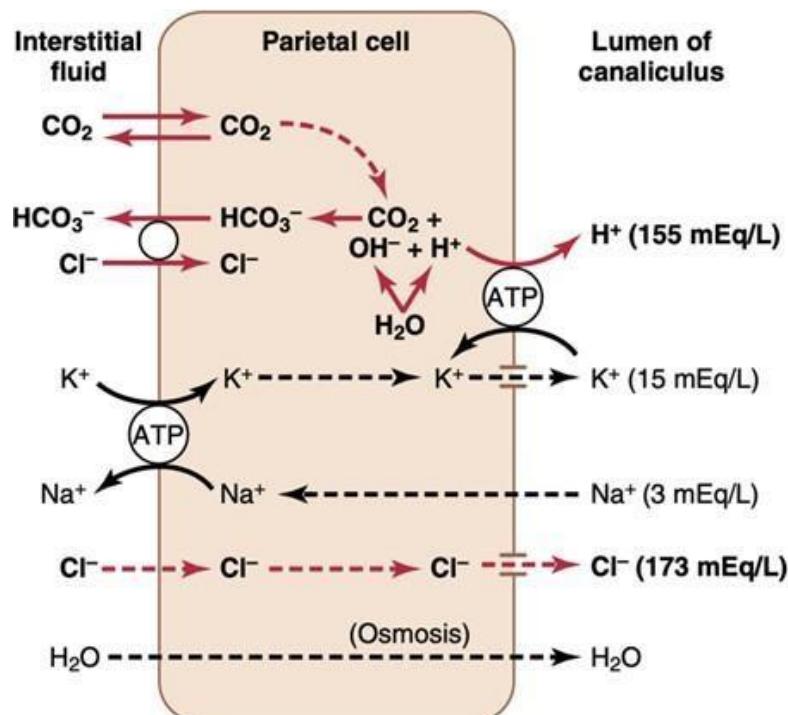
plasma. So, H^+ ions are secreted against a very high gradient.

- HCl secretion occurs in lumen of canaliculi inside oxytic cells.

Mechanism of HCl secretion: In parietal cell CO_2 (from metabolism or blood) \rightarrow



1. $H_2CO_3 \rightarrow H^+ + HCO_3^-$. The bicarbonate diffuses to blood in exchange with Cl^- .
2. H_2O in cytoplasm $\rightarrow H^+ + OH^-$. The H^+ is secreted in lumen in exchange with K^+ by $H^+ - K^+$ pump and OH^- form H_2O with H^+ from carbonic acid.
3. K^+ transported into the cell by the $Na^+ - K^+$ ATPase pump on the basolateral (extracellular) side of the membrane tend to leak into the lumen but are recycled back into the cell by the $H^+ - K^+$ ATPase.
4. Cl^- is secreted into the lumen to unite with $H^+ \rightarrow HCl$.
5. Water diffused to lumen \rightarrow iso-osmotic HCl acid.
6. Diffusion of HCO_3^- to blood $\rightarrow Na HCO_3^- \rightarrow$ post prandial alkaline tide (\uparrow Ph in blood and urine after gastric secretion).



Factors affecting HCL secretion (receptors on parietal cells):

- **Histamine** →↑ HCl secretion via stimulation of ***H2 receptors*** by ↑ cAMP (these receptors are blocked by cimetidine).
- **Acetyl choline** →↑ HCl secretion via ***muscarinic M3 receptors*** by ↑ Ca⁺² & this effect is blocked by atropin.
- **Gastrin** →↑ HCl secretion via ***Gastrin CCK-B Receptors*** by ↑ intra cellular Ca⁺².
- **Prostaglandin E2** causes ↓HCl secretion via ↓ cAMP (used in treatment of peptic ulcer).
- **Somatostatin:** causes ↓HCl via Gi which ↓ cAMP

Functions of HCL

- 1) Sterilization by acidity which kills bacteria.
- 2) Digestion of protein by activation of pepsinogen → pepsin & give optimum pH of its effect and hydrolysis of protein.
- 3) HCl enters the duodenum →↑ secretin hormone →↑ bile and pancreatic secretion.
- 4) Produces curdling of milk.
- 5) Initiate enterogastric inhibitory reflex →↓ gastric secretion and evacuation.
- 6) ↑ absorption of iron (by converting ferric state into ferrous) and calcium (by prevention of calcium salts precipitation).

2) Secretion of enzymes:

A- Pepsinogens (I & II)

- Secreted by chief (peptic) cells.
- Inactive pepsinogen by (HCL) converted to active pepsin.
 - Of optimum pH 1.8 – 3.5.
 - Digest proteins → proteases & polypeptides.
 - **Pepsinogen I** is large amount, secreted by the chief cells and its secretion is linked with HCL secretion.
 - **Pepsinogen II** is less in amount, secreted by mucosal cells and not linked with HCL secretion.

B- Gelatinase :which liquefies gelatin.

C- Gastric lipase:

act on short chain fat. Its optimum pH = 3.

D- Amylase (from saliva).

E- Rennin: milk clotting enzymes (not present in humans).

3) Secretion of intrinsic factor:

- It is a glycoprotein secreted from oxytic cells with HCL.
- It is essential for vit B12 absorption in ileum.
- In gastritis → pernicious anemia (\downarrow B12 anemia).

4) Secretion of Mucus:

There are two types of mucus:

- **Soluble thin mucus:** secreted by mucus neck cells by vagal as mucoproteins to lubricate gastric chyme.
- **Insoluble thick mucus:**
 - Secreted by the surface epithelium.
 - Viscid alkaline mucus layer to protect gastric wall from digestion & acidity.

Mechanism of protection of the gastric mucosa from pepsins and HCL:

- 1) Mucosal barrier: insoluble thick alkaline mucus gel layer (1 mm) together with HCO_3^- (Ph is 6-7 at surface of mucosal epithelial cells).
- 2) Prostaglandins stimulate the secretion of this alkaline mucus and decrease HCL secretion.
- 3) Tight junctions between mucosal cells to prevent passing HCL in between cells.
- 4) Gastric mucosa contains *trefoil peptides* which are acid resistant.
- 5) *Continuous regeneration of gastric mucosa by growth factors*
- 6) The oxytic cells are protected from HCL by forming it in *intracellular canaliculi* then secreting it in the gastric lumen.

Duodenum is protected by mucosal barrier + pancreatic alkaline secretion.

5) Secretion of gastrin hormone:

- **It is a polypeptide belong to gastrin -CCK group** of 3 types according to number of amino acids G34, G17 (most important) and G14
- **It is secreted from G-cells in pyloric antrum.** It is also present in the anterior pituitary gland, hypothalamus and medulla oblongata.
 - **Receptors (CCK -B). Action of gastrin on:**
 - Stomach: \uparrow growth of gastric mucosa (trophic effect), secretion &

motility.

- Pancreas: ↑ insulin secretion.
- Sphincters: - Lower oesophageal sphincter → Contraction.
- Ileocecal sphincter → Relaxation.
- ↑ growth of intestinal mucosa & Stimulation of small and large intestinal motility

NB: Persons with gastrin-secreting tumors (**Zollinger-Ellison syndrome**), H⁺ secretion is increased, and the trophic effect of gastrin causes the gastric mucosa to hypertrophy.

Conversely, in persons whose gastric antrum is resected, H⁺ secretion is decreased and the gastric mucosa atrophies.

Regulation of gastrin secretion:

	Stimulation	Inhibition
• Chemical factors	• Polypeptides, amino acids, caffeine and alcohol.	• ↑ acidity PH < 2 -ve feedback inhibition via release of somatostatin.
• Luminal	• Distension of the stomach.	-----
• Blood born	• Calcium, adrenaline.	• Secretin, GIP, VIP, calcitonin, glucagon
• Neural	• Vagal by gastrin releasing peptide	-----

Control of gastric secretion:

Nervous and hormonal:

Three phases:

1) Cephalic phase (30 %):

- It is a nervous phase activated by conditioned and unconditioned reflexes:
- ***In the conditioned reflex:*** Psychic stimulation of cerebral cortex, appetite centers of

the amygdala and hypothalamus will stimulate the vagal center (dorsal motor nuclei)

In the unconditioned reflex: direct contact of food stimulates taste buds which give afferent to the vagal center.

- The vagal nuclei stimulate gastric secretion by:

1. Direct stimulation of gastric glands (ACh).
2. Release of gastrin hormone (Gastrin releasing peptide).

- This phase increases by anxiety and decreases in depression.

The role of unconditioned reflexes is proved by:

- **Sham feeding** experiment: The esophagus of a dog is exposed and divided in the neck, so the food swallowed will pass to outside. At the same time a gastric fistula is inserted. Although no food reaches the stomach, Sham feeding increases gastric secretion.

2) Gastric phase (60 %): The presence of food in the stomach → increase gastric secretion by mechanical, chemical, and neural stimuli as the following:

- **Gastrin secretion:** by direct stimuli as polypeptides, alcohol and caffeine or via local and vago-vagal reflex to stimulate the vagal center.
- **Local nerve plexus:** by distension or polypeptides → stimulate Meissner's plexus →↑secretion.
- **Vago-vagal long reflex:** food in stomach → afferent vagus to vagal center & efferent vagal increase in gastric secretion so inhibited by atropine.

N.B : hypoglycemia →↑ vagal stimuli →↑ secretion.

3) Intestinal phase (10%) :

The presence of food in the duodenum, will continue to cause stomach secretion of small amounts of gastric juice (10%), because of small amounts of gastrin released by the duodenal mucosa.

- Although intestinal chyme slightly stimulates gastric secretion during the early intestinal phase of stomach secretion, **it paradoxically inhibits gastric secretion** at other times. This inhibition results from at least two mechanisms.

A- Nervous mechanism (Enterogastric reflex):

- **It is stimulated by** presence of acid, fats or hyperosmotic solution in the duodenum or distention of the duodenum will inhibit the gastric secretion.
- **The reflex is conducted** in the three ways: local, ganglionic or vago – vagal reflex.

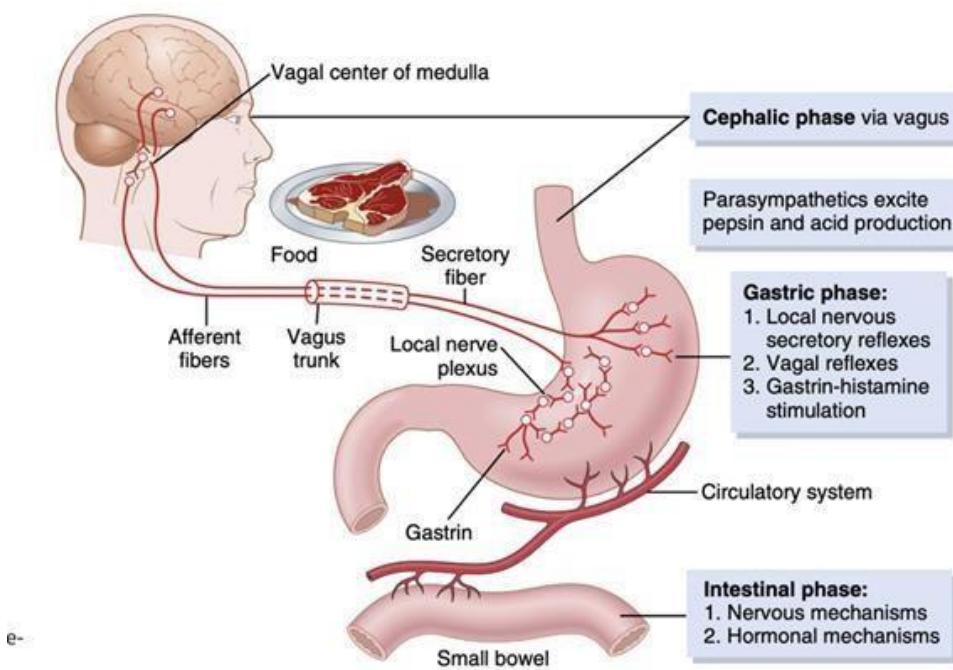
- **The response and the importance:**

1. Inhibition of gastric secretion and motility
2. Protection of duodenum from over distention by increase in the tone of pyloric sphincter → delays the emptying.
3. Protection of duodenum from hyperacidity (till neutralized by alkaline duodenal secretion).
4. Insure protein digestion.
5. Prevent rapid electrolyte changes during intestinal absorption.

B- Hormonal mechanism (Enterogastric hormones):

It is stimulated by the presence of fats, acid, protein breakdown products, hyperosmotic or hypo-osmotic fluids → release of 4 hormones from the duodenum [cholecystokinin (CCK), secretin, gastric inhibitory peptide (GIP) & VIP] → hormonal feed – back inhibition of gastric secretion and motility for complete digestion of fat.

Gastric Secretion During the Interdigestive Period: stomach secretes a few ml of gastric juice each hour during the “interdigestive period,” when no digestion is occurring anywhere in the gut composed mainly of *mucus* but little pepsin and almost no acid. Emotional stimuli may increase this secretion (which is highly peptic and acidic) to 50 ml or more per hour, which may contribute to the development of peptic ulcer.



Peptic ulcer

- It is an area of erosion of mucosal membrane of GIT due to increase gastric secretion (as in stress, depression, anxiety and gastrinoma)or disruption of mucosal barrier (*by excess intake of aspirin, alcohol, smoking or by infection with H Pylori*) mostly occur in common sites as prepyloric portion in lesser curvature of stomach, proximal duodenum, lower esophagus and rare in jejunum.
- Duodenal ulcers are most common and occur more in elderly men and occur in hyperparathyroidism as calcium stimulate gastric acid secretion. Also, in patient with renal transplant and the pain occur with hungry.
- The patient of peptic ulcer complains of attacks of severe pain in epigastric region, related to meals and associated with nausea, flatulence, and heart burn.
- Gastric ulcer is associated with anorexia and weight loss.

Gastric Motility

Filling and Storage of food in the stomach:

The stomach accommodates up to one liter of food without increase of intragastric pressure because:

- a. Plasticity of gastric wall.
- b. Receptive relaxation.
- c. **Law of LaPlace:** $P=T/r$ states that distending pressure (P) in a hollow viscus equals the tension in its wall (T) divided by its radius (r).

In the stomach, since food entry increases its radius with a little increase in tension, the intragastric pressure will be kept at a low level.

Gastric basic electrical rhythm (BER) (gastric slow waves):

- 3-5 cycles/min. due to partial depolarization of circular smooth muscle cells in the stomach wall.
- Some lead to spike potential → peristalsis. (*Frequency of slow waves in all GIT determines* rate at which *action potentials & contractions occur*.
- Start at midpoint of greater curvature (**pacemaker** of the stomach).
- Vagal stimulation, gastrin & motilin →↑ spike potential rate.
- Sympathetic stimulation, secretin & GIP→↓ spike potential rate.
- **N.B.** Slow waves are more frequent in the duodenum (12 waves per minute) than in the stomach. In the ileum, the frequency of slow waves decreases slightly, to 9 waves per minute.

Types of movements of the stomach:

1. Tonic gastric waves:

- Regular weak contractions (3 waves/min) which take place in the fundus and body to maintain the intra-gastric pressure & mix gastric secretion with food.

2. Receptive relaxation:

- It is a reflex relaxation of the fundus and body to receive the bolus of food.
- Initiated by vagovagal reflex that is triggered by movements of the pharynx and esophagus. (neurotransmitter released is VIP)

- Also, by plasticity of gastric muscles.

3-Peristaltic movement:

- It occurs at a rate of 3-4 / min. & coordinated by BER of stomach.
- Distension of stomach by food → stimulates stretch receptors → vago – vagal reflex peristalsis at the middle of stomach and proceeds toward the pyloric antrum with gradual increase in strength leading to:
 - Grinding of food to fine particles.
 - Emptying of fine particles into the duodenum (***propulsive movements***).
 - Peristalsis in opposite direction from pyloric antrum to fundus (***Antiperistalsis***) → ***pyloric mill or retropulsion*** for mixing of food with gastric secretion.

4. Hunger contractions:

Hypoglycemia (fasting for 12h) → activation of the feeding center in hypothalamus → Sends impulse to limbic cortex → hunger sensation.

- Also, sends impulse to vagal nucleus → hunger strong painful contraction near the fundus (Atropine injection or vagotomy abolish hunger contraction but not hunger sensation).
- They start slowly, then increase → tetanic contraction for 2 minutes then disappears and reappear in the next feeding time to reach maximal intensity in 3-4 days then gradually disappear. (May due to ↓ sensitivity of feeding center to hypoglycemia)
- **N.B.** During fasting, there are periodic gastric contractions, called **migrating myoelectric complexes**, which are mediated by **motilin**. These contractions occur at 90-minute intervals to clear the stomach of any residue remaining from the previous meal.

Nervous regulation of gastric motility:

- a- **Vagal (parasympathetic)**: Excitatory cholinergic effect.
- b- **Sympathetic**: Inhibitory (nor adrenergic).
- c- **Myenteric plexus**: Involved in short & long reflexes.

Factors affecting gastric emptying:

With a mixed meal the stomach usually empty in about 3 hours through the pyloric pump which regulates the rate of gastric emptying.

The rate of emptying is controlled by:

A. Factors in the stomach:

1. **Type of food:** carbohydrate is the most rapid, then proteins followed by fats.
2. **Consistency of food:** liquids more rapid which depends on type of food, degree of mastication and the strength of gastric peristalsis.
3. **Volume of food:**
 - Moderate volume of chyme → ↑ emptying via vago-vagal reflex and release of gastrin hormone.
 - Large volume → over distension → ↓ emptying.

B. Factors in the duodenum:

- **Degree of duodenal distention:** Excessive duodenal distention delays gastric emptying through the enterogastric reflex.
- **Type of food in the duodenum:** Presence of excess fat in the duodenum delays gastric emptying stimulating via release of CCK that inhibit gastric motility. This effect is providing adequate time for fat to be digested and absorbed.
- **Duodenal acidity:** excess duodenal acidity delays gastric emptying by both stimulating release of gastric inhibitory hormone & enterogastric reflex.
- **Duodenal osmolality:** hyperosmolality and hypoosmolality stimulate *duodenal osmoreceptors* that lead delayed gastric emptying via initiating *enterogastric reflex*. so, preventing rapid flow of non-isotonic fluids into the small intestine (which disturbs the electrolyte balance).

C. Emotional factors:

1. *Pain*: visceral and somatic pain → reflex inhibition of gastric emptying.
2. *Depression & sudden fear* → reflex sympathetic inhibition.
3. *Anxiety & anger* → reflex parasympathetic stimulation of emptying.

D. Chemical factors:

Gastric emptying is accelerated by cholinergic drugs, alcohol, bicarbonate and coffee while it is delayed by adrenergic drugs, atropine and excessive smoking.

Vomiting

Definition: It is the expulsion of gastric contents through the esophagus, pharynx and mouth.

-It is a complex act controlled by vomiting center in the medulla oblongata and mediated by cranial nerves V, VII, IX, X & XII and spinal nerves to

diaphragm and abdominal muscles.

-It is preceded by nausea, salivation and increase respiration.

Centers:

a. Vomiting center: in the medulla oblongata.

b. Chemo receptor trigger zone (CTZ):

-In close to vomiting center in M.O in the wall of fourth ventricle.

-Its stimulation by emetic drugs, motion sickness or metabolic causes → stimulation of vomiting center (its lesion leads to loss of this reflex).

Causes of vomiting:

1-Central vomiting:

Direct stimulation of CTZ by drugs as morphine, alcohol drinking, diabetic ketoacidosis, renal failure, and early pregnancy.

2-Reflex vomiting: Stimuli:

Unconditioned:

- Irritation of back of tongue.
- Irritation of gastric mucosal.
- Severe visceral pain (Renal colic, coronary thrombosis...).
- Irritation of semicircular canal.

Conditioned: (Cortical excitation of vomiting) Visual, olfactory, and psychic stimuli

Afferent: According to site of stimuli.

Center: Direct on vomiting center.

- Some to CTZ as semicircular canal irritation and psychic.

Efferent:

- Via cranial nerves V, V11, 1X, X, X11.
- Phrenic nerve to diaphragm.
- Spinal nerves to abdominal muscles.

Response: → vomiting.

Mechanism of vomiting:

1- Nausea: with salivation, ↑ H.R, sweating, stomach wall is relaxed and antiperistalsis may occur in duodenum.

2- Retching: intermittent contraction of diaphragm and abdominal muscles against closed L.E.S, glottis, and diaphragmatic opening is also contracted.

3-Gastric evacuation:

- Strong contraction at the incisura separating the body from the pylorus.
- The cardiac sphincter relaxes and the stomach wall is completely relaxed (passive stomach).
- Powerful contraction of the diaphragm, abdominal muscles, and pelvic floor muscles →↑ intra-abdominal pressure → squeezing the relaxed stomach and expulsion its contents to the mouth (anti peristalsis may occur in oesophagus).
- During vomiting the soft palate elevated, closure of glottis and inhibition of respiration to prevent the vomitus to pass to respiratory passages (as in swallowing).
- When the stomach is empty, antiperistalsis waves may drive the intestinal contents into the stomach (as bile juice).

Effect and complications of vomiting:

- **Dehydration** (loss of secretion).
- **Alkalemia:** due to loss acid and the resynthesis of acid is associated with ↑ alkaline tide in plasma.
- **Tetany:** Alkalemia →↓ ionized Ca^{+2} → **tetany**
- **Hypokalemia** (↓ K^+ level).

Physiology of Intestine and Pancreas

Small intestine

Motility of small intestine of two types:

1) The segmenting movements:

Nature: it is myogenic in nature (controlled by the myogenic basic electric rhythm), accentuated by the local plexus, not controlled by vagus.

Mechanism: several constrictions divide the loop of intestine into equal segments (2-3cm), then, these constrictions disappear and new constrictions occur in the middle of each segment and so on

Rate: 12/min in duodenum & decrease along small intestine

Value:

- A. Help digestion by mixing the chyme with digestive juice.
- B. Help absorption as the food comes in contact with the mucosa.
- C. Aids the blood and lymph circulation.

2) The peristaltic movements:

Nature: it is neurogenic in nature (depend on local enteric plexus) and regulated by:

- ✓ **Gastroenteric reflex:** distension of the stomach stimulates intestinal peristalsis reflexly.
- ✓ **Hormones:** as gastrin, CCK, insulin and glucagons.
- ✓ **Vagus.**

Mechanism: distension by food bolus →local reflex contraction of circular muscle above distension (with relaxation of longitudinal m. by ACh, substance P, neuropeptide Y) while relaxation of circular muscle Infront of bolus with contraction of longitudinal m. by VIP, NO)

Rate: It propagates at a speed of 1-5 cm/second for short distance (20 cm) then dies out.

Value: propulsive for chyme analWards.

Types: 3 types of peristalses: **a. Ordinary peristalsis.**

b-Peristaltic rush (mass peristalsis):

If the intestinal mucosa is irritated by toxins, a strong peristaltic wave passes rapidly over the whole small intestine by local enteric or vago vagal

reflex – normally occur 1 – 2 times/day.

c-Antiperistalsis: Peristalsis in *reverse direction* at:

- 1- *Duodenum*: for mixing the chyme with alkaline duodenal secretion.
 - 2- *Ileocecal sphincter*: to complete absorption of fluids by small intestine.
Peristalsis is very strong in the esophagus then becomes weaker gradually.

Intestinal BER initiated by pacemaker interstitial cells of Cajal. in circular muscle & its rate is about 12/minute in duodenum & 9/minute in distal ileum. Spike potentials superimposed on depolarizing portions of BER increase intestinal muscle tone (BER itself rarely causes muscle contraction its function is to coordinate peristaltic activity)

Control of small intestinal motility:

Nervous:

- Extrinsic: vagus nerve →↑ motility but sympathetic→↓ motility
 - Intrinsic: local myenteric plexus.

Hormonal:

Gastrin & CCK → ↑ motility. Secretin & glucagon → ↓ motility.

The ileocecal sphincter:

- ***It is*** the last few cm of ileum.
 - ***It is controlled*** mainly by the ***local intrinsic nerve plexus***; it is tonically contracted to prevent return of cecal contents into the ileum.
 - ***It is relaxed by:***
 - Distension of the stomach → ***gastro-ileal reflex***.
 - Distension of ileum → local reflex.
 - Gastrin hormone
 - ***It is contracted by:*** Over distension of cecum → local reflex or sympathetic stimulation. (colono-ileal reflex) to inhibit ileal peristalsis.

Movements of intestinal villi:

- In the form of shortening and elongation → aid the lymph flow.
 - Controlled by local plexus and villikinin hormone.

GIT movement during fasting:

- **Migrating motor complex** of peristaltic waves occurs every 90 minutes
 - It proceeds anal wards at a speed 10 cm/min.

-It is a **local enteric reflex** aims to sweep any excess of GIT secretion towards the colon to prevent their accumulation.

Paralytic ileus: one of the common complications following abdominal operations, trauma to intestine & peritonitis.

-It is caused by increase sympathetic tone → relaxation and accumulation of chyme, fluids and gases.

-It is treated by aspiration of fluids & gas by nasal tube and I.V fluids to treat the dehydration due to ↓ absorption until the motility reappear.

Intestinal secretion (succus entericus)

The small intestine has 3 types of secretory cells:

- Crypts of lieberkuhn.
- Brunner's gland and Goblet cells.
- Enterochromaffin cells which secrete serotonin.

***The Villus:**

is finger like projection 0.5-1 mm Long. Covered by single layer of epithelium. Has smooth muscle to help its movements and a brush border of minute microvilli to increase the absorption surface to 200 m². The life span of mucosal cells is 3-5 days.

The small intestine secretions are made up of:

Mucus:

- Secreted by Brunner's glands & goblet cells.
- Important for protection and lubrication.
- Stimulated by vagus, local distension or acidic chyme & secretin.
- Inhibited by sympathetic stimulation so, irritable persons have high incidence of duodenal ulcers.

Alkaline fluid: (Na HCO₃):

- Dissolves the chyme.

- Stimulated by secretin, CCK, VIP and PGs.
- Inhibited by sympathetic.

Sloughed Mucosa (enzymes):

- The intestinal secretion is about 1 liter/day of pH 7.5 and have no enzymes secreted from Crypts of Lieberkühn.
- The sloughed cells contain disaccharides (sucrase, maltase & lactase) dipeptidases (Aminopeptidase, enterokinase) and phosphatases.

Control of small intestine secretions:

Nervous: - local enteric reflexes →↑ secretion.

- Vagal →↑ mucus secretion only.

Hormonal: VIP, secretin, CCK →↑secretion.

Vaso active Intestinal Peptide (VIP):

It is released from the nerves of GIT and act as a hormone or co-transmitter and has the following effects:

- 1- It stimulates intestinal secretion (water and electrolytes) and relaxation of intestinal muscle including sphincters
- 2- It induces Vasodilatation.
- 3- It inhibits gastric acid secretion.
- 4- It relaxes Lower esophageal sphincter.
- 5- Potentiation of the action of acetylcholine in the salivary glands.

The large intestine

Motility of the large intestine:

1) - Mixing segmenting movement:

Predominant movement for H₂O and ions absorption. The large intestine characterized by the presence of outer muscular three bands (teniae coli) → bag like sacs called haustrations with contraction of circular muscle layer.

2) - Peristaltic (propulsive) movements:

A- Weak peristalsis movements.

-The colon is able to restore its contents for days. It propels the chyme from the cecum to the transverse colon.

B- Antiperistalsis: It may occur from transverse to ascending colon to complete water absorption.

C - Mass movements:

- It occurs to propel the faecal matter from transverse to sigmoid colon.
- About 20 – 25 cm contract as one unit to push the contents into the rectum, usually occur after breakfast (1 to 3 times per day)
- It is initiated by gastrocolic and duodenocolic reflex by presence of food in stomach and duodenum → reflex colonic contraction through released gastrin hormone which stimulate colonic motility or local enteric or prevertebral ganglionic reflex.

Functions of large intestine:

1. *Absorption of water, electrolytes, some vitamins, and some drugs:*

- i. About 2 lit of water follow Na Cl absorption by osmosis.
- ii. Large water rectal enema →↑ water absorption & water intoxication may occur.
- iii. Some drugs as sedatives, steroids, anesthetics could be taken suppository.

2. *Storage and evacuation of stool:*

- i. The colon stores feces and the rectum is usually empty except just before defecation.
- ii. When the rectum contains 100 ml of feces, there is urge to defecate

which is completed by relaxation of internal sphincter and voluntary relaxation of external anal sphincter.

3. Bacterial action in the large intestine:

a. Useful bacteria:

1. Synthesis of vitamins as vit. K, thiamine, biotin & folic acid.
2. Stimulate lymphocytes in intestinal wall to secrete IgA & IgM.
3. Prevention of cecal enlargement via digesting the macromolecules.

b. Harmful bacteria:

1. Ammonia formation → ↑ ammonia in bl.
2. Cholesterol → hypercholesteronemia.
3. Histamine & serotonin.
4. Utilize vit B12 and ascorbic acid.

4. Secretion of alkaline mucus:

1. High alkaline (pH= 8) to protect the mucosa from acids produced by bacteria.
2. It is produced by crypts of lieberkuhn and goblet cells in response to:
 - a- The contents of food.
 - b- Emotional stress → stimulate pelvic nerve → ↑ mucus secretion & motility → diarrhea.

Guanylin :

1. It is paracrine regulator produced by the ileum & colon.
2. It has the ability to activate guanylate enzyme and production of c-GMP within cytoplasm of intestinal cells. Which stimulate epithelial cells to secret Cl^- & water with inhibition of Na^+ absorption → ↑ salt & water loss in faeces.
3. The enterotoxins of Eschericia coli bacteria → same effect.
4. Uroguanylin is a related polypeptide found in urine & stimulate the kidney to excrete salts in urine.

Defecation

Definition: It is the act of emptying of the colon through the anus.

The anus is controlled by:

- **Internal anal sphincter:** smooth involuntary muscle, controlled by

autonomic nervous system.

- **External anal sphincter:** striated voluntary muscle controlled by somatic (pudendal) nerve which originate from the anterior horn cells of S2, S3, S4.

Defecation centers: lateral horn cells of sacral S2, S3& S4 for involuntary defecation. These centers are under control of medullary centers and cortical control for voluntary defecation.

Role of innervation in defecation:

The distal colon, rectum and anal canal are innervated by:

- **Somatic** pudendal nerve which arises from AHC of S2, S3& S4 to supply the anal canal and external anal sphincter, but its afferent fibers carry friction sensation during stool passage.
- **Parasympathetic** pelvic nerve which arises from LHC of S2, S3& S4 to supply the wall of rectum and the internal anal sphincter. Its afferent fibers carry fullness sensation.
- **Sympathetic** nerve which arises from LHC of L1&2 to inhibit defecation.

Defecation mechanism (reflexes):

1. Preparatory reflexes:

- a. **Gastro-colic reflex:** distention of stomach → reflex contraction of the colon.
- b. **Duodeno-colic reflex:** distention of duodenum → reflex contraction of the colon.

2. Intrinsic defecation reflex: distension of the rectum → weak peristaltic waves in the colon and relaxation of internal anal sphincter.

3. Spinal defecation reflex:

-Stimulus: distension of the rectum.

-Receptor: mechanoreceptors.

-Afferent: Pelvic nerve and pudendal N.

-Center: L.H.C of S2, S3, S4 (parasymp) & A.H.C of S2,3,4 (somatic).

-Efferent: pelvic nerve & pudendal N.

-Response:

- Pelvic N → contraction of wall & relaxation of internal anal sphincter.
- Pudendal N → relaxation of external anal sphincter.

This reflex is potentiated by passage of fecal materials through the anal canal via afferent pudendal nerve to S2, S3 & S4.

Voluntary control of defecation:

Once the rectum fills to 25% of its capacity, there is an urge to defecate. Signals are sent to carry a sense of rectal fullness and the desire to defecate to the brain.

1- If the conditions are suitable:

- a. The cerebral cortex sends excitatory impulses to activate the defecation center in the spinal cord → more peristalsis and relaxation of anal sphincters.
- b- The act of defecation is facilitated by straining (forced expiration against closed glottis) → ↑ intra-abdominal pressure and squeezes the rectum.
Also, contraction of the levator ani muscle helps defecation.

2- If the conditions are unsuitable:

The cerebral cortex sends inhibitory impulses to inhibit the defecation center with rectal wall relaxation and internal sphincter contraction by sympathetic effect.

The external anal sphincter contracts voluntary via pyramidal fibers → prevent defecation.

Constipation

Definition: It is the decrease in frequency of defecation → more absorption of water from the feces → dry and hard feces.

Causes:

1. Mainly by frequent inhibition of defecation → weak reflex and atonic colon.
2. Overuse of laxatives → weakens the reflex.
3. Other causes: anal pain, hypothyroidism, depression, hypercalcemia.

N.B: Spastic colon:

In anxious persons, paroxysmal attacks of colon spasm and constipation followed by diarrhea. Laxatives not used in this case but may be treated by fiber diet, antispasmodic and stress treatment.

Diarrhea

Definition: It is a frequent defecation of large volume of soft stool.

Caused by:

- a- Irritation of intestinal mucosa by bacteria, viruses (enteritis), parasites or enterotoxins (cholera) substances →↑ secretion and colonic motility.
N.B: in cholera →↑ secretion of Na Cl & H₂O → secretory diarrhea
Or in inflammation →↓ absorption in colon → inflammatory diarrhea.
N.B: traveller's diarrhea is acute case with travelling.
- b- Psychic diarrhea in nervous tension.
- c- Osmotic diarrhea by undigested lactose or magnesium sulphate.

Complications:

1. Dehydration may lead to hypovolemic shock.
2. Hypokalemia (due to K⁺ loss).
3. Acidosis (loss of bicarbonate & reformation of bicarbonate is anticipated with ↑ acidic tide).

Physiology of Pancreas

Pancreatic secretion

The pancreas has both:

1- Endocrine gland: Alpha cells → glucagon & Beta cells → insulin.

2- Exocrine gland: consisted of blind secretory acini, ducts which drain in pancreatic duct which unites with common bile duct and open together at the ampulla of Vater in the duodenum. The common opening is surrounded by sphincter of Oddi.

Exocrine pancreatic secretion:

- **Volume:** 1 – 1.5 L/day. **PH:** 7.8 – 8.3
- **Osmolarity:** iso-osmotic with plasma.
- **Ions:**
 - Na^+ & K^+ : the same concentration of plasma.
 - HCO_3^- : higher than in plasma (145 mEq/L).
 - Cl^- : lower concentration than plasma.
- **Types:**

1- Aqueous alkaline juice:

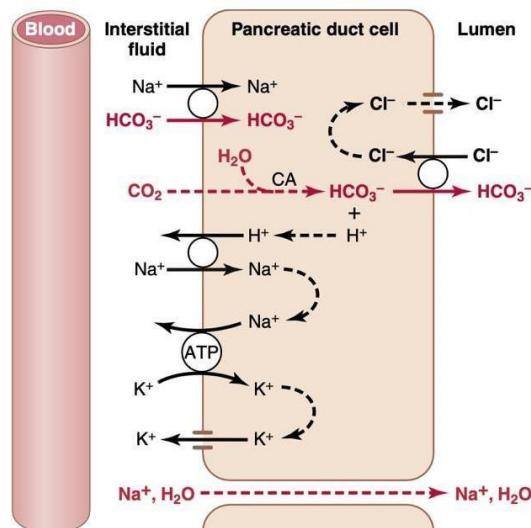
- Large in volume, rich in bicarbonate & secreted by duct cells.
- Stimulated by secretin hormone & inhibited by sympathetic.

Mechanism of secretion:

1. CO_2 from the blood diffuses to interior of duct cells and by carbonic anhydrase combines with water to form carbonic acid (H_2CO_3).
2. carbonic acid dissociates into HCO_3^- and H^+ . Also, Additional HCO_3^- enters the cell through the basolateral membrane by co-transport with Na^+ .
3. HCO_3^- is then exchanged for Cl^- by secondary active transport through the luminal border into the lumen of the duct. The Cl^- that enters the cell is recycled back into the lumen by special chloride channels.
4. H^+ ion is pumped out to the plasma (*acid tide*) in exchange for sodium which is pumped into the cell then diffuses to lumen.

5. Na^+ also enter the cell by co- transport with HCO_3^- across the basolateral membrane. Sodium ions are then transported across the *luminal border* into the pancreatic duct lumen.
6. Movement of Na and HCO_3^- from the blood into the duct lumen creates an osmotic pressure gradient that causes osmosis of water also into the pancreatic duct, thus forming an almost completely isosmotic bicarbonate solution.

Acid-tide: ↑ H^+ concentration in venous blood drain the pancreas to neutralize alkaline tide of gastric secretion → acid – base balance.



2- Enzymatic juice:

- Small in volume, rich in enzymes.
- Secreted by acinar cells.
- Stimulated by cholecystokinin-pancreozymin (CCK – PZ) & vagus nerve.

Pancreatic enzymes:

- **Pancreatic amylase:** starch, glycogen → maltose.
- **Pancreatic lipolytic enzymes:** *Lipase and phospholipase* (facilitated by bile).
 - Triglycerides → FFA & monoglyceride.
 - Phospholipase A: act on lecithin → lysolecithin.
 - cholesterol esterase*: hydrolysis of cholesterol esters
- **Proteolytic enzymes:**
 - Endopeptidases* as **trypsinogen, chymotrypsinogen** and **proelastase**
 - Exopeptidases: Procarboxypeptidases*.

They are secreted in inactive form and activated by **enterokinase** (in small intestine) and the active trypsin to prevent autodigestion of pancreas (also the pancreas has **trypsin inhibitor**).

- **Pancreatic nucleases:** *ribonuclease and deoxyribonuclease*, act on RN A and DNA leading to formation of *nucleotides*.

Control of exocrine pancreatic secretion:

I. Nervous: three phases: *cephalic phase, gastric phase, and intestinal phase*.

- 1) **Cephalic Phase:** conditioned & unconditioned reflexes → vagal stimulation of enzymatic secretion from acini about 20% of the total secretion of pancreatic enzymes after a meal. Little of secretion flows immediately through pancreatic ducts into the intestine because only small amounts of water and electrolytes are secreted along with enzymes.
- 2) **Gastric phase:** the nervous stimulation of enzyme secretion continues about 5% to 10% of pancreatic enzymes secreted after a meal, only small amounts reach the duodenum because of continued lack of significant fluid secretion.
- 3) **Intestinal Phase:** After gastric chyme enters the Duodenum, pancreatic secretion becomes copious, mainly in response to the hormone *secretin*.

II. Hormonal: Secretin →↑ aqueous alkaline secretion from ducts. CCK. PZ →↑ enzymatic secretion from acini (70% to 80% of the total secretion of the pancreatic digestive enzymes after a meal.)

	Cholecystokinin pancreozymin (CCK)	Secretin
Structure	33 A.A (gastrin-CCK family) 2 receptors CCK A & CCKB	27 A.A (secretin-glucagon family)
Site	Upper part of small intestine	
Stimuli	- Digestive products of protein and fat - Polypeptides & AA -Fats & F.A. in duodenum	- Acidic chyme from stomach ↑ HCL pass to the duodenum with decrease its pH.
Effect on: Stomach	Inhibition of gastric functions (motility and secretion).	
Intestine	↑motility & enzymes secretion.	↑mucus secretion.
Pancreas	<ul style="list-style-type: none"> • ↑ Secretion of enzymes. • It potentiates the effects of secretin on HCO_3^- secretion. • ↑ insulin H. • Trophic effect 	↑ Secretion of alkaline juice. ↑ Insulin hormone.
Bile	↑ Evacuation of bile from gall bladder (cholagogue).	↑Secretion of bile Na HCO_3 .
Control	Positive feedback between CCK & A.A as CCK causes more digestion of protein leading to production of AA which re-stimulates CCK	Negative feedback as HCL causes release of secretin which in turn inhibit HCl secretion from the stomach.
Second messenger	Increase Ca^{++}	cAMP

Physiology of Liver and Biliary system

Liver & bile

The liver is the largest gland in the body (1.5 kg).

Function of the liver:

1) Metabolic function:

- **CHO metabolism:**

- Conversion of galactose and fructose to glucose
- ***Glucostat function:*** liver maintain the blood glucose within 70-110 mg % ; If the blood glucose level increases, the excess is taken by the liver and is converted to glycogen (*glycogenesis*) and fat (*lipogenesis*), and if it decreases, it is added by the liver into the bloodstream (through the processes of *glycogenolysis and gluconeogenesis*).

- **Protein metabolism**

- (a) ***Deamination of amino acids***, and the resulting products are either oxidized (to supply energy) or converted into carbohydrates and fats.
- (b) ***Conversion of ammonia to urea:*** Ammonia is formed in the gut by bacteria and its conversion to urea is lifesaving because it produces toxic effects specially to the nervous system (*hepatic encephalopathy*).
- (c) ***Formation of uric acid*** (end-product of nucleoprotein metabolism).
- (d) ***Synthesis of non-essential amino acids*** (through transamination).
- (e) ***Synthesis of the plasma proteins*** (except gamma-globulins).

- **Fat metabolism:**

- (a) ***Oxidation of fatty acids to supply energy & formation of ketone bodies:*** Fat is first split into glycerol and fatty acids (lipolysis), then the fatty acids by beta- oxidation into acetyl radicles which combine with coenzyme A (CoA) forming acetyl-CoA . Part of acetyl-CoA is oxidized in the citric acid cycle while the other part is converted by condensation of 2 molecules into acetoacetic acid which is delivered by the liver cells to the bloodstream and is oxidized at other tissues.

- (b) ***Synthesis of cholesterol, lipoproteins, and phospholipids.***

80 % of cholesterol is converted into bile salts. while the remainder (together

with phospholipids and lipoproteins) is transported to the tissues. In the tissues lipoproteins are split and fat is stored or oxidized while phospholipids and cholesterol form cell membranes and certain intracellular organelles.

(c) *Fat synthesis from carbohydrates and proteins (lipogenesis).*

2) Storage function:

- The liver stores glycogen, vitamins A, D, E, K & B12 and metals as iron & copper.
- Iron is stored in the form of ferritin. When the blood iron level decreases the liver ferritin releases its iron content to the blood while if the blood iron level increases, it is taken by the liver where it is stored (blood iron buffer).
- Liver is essential for erythropoiesis (since it supplies vitamin B12, iron and the globin fraction of hemoglobin). The erythrocytes are also formed in the liver during fetal life .

3) **Plasma proteins and Blood clotting factors formation :** the liver needs vit. k to synthesize factors II, VII, IX, X.

4) Vascular function:

- **Storage of blood about** 10% of the total blood volume (450 ml) in the sinusoids and hepatic veins. When needed, this blood, can be added to the general circulation (e.g. in cases of severe hemorrhage).
- **Blood filtration :** By kupffer cells removal of *blood clots* &bacteria that enter the portal blood from the intestine.

5) **Drug and hormonal inactivation:** e.g. steroid H., pencillin & others.

6) **Immune response:** the liver is a part of the reticule endothelial system

7) Bile formation:

- Formation and secretion of about 0.2gm of bile salts/day.
- Formation and excretion of bile pigments

8) **Synthesis of vitamin d (1,25 cholecalciferol).**

Gall bladder

Motility of the gall bladder

- At meal time the gall bladder contract and sphincter of Oddi relaxes → evacuation of bile.

- Cholagogues: factors increase evacuation of the bile as vagal stimulation, cholecystokinin hormone and magnesium sulphate.

Functions of gall bladder:

- Storage of bile** in between meals as the sphincter is closed and the liver continue to secrete bile (*max. volume up to 30-60 ml*)
- Concentration of bile:** by active absorption of Na^+ followed by passive absorption of water, Cl^- and HCO_3^- except Ca^{++} to accommodate large volume of stored hepatic bile.
- Help continuous flow** of hepatic bile in between meals by storage and concentration (Decreasing the pressure in the bile ducts).
- Acidification of bile** by absorption of Na^+ bicarbonate to prevent precipitation of Ca^{++} bile stones (pH changed from 7.8 to 7).
- Evacuation of bile** in the duodenum.
- Secretion of white bile** as mucus to protect the bladder wall from the concentrated bile. And acts as a lubricant and buffer in duodenum.

Gall stones:

- The formation of biliary calculi is caused by:
 - 1) Too much absorption of water from bile.
 - 2) ↓ Bile salts or lecithin or increase in cholesterol → **cholesterol stones**.
 - 3) Inflammation of gall bladder: bacteria and glucuronidase enzyme convert bilirubin glucuronide into free bilirubin which combines with Ca^{++} → **calcium bilirubinate stones**.
- The patient is treated by intake of bile acids → ↑ bile salts → dissolve cholesterol stone.
- The inflammatory (bile pigment) stone is treated by surgical removal.

Bile

- * **Volume:** 600 - 1000 ml/day
- * **pH:** in liver bile: alkaline - in gall bladder bile: acidic.
- * **Constituents:**

Liver bile	Gall bladder bile
• H_2O : 97.5 gm%.	• 92 gm %.
• Inorganic: Na^+ , HCO_3^- and Cl^- .	• Less concentrated ions

<ul style="list-style-type: none"> Organic: less <ul style="list-style-type: none"> - bile salts: 1.1 gm % -others: cholesterol, fat lecithin, F.A, bile pigments, <i>alkaline phosphatase enzyme</i> PH: 7.8 – 8.5. 	<ul style="list-style-type: none"> - 6 gm %. - More concentration. <ul style="list-style-type: none"> • 7.0 – 7.4.
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Regulation of bile secretion:

a. Choleretics: factors stimulate bile flow by increasing its formation by liver as:

- 1- Vagal stimulation to liver and gall bladder.
- 2- Bile salts (via enterohepatic circulation): the most potent.
- 3- Secretin hormone is hydrocholeretic, as it increases the bile flow via increasing bicarbonate and water secretion.
- 4- Vasodilator drugs which increase hepatic blood flow

b. Cholagogue: factors evacuate the bile from gall bladder and increase flow of bile as:

- 1- Vagal. 2- Mg⁺⁺ sulphate. 3- CCK – PZ. H.

Mechanism of bile secretion:

a. Between meals: The sphincter of Oddi is closed and the hepatic bile is stored in the bladder to be concentrated and acidified.

b. During food intake:

- Swallowing causes reflex vagal relaxation of sphincter and evacuation of bile. Vagal stimulation normally occurs on taking a meal through both *conditioned and unconditioned reflexes* during the cephalic phase of gastric secretion.
- The CCK enzyme from duodenum → evacuation of bile into the intestine. (so, after a fatty meal, the gallbladder empties completely in about 1 hour).

c. After meal: 90 % to 95 % of bile salts are actively reabsorbed from the terminal ileum back to the liver via the portal vein and re-excreted in the bile stimulating more bile secretion (*enterohepatic circulation*), the normal rate of bile salts secretion is 0.3 gm/day and recycles 6 – 8 times/day → total amount of 3.5 gm/day of bile salts.

Bile salts

Types:

- **Primary bile salts** are tauro – and glyco salts of cholic and chenodeoxycholic acids which are formed from cholesterol (Na^+ taurocholate & Na^+ glycocolate).
- **Secondary bile salts** are formed in the intestine by bacterial effect on the dry salts (Na^+ glyco-lithocholic & Na^+ tauro-lithocholic).

Functions of bile salts:

1- Digestion of fats:

- Reduce the surface tension and with phospholipid help in emulsification of fats into small particles with more surface area exposed for enzymatic actions.
- Activate lipase enzymes.

2-Absorption of fats and fat-soluble vitamins (*vitamins A, D, E and K*)

- Bile salts combine with fatty acids, cholesterol and fat-soluble vitamins to form micelles (water soluble compounds) which can be easily absorbed (Hydroscopic effect).

3-Choleretic action: stimulate bile secretion (*enterohepatic circulation*).

4- Solvent action: bile salts keep cholesterol and F.A. in solution preventing formation of gall bladder stones.

5-Prevent protein putrefaction by:

- Digestion and absorption of fats.
- Increase intestinal peristalsis
- Hence, they lead to protein digestion & prevent its putrefaction and colonic distension.

6-Antibacterial effect stimulate intestinal motility (laxative effect)

Functions of bile:

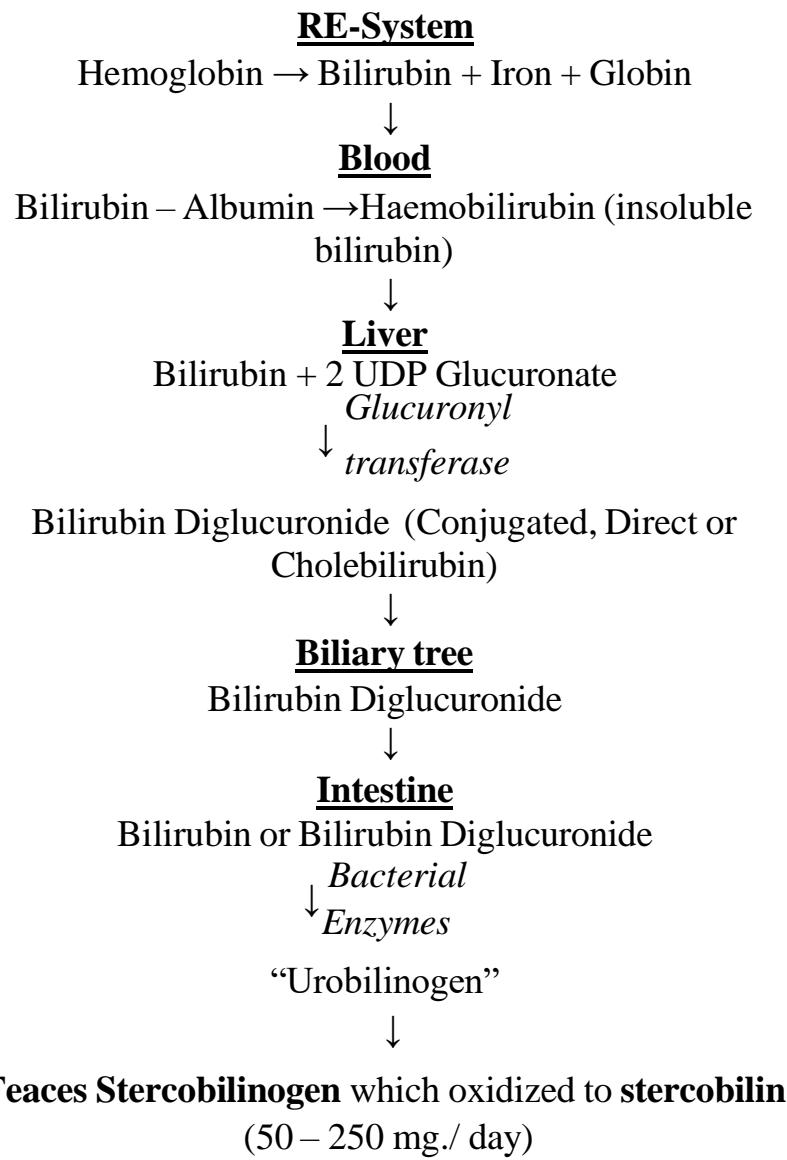
In addition to the functions of bile salts. bile performs the following functions:

- (1) Its HCO_3^- content shares in *neutralization of HCl* in the duodenum (with the pancreatic and intestinal juices).

- (2) Its mucin content (white bile) acts both as a *lubricant*, and as a *buffer* in the small intestine.
- (3) It is an *excretory route* for:
 - (a) Bile pigments (which have no functions)
 - (b) Certain heavy metals, toxins and bacteria
 - (c) The alkaline phosphatase enzyme
 - (d) Cholesterol and lecithin.

Bile pigments

Steps of bile pigments formation:



N.B: There is an enterohepatic circulation for both bile salts and bile pigments (mostly urobilinogen) In plasma: hemobilirubin , cholebilirubin , urobilinogen.

- In urine: conjugated bilirubin + urobilinogen
- In feces: conjugated bilirubin + stercobilinogen

Jaundice (Icterus)

Definition: It is a yellowish colouration of skin and mucous membrane caused by hyperbilirubinemia in which bilirubin level in the plasma is more than 2 mg% (normal level 0.2-0.8 mg%).

Types and causes :

	Hemolytic (Pre-hepatic) J.	Hepatic J. (Intrahepatic cholestasis) (toxic)	Obstructive (post-hepatic) extrahepatic cholestasis
Causes	↑RBCs hemolysis -hereditary spherocytosis -Thalasthemias -Drugs (sulpha) Erythroblastosis fetalis.	Diseased hepatic cells as in : - Hepatitis. - Liver cirrhosis. - Some drugs. - Pregnancy.	Obstruction of bile ducts as in: - Biliary stone. - Tumor in head of pancreas → pressure on bile duct → closed.
Pathogenesis	The rate of formation of bilirubin exceeds the rate of hepatic uptake → ↑ Hemo bilirubin in the bl. (not diffused to urine because it is carried on albumin)	The diseased liver cells can't uptake all hemobilirubin → ↑Hemobilinogen in the blood and with inflammation there is obstruction of some canaliculi, so it causes obstruction → back diffusion of cholebilirbin to bl.	- Retention of cholebilirubin and back diffusion to the blood → ↑cholebilirubin in the blood and ↑ its secretion in the urine (diffused easily in urine).
Blood	- Hemolytic anemia. - ↑ hemobilirubin.	- Hemo and chole bilirubin. - Biphasic	↑ cholebilirubin. - ↑alkaline phosphates, bile salts and cholesterol in plasma

	<ul style="list-style-type: none"> - Indirect (van den Bergh reaction. 		<ul style="list-style-type: none"> - Direct reaction
Urine	<ul style="list-style-type: none"> - Urobilinogen. - Normal at first then oxidized to urobilin → dark brown. 	<ul style="list-style-type: none"> - ↑ cholebilirubin. - Dark brown colour from start. 	<ul style="list-style-type: none"> ↑ cholebilirubin. - Dark brown.
Feces	<ul style="list-style-type: none"> - ↑ stercobilin. - deep brown. 	<ul style="list-style-type: none"> - ↓stercobilin. - Pale. 	<ul style="list-style-type: none"> - Absent stercobilin. - Very pale (clay)
Clinical picture	<ul style="list-style-type: none"> - Anemia - splenomegaly - gall stones - No itching 	<ul style="list-style-type: none"> - hepatic disease - No itching 	<ul style="list-style-type: none"> -, Retention of bile salts → 1. bradycardia (deposit in heart) 2. pruritis (itching) 3. steatorrhea. 4. ↓ of vit.k → bleeding tendency.

Neonatal or physiological jaundice:

- It occurs in newly born infants (2-7 days after birth).
- Due to rapid destruction of hemoglobin after birth and mild glucoronidyl transferase deficiency in premature liver → defect in conjugation → jaundice for one week then disappear.
 - These infants are exposed to blue light which is absorbed by bilirubin in the plasma of the skin vessels and changed into more water-soluble isomer and excreted in bile & urine.

Non – hemolytic jaundice (Congenital hyperbilirubinemias)

1) Gilbert's syndrome:

- Common familial disease 2-5% of population.
- A symptomatic increase in unconjugated bilirubin due to ↓ bilirubin uptake, ↓ glucuronidyl transferase, ↓ RBCs life span.

2) Crigler – Najjar syndrome:

- It is a sever type of congenital jaundice in neonates.

- It is of 2 types:

Type 1: absence of glucuronyl transferase enzyme.

Type 2: decrease of glucuronyl transferase enzyme.

3) Dubin – Johnson syndrome:

- Type of congenital hyperbilirubinaemia in which increase conjugated bilirubin due to defect in bilirubin excretion.

N.B: Salicylates and sulfonamides drugs must not be given to jaundiced children because these drugs displace the bilirubin from its binding sites with albumin → bilirubin penetrate the blood brain barrier → destruction of basal ganglia → Kernicterus.

Van den Bergh reaction:

- a. **Cholebilirubin** *reacts directly* with Erlich's reagent to give pink colour.
(Direct reaction) in obstructive J.
- b. **Haemobilirubin** *reacts* with diazo reagent only after separation from albumin by methyl alcohol (*indirect reaction*) as in hemolytic J.
- c. When serum contains both haem- and cholebilirubin, it gives a pink colour with diazo-reagent and the colour increased with addition of alcohol (*Biphasic reaction*) as in hepatocellular jaundice.

Gastrointestinal absorption

All parts of the GIT are capable of absorption e.g. alcohol and water are absorbed from the gastric mucosa and water and electrolytes are absorbed from the large intestinal mucosa. However, *the small intestine is the chief site of absorption because of the presence of the valvulae conniventes, villi and microvilli.* It is primarily a vital process as evidenced by:

- (1) The intestinal O₂ consumption markedly increases during absorption.
- (2) If the temperature of an intestinal loop is raised, the rate of absorption in this loop markedly increases, and vice versa.
- (3) Occlusion of the blood supply markedly decreases the rate of absorption.
- (4) If serum is placed in the intestine, it will be completely absorbed although it has the same osmolality as the plasma.
- (5) The selective absorption of carbohydrates (e.g. galactose is absorbed faster than glucose although both have the same molecular weight).

Factors that affect intestinal absorption

- (1) Vitality of the intestinal mucosa:** depends on adequate blood blow , O₂ supply and certain vitamins specially vitamin B.
- (2) State of digestion:** Proper digestion is essential for good absorption.
- (3) Bile salts and lymph flow:** These are essential for fat absorption.
- (4) Duration of contact of food to the intestinal mucosa:** If this is shortened (e.g. due to diarrhea), the rate of absorption will be reduced.
- (5) The extent of the absorptive surface:** Pathological or surgical conditions that reduce the intestinal surface by more than 50 % markedly decrease the rate of absorption.

(6) Intestinal mixing movements: These help absorption by (a) Exposing the intestinal contents to the absorbing surface (b) Improving blood and lymph flow (c) Increasing the intra-intestinal pressure.

(7) Movements of the villi: *lashing movement; side to side movement and pumping movement (shortening and elongation)*. produced by branches of the *muscularis mucosae*. They are stimulated mainly by mechanical and chemical irritation of the villi.

(8) Physico-chemical factors:

(a) Concentration gradient: Absorption of a substance by passive diffusion is favored when its concentration in the intestinal lumen exceeds its concentration in the blood.

(b) Intestinal osmolality: The presence of hyperosmotic solutions in the intestine reduces the rate of absorption and vice versa.

(c) Intra-intestinal pressure: The higher this pressure, the greater will be the rate of intestinal absorption and vice versa.

(d) Solubility of the intestinal contents: Increased solubility of a substance ²⁺ promotes its absorption e.g. acids help Ca absorption, and bile salts help fat absorption

N.B: the small intestine receives about 9000 ML of fluid daily (2000 ml ingested and 7000 ml in the various digestive juices), about 8800 ml are absorbed in the small and large intestines while 200 ml are excreted in the stool.

***Mechanism of absorption:**

- Active: with carrier, energy & against gradient.
- Simple: (passive) according to conc. & electrical gradient

(1) Absorption of water:

- By simple diffusion (osmosis) following absorption of electrolytes and nutrients.
- Only a small amount of water moves across the gastric mucosa.
- However, in the small and large intestines, it moves in both directions across the intestinal mucosa in response to osmotic gradients until the osmotic pressure of the intestinal contents equals that of the plasma.

The osmolality of the duodenal contents may be hypertonic or hypotonic (depending on the ingested meal) but by the time the meal enters the jejunum its osmolality becomes close to that of the plasma.

(2) Absorption of sodium:

- By active transport about 25-35 gm sodium/day is absorbed from small intestine. By three mechanisms:
 - a. Uniport: Active Na^+ pump to the blood.
 - b. Symport: cotransport of Na^+ with glucose or amino acid by common carrier.
 - c. Antiport: absorption of Na^+ in exchange with H^+ .
- Na^+ is actively transported to the interstitial space in exchange with K^+ (Antiport) so the concentration of Na^+ intracellular decreased and the sodium in the chyme is transported through the brush border into the cytoplasm.

- Because Na^+ and glucose use the same carrier, they facilitate the absorption of each other. This is the physiologic basis of treating acute loss of water and Na^+ in cases of severe diarrhea (e.g. in cholera) by oral administration of fluids that contain both NaCl and glucose (the symport carrier of Na^+ and glucose is not affected).

(3) Absorption of K^+ :

- Little K^+ absorption occurs actively in exchange for H^+ secretion (H^+/K^+ ATPase) and K^+ is mostly transported into the intestinal lumen.
- Some K^+ is secreted with mucus but most K^+ moves passively down its electrochemical gradient into the intestinal lumen specially in the colon. That is why loss of the ileal and colonic fluids in cases of chronic diarrhea may lead to severe hypokalemia.
- Aldosterone stimulates Na^+ absorption and K^+ secretion by Na^+/K^+ pump at the basolateral border of intestinal mucosal cells.

(4) Absorption of chloride:

- Cl^- is absorbed in the small and large intestines mostly by **passive diffusion** following Na^+ absorption down an electrical gradient.
- Cl^- also normally enters the enterocytes from the interstitial fluid (utilizing $\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransporters in their basolateral borders) and is then **secreted** into the intestinal lumen via channels that are activated by cyclic AMP.
- Cholera vibrio produces a toxin that activates adenylyl cyclase enzyme, leading to increased intracellular cyclic AMP, increases Cl^- secretion and inhibits the function of the Na^+ mucosal uniport carrier (so NaCl absorption is decreased).
- The accumulation of Na^+ and Cl^- in the intestinal lumen causes water retention by osmosis and leads to severe diarrhea (rapidly fatal if not treated by administration of large amounts of solutions containing NaCl , K^+ and glucose).

(5) Absorption of HCO_3^-

- Active absorption of HCO_3^-** in Duodenum and Jejunum. ;in an indirect way as follows: When Na^+ is absorbed, H^+ is secreted

into the lumen .These H⁺combine with HCO₃⁻ to form H₂CO₃, which then dissociates to form water &CO₂which is readily absorbed into the blood and subsequently expired through the lungs.

- **Secreting HCO₃⁻** in exchange for absorption of Cl⁻ in Ileum &Large Intestine

(6) Absorption of calcium: 1. Active at basolateral border.

2.Facilitated diffusion at luminal border. 3.Controlled by parathormone H & vit D3.

(7) Absorption of iron: Active at duodenum. Stimulated by erythropoietin.

(8) Carbohydrate absorption: at luminal border:

- Absorption of glucose is an active sodium depend on transport (common carrier for Na⁺ & glucose) if Na⁺ abs. Is inhibited by glycosides →↓ glucose abs.
- Galactose: the same as glucose.
- Fructose: by facilitated diffusion (passive).

(9) Absorption of proteins:

- L-Amino acid absorption: the same as glucose by 4 types of carriers for neutral, basic, acidic amino acids.
- Absorbed mainly in the jejunum.
- Small amount of proteins is absorbed intact by pinocytosis (endocytosis).

(10) Absorption of lipids:

- By aid of conjugated bile salts, lipids are emulsified and form micelles (small water-soluble particles formed of pancreatic lipase phospholipase, cholesterol esterase and fat-soluble vitamins) covered with a shell of bile salts. Then micelles enter the intestinal mucosa by simple diffusion.
- Inside the mucosal cell:
 - ✓ Short F.A pass directly to the portal blood.

- ✓ Long F.A are esterified to triglycerides.
- ✓ Some cholesterol esters are esterified.
- ✓ Triglycerides and cholesterol esters are coated by protein, cholesterol and phospholipids in the Golgi complex → chylomicrons → pass into lymphatic vessels by exocytosis.

(11) Absorption of vitamins:

- Water soluble vit.: are absorbed from jejunum by simple diffusion.
Vit B12 needs intrinsic factor for its absorption.
- Fat soluble vit.: absorbed by simple diffusion depend on fat digestion and absorption.

The malabsorption syndrome:

- If more than 50% of the intestine is removed by resection → signs of malnutrition as:
 - ↓ Abs. of A.A → body wasting & edema.
 - ↓ Abs. of fat →↓ abs. of fat soluble vit.
 - ↓ Abs. & steatorrhea bleeding tendency.
- Malabsorption may be caused by maldigestion as in:
 - Inadequate lipolysis (↓ pancreatic sec.)
 - Obstructive jaundice →↓ digestion and absorption of fats & vitamins.

GIT hormones

2 families (gastrin-CCK & secretin-glucagon)

Hormone	Stimuli for Secretion	Site of Secretion	Actions
Gastrin	Protein Distention Nervous <i>(Acid inhibits release)</i>	G cells of the antrum, duodenum, and jejunum	Stimulates Gastric acid secretion. & Mucosal growth (trophic effect) ↑ insulin secretion. Sphincters: - Lower oesophageal sphincter → Contraction. - Ileocecal sphincter → Relaxation. ↑ growth of intestinal mucosa & Stimulation of small and large intestinal motility
Cholecystokinin	Protein Fat Acid	I cells of the duodenum, jejunum, and ileum	Stimulates: Pancreatic enzyme secretion Gallbladder contraction Growth of exocrine pancreas Inhibits: Gastric emptying & appetite
Secretin	Acid Fat	S cells of the duodenum, jejunum, and ileum	Stimulates: Pepsin secretion Pancreatic bicarbonate secretion Biliary bicarbonate secretion Growth of exocrine pancreas inhibits: Gastrin release and gastric acid secretion
Glucose-dependent insulinotropic peptide (gastric inhibitory peptide) GIP	Protein Fat Carbohydrate	K cells of the duodenum and jejunum	Stimulates Insulin release (incretin) Inhibits: Gastric acid secretion & gastric emptying.
Motilin	Fat Acid Nervous	M cells of the duodenum and jejunum	Stimulates Gastric motility Intestinal motility
Vaso active intestinal peptide VIP		Nerves of GIT, blood, brain and autonomic nerves	It stimulates intestinal secretion (water and electrolytes). Relaxation of intestinal motility and (sphincters) It induces Vasodilatation. It inhibits gastric acid secretion. It Relaxes Lower esophageal sphincter
Pancreatic	carbohydrates	pancreas	inhibits pancreatic secretion of

polypeptide	proteins, lipids.		HCO ₃ ⁻ and enzymes.
Enteroglucagon	decrease in blood glucose concentration.	intestinal cells	Increase liver glycogenolysis and gluconeogenesis
Glucagon-like peptide-1 (GLP- 1)		L cells of the small intestine	stimulates insulin secretion (incretin) inhibits glucagon secretion, increases the sensitivity of pancreatic β cells to glucose, decreases gastric emptying, inhibits appetite
Guanylin		cells of the intestinal mucosa from the pylorus to the rectum.	paracrine regulator increases production of c-GMP Which stimulate epithelial cells to <i>secret Cl⁻ & water</i> <i>with inhibition of Na⁺ absorption</i> →↑ salt & water loss in faeces.
Somatostatin	decreased luminal pH.	D cells of the gastrointestinal mucosa, hypothalamus, delta cells of endocrine pancreas	<i>Paracrine function:</i> inhibits secretion of other gastrointestinal hormones, inhibits gastric H ⁺ secretion.
Ghrelin.	Just before ingestion of a meal	gastric cells	It acts oppositely to leptin and insulin to stimulate orexigenic neurons and inhibit anorexigenic neurons, thus increasing appetite and food intake. Periods of starvation and weight loss strongly stimulate ghrelin secretion.
Peptide YY (PYY).	following a meal.	intestinal L cells	decrease appetite, both through a direct effect on the hypothalamus and by inhibiting ghrelin secretion. inhibits pancreatic secretion,
Glicentin		L cells of the small intestine	Has a glucagon activity
Substance P		endocrine and nerve cells in the GIT.	Increases motility of small intestine
Neurotensin	fatty acids	neurons and special cells in the ileal mucosa	It inhibits GIT motility and increases ileal blood flow

Energy Balance And Metabolic Rate

Metabolism: It includes all chemical reactions and energy transformations that occur in the body.

These reactions are 2 types:

Anabolism: the chemical reactions involved in the synthesis of large molecules from smaller ones with energy consumption e.g. protein from amino acids.

Catabolism: the chemical reactions involved in oxidation of various organic food stuffs to release their chemical energy.

- 70-75% of this energy appears immediately as heat.
- 20-25% of this energy is stored as high energy phosphate bonds e.g. ATP, that can be transformed into work:
 - Mechanical work e.g. contraction of muscle.
 - Electrical work for maintenance of resting membrane potential
 - Chemical work for chemical reactions
 - Osmotic work for active transport of different substances.

Energy Balance

Definition:

Energy input **equal** energy output----- total body energy remain constant----- body weight remain constant.

Energy intake: energy in the nutrients (diet)

Energy output: Combination of work performed, and energy returned to the environment as heat:

Energy output = work + heat

In the human body, at least half the energy released in chemical reactions is lost to the environment as unregulated “waste” heat.

Total body energy = energy stored + energy intake - energy output

The work takes one of three forms.

1-Transport work:

Energy used in transport of molecules from one side of a membrane to the other.

2. Mechanical work:

A- External work: such as movement created by skeletal muscle contraction.

B- Internal work: such as the movement of cytoplasmic vesicles and the pumping of the heart

C- Chemical work : subdivided into synthesis and storage

Synthesis: as growth & maintenance

Storage:

A-short-term energy storage: in high-energy phosphate compounds such as ATP

B-long-term energy storage: in the chemical bonds of glycogen and fat

N.B:

Most of this energy-consuming work in the body is not under conscious control. The only way people can voluntarily increase energy output is through body movement, such as walking and exercise.

The calorie:

- It is the unit used to measure the quantity of energy.
- It is the amount of heat needed to raise the temperature of 1 gm of water 1°C from 15°C to 16°C
- Kilo calorie (Kcal, C) = 1000 calories

Heat Value of Food:

1- Physiological heat value:

- It is the amount of heat liberated from the oxidation of foodstuffs inside the body.
- Each gram of carbohydrates supplies 4.1 kcal of fat 9.3 kcal and of protein 4.1 kcal

2- Physical heat value:

- It is the amount of heat liberated from the oxidation of foodstuffs outside the body.
- Each gram of carbohydrate gives 4.1 kcal of fat 9.3 kcal and of protein 5.3 kcal.
- The physiological heat value of protein is less than its physical heat value because inside the body the nitrogen content of protein (16 % of it) is transformed into urea, uric acid and creatinine which are excreted in urine taking with them part of the chemical energy of protein.
- This indicates that protein is not completely oxidized in the body, as if nitrogen is completely oxidized in the body, it will produce large amount of nitric acid decreasing the pH to a fatal level.

Respiratory quotient “R.Q.”

Respiratory exchange ratio

- It is the ratio of the volume of CO₂ produced to the volume of oxygen consumed during the same period.

$$RQ = \frac{\text{CO}_2 \text{ produced}}{\text{O}_2 \text{ consumed}} \text{ per unit of time}$$

- **Significance of RQ:**

1-Determination of the nature of food substance oxidized during the time of estimation. RQ of carbohydrate is 1, because the O₂ and H are present in the same proportion as in H₂O, so the consumed O₂ in this

case is used only for oxidation of carbon to CO_2 . Consequently, the volumes of the consumed O_2 and the produced CO_2 will be equal:



RQ of fat is 0.7 and that of protein is 0.8, (O_2 is needed not only for oxidation of CO_2 , but also for oxidation of H to water). Normally, the RQ of mixed diet is 0.85.

2- It indicates the transformation of one food substance into another in the body.

- When carbohydrates (substances rich in O_2) are transformed into fats (substances poor in O_2), RQ rises above 1. This is because the released O_2 is utilized in the oxidation processes leading to liberation of CO_2 without increasing the O_2 consumption.

-On the other hand, when fats are transformed to carbohydrates, RQ is decreased as extra amount of O_2 is used.

3- Determination of O_2 heat value (the energy equivalent of O_2) to calculate metabolic rate.

- O_2 heat value is the amount of heat in Calories resulting from the oxidation of food substance using one liter of O_2 .

-It equals 5 kcal for carbohydrate, 4.7 kcal for fat, 4.8 kcal for mixed diet.

-If RQ is known, O_2 heat value can be known from a special table which shows the energy equivalent of O_2 at various RQ , and M.R can be calculated as follows:

$$\text{MR} = \text{O}_2 \text{ used/hour} \times \text{O}_2 \text{ heat value at RQ provided.}$$

• Factors affecting RQ:

1- Factors increase RQ:

- Transformation of carbohydrate into fat ($\downarrow \text{O}_2$ consumption).

-Hyperventilation ($\uparrow \text{CO}_2$ produced) e.g. voluntary hyperventilation, muscular exercise, fever and metabolic acidosis.

2- Factors decrease RQ:

1-↑O₂ consumption.

- Transformation of fat into carbohydrate
- Diabetes mellitus and starvation because fat is used as a source of energy.
- During recovery period following exercise, because O₂ consumption is increased to oxidize the formed lactic acid.

2-Hypoventilation:(↓CO₂ produced) e.g. voluntary hypo-ventilation and metabolic alkalosis.

• The Excess RQ

It is the RQ of the excess metabolism due to muscular exercise.

$$\text{Excess RQ} = \frac{A-a}{B-b}$$

A= CO₂ produced during the period of exercise and recovery.

a= CO₂ produced during a similar period of rest.

B= O₂ produced during the period of exercise and recovery.

b= O₂ produced during a similar period of rest.

Significance of excess RQ:

It indicates the duration and the fuel utilized during a certain muscular exercise:

RQ is 1 in short exercise.

RQ is 1 then drops gradually in long exercise.

RQ is 0.7 from the start in diabetic person and in starvation.

Basal Metabolic Rate (BMR)

Definition:

It is the rate of energy expenditure in hour divided by body surface area under following basal conditions:

- a) Complete physical and mental rest but not sleeping.
- b) 12 hours after last meal to avoid Specific Dynamic Action.
- c) Comfortable external temperature: 25°C for to avoid sweating (heat loss) and shivering (heat gain).

Method of determination of BMR: by Indirect calorimetry

BMR = O₂ used (Liter/hour) x O₂ heat value divided by body surface area

- The surface area can be determined from **Du Bois** chart, which correlates body height and weight with its surface area.

Normal value of BMR:

- BMR = 40 Kcal / m²/ hour ± 15%.
- BMR represents unavoidable cost of life e.g. metabolic activity of heart, liver, respiratory muscles, movement of intestine and muscle tone.

Clinical expression of BMR:

- BMR is clinically expressed as a percentage of increase or decrease from normal standard values.

Significance of BMR:

- It is a prognostic test not diagnostic.
- To follow the progress of already diagnosed disease.

Factors affecting BMR:

I) physiological factors:

1) Age:

- In newborn (BMR = 25 kcal/hr/m²)

- At age of 2-5 years (BMR = 60 kcal/hr/m² due to rapid growth).
- At age of 20 years (BMR = 40 kcal/hr/m²)
- Then, it decreases gradually at a rate of 1 kcal / 10 years.

2) Sex:

- ↓ BMR in female by about 7% than male of the same age due to:
 - a) Endocrine differences.
 - b) More fat stored in female.

3) Race:

- Pure races e.g., Chinese have lower BMR than mixed race e.g. Egyptians.
- Black races have lower BMR than white races.

4) Climate:

- BMR is higher 10% in cold temperature zone than in hot zone.

5) Dietetic Habit:

- Prolonged ingestion of protein ↑↑ BMR by 10% (due to 2ry SDA).

6) Physical Habit:

- ↑ BMR in athletes due to greater muscle bulk and less fat.

7) Emotion & Anxiety:

↑ BMR due to ↑ muscle tone & ↑ level of stress hormones e.g. adrenaline & Cortisol.

8) Pregnancy:

↑ BMR Due to Additional metabolism of fetus & ↑ level of some hormones e.g. progesterone & thyroxin.

II) Chemical factors:

- 1) Hormones: Thyroxin, TSH, Cortisol, ACTH, Growth hormone, Catecholamines and male sex hormones → ↑BMR

2) Drugs: Caffeine, amphetamine, and alcohol ↑↑BMR.

Anti-thyroid drugs ↓ ↓BMR.

III) Pathological conditions:

Factors that ↑↑ BMR

- Hyperthyroidism (BMR↑↑ by 100%).
- Hyperpituitarism (↑↑ GH, TSH, ACTH).
- Hypercortism (Cushing).
- Hypoadrenalinism (catecholamines).
- Hyperpyrexia (fever): ↑↑BMR by 10% for each 1 °C rise. Diabetes insipidus to maintain body temperature.
- Heart failure due to ↑↑ activity of Resp. muscles.
- Blood diseases (polycythemia & anemia) due to ↑↑ Cardiac work.
- Diseases in which healing & replacement of tissues occur.

Factors that ↓ ↓ BMR

- Hypothyroidism
- Hypopituitarism
- Hypocortism (Addison)
- Hypoadrenalinism.
- Hypothermia.
- Starvation due to:
 1. ↓ ↓ Sympathetic activity.
 2. ↓ ↓ Energy production.
 3. ↓ ↓ Cortisol, NA, A &T4.

Specific Dynamic Action (SDA)

Definition:

- It is the power of food that stimulates MR above BMR.
- It starts 1 hour after food intake, reaches a maximum in 4 hours, and declines to its original level in 12 hours.

Fate of SDA: It is a waste heat. However, it is useful in exposure to cold to maintain body temperature.

Causes: Due to metabolic processes in liver as SDA is zero in hepatectomized animals. It is not due to digestion & absorption of ingested food as injection of amino acids produce the same effect as oral intake of amino acids.

Factors affecting SDA:

1) External temperature:

- SDA is absent at 3°C & SDA is maximal at 33°C.

2) Amount of food:

- SDA is directly proportional to amount of food.

3) Types of food:

- 6% in case of carbohydrates (due to extra energy needed to form glycogen).
- 4% in case of fat (due to stimulation of metabolism by fatty acid).
- 30% in case of protein (due to several metabolic processes as deamination, urea formation & transformation to glucose or ketone bodies).
- SDA of protein is not related to biological value of protein.
- If 100 gm protein gives 410 kcal, 30% of this caloric value is used in assimilation of protein in body & lost as a waste heat. So, protein is preferred in cold climates & weight reduction.

Secondary SDA: Prolonged ingestion of protein increases BMR by 10%.

Control of food intake

Food intake is controlled by:

A. Organic sensation

- Hunger: need for food
- Appetite: desire for a specific type of food
- Satiety: (enough) sense of fulfilment in quest of food
- Hypothalamic centers regulating food intake (**Appestat center**)

B. Appestat center:

Feeding center

- Site: lateral hypothalamic nuclei
- Continuously (tonically) active
But inhibited by activity of satiety center.
- Its stimulation: eating behavior (food intake)
- Its destruction: anorexia

Satiety center

- Site: ventromedial hypothalamic nuclei
- its stimulation decreases food intake by --- feeding center
- Its destruction overeating (hyperphagia)

Factors regulating food intake:

1-Short term regulation:

A- Afferent impulses from GIT:

Distension of stomach& duodenum → vagus → Decrease food intake.

B-Afferent impulses from buccal & esophageal receptors: Certain amounts of food pass through these receptors (chewing and swallowing) → send signals → stimulate satiety center.

C- Humoral & hormonal factors:

Presence of food in stomach & duodenum release many hormones CCK& GLP1 → inhibit feeding center → ↓ food intake.

2-Long term regulation:

Aim to maintain nutrient store & blood level of nutrient constant.

1- *Glucostatic hypothesis*:

↓blood glucose level → stimulate feeding center

↑blood glucose level → stimulate satiety center

2- *lipostatic hypothesis*

↑fat stores → ↓ food intake

Leptin: discovered in 1994 (leptos, thin):

Protein synthesized in adipocytes under control of ob gene ----- provide evidence for a lipostatic theory.

Leptin acts as a negative feedback signal between adipose tissue brain

Neuropeptide y (NPY): brain neurotransmitter-----stimulate food intake--

-Leptin inhibits NPY release --- decrease food intake

N.B: majority of obese human have elevated leptin----leptin resistance--- abnormal tissue response rather than too little hormone.

Peptides that increased food intake

Peptide hormone	Source of secretion
Ghrelin	Stomach
NPY and Agouti-related protein (AgRP)	Hypothalamus
Orexins (hypocretins)	Hypothalamus

Peptides that decreased food intake

Peptide	Site of secretion
CCK	Small intestine, neurons
Glucagon-like peptide-1 (GLP-1)	Small intestine

PYY	Small intestine
Leptin	Adipose tissue
Corticotropin-releasing hormone (CRH)	Hypothalamus
a-Melanocyte-stimulating hormone (a-MSH)	Hypothalamus
CART (cocaine-and- amphetamine regulated transcript)	Hypothalamus
POMC (pro-opiomelanocortin)	Hypothalamus

3- Other Factors:

1- voluntary control & psychological factors: can ↑ food intake or ↓ food intake

2- Cold: can increase food intake

OBESITY

Obesity is the deposition of excess stored fat in the body more than 20% of body weight in male, more than 25% of body weight in female.

- **Causes:**

Obesity caused by increase food intake over energy expenditure i.e. positive energy balance.

I- Hyperphagia: the direct cause of obesity is overeating which may be:

a- **Absolute hyperphagia:** increase food intake.

b- **Relative hyperphagia:** decrease energy output with normal amount of food intake as each 9.3 kcal excess to body need is deposited in the form of 1 gm fat.

Hyperphagia may be caused by:

- 1- Psychogenic obesity: resulted from false habit e.g. parents force the child to overeat to be healthy. Overeating in some persons is a mean of relieve from tension.
- 2- Hypothalamic abnormalities: lesion in satiety center or some tumor.

II- Other causes of obesity:

Genetic factors has a role in obesity and this role may be due to abnormal increase in the set point, abnormal hereditary psychic factor or ineffective fat mobilization from adipose tissue with continuous synthesis and storage of fat due to congenital deficiency of lipoprotein lipase enzyme.

Types of obesity:**1- Hyperplastic hypertrophic obesity:**

- There is increase in number of fat cells and increase in fat content inside the fat cells.
- It is due to hyperplasia and hypertrophy of fat cells.
- It occurs early in the first few years of life.
- It is a sever type of obesity and difficult to treat.

2-Hypertrophic obesity:

- There is increase in the fat content inside the fat cells without increase in their number.
- It is due to hypertrophy of the existing fat cells.
- It occurs in adult.
- It is not severe, and it is easy to treat.

Complication of obesity:

1. The increase in body weight may cause flat foot and osteoarthritis of lumbar vertebrae , hip and knee joint.
2. Excessive fat leads to deposition of cholesterol in arterial wall which predispose to atherosclerosis, hypertension and coronary heart disease.
3. Obesity predisposes to gall bladder diseases.
4. Obesity predisposes to diabetes mellitus as it inhibits the response of beta cells of the islets of Langerhans to hyperglycemia, inhibits the response of insulin receptors to insulin, moreover, hyperphagia exhausts the beta cells of islets of Langerhans.
5. Obese people are less resistance to surgical operation.
6. Mortality rate is 10% higher in obese persons than in normal persons of the same age group.

Management of obesity:

1. Decrease energy input by decreasing food intake and eat special type of food which contains large quantities of bulk made up of cellulose, green vegetables, salads, and fruits together with low content of carbohydrates and fat.
2. Increase energy output by muscular exercise.
3. Drugs in early treatment only e.g. Amphetamine decrease the appetite and increase the metabolic rate, however amphetamine has excitatory effect on CNS e.g. insomnia and irritability.
4. Acupuncture may help to inhibit feeding center.
5. Massage and surgical interference.
6. Psychotherapy.

Starvation

Physiologic aspect of starvation (negative energy balance)

- Severe deficiency in caloric energy intake either partial or complete for a long time but water intake is maintained.

Causes:

- Absence of food. Coma.
- Surgical operation. - Anorexia nervosa: Psycho-pathological condition in which the person losses all desire for food intake, nauseated by even thinking of food and vomiting on seeing food.
- Lesion in feeding center in hypothalamus.
- The body depends on its own stored food during starvation, and the duration from start of starvation till death is variable, may reach 60 days depending on body store.
- Prolonged starvation (>30 days) eventually results in death from myocardial infarction, pneumonia, or organ failure.

Effects of starvation:

I- General effects:

1. Hunger pain starts 12-24 hours after the last meal, reaches maximum after 3-4 days and gradually disappears after that.
2. Mental depression.
3. Reduced glandular activity.
4. Decreased BMR.
5. Decreased cardiovascular system activity e.g. bradycardia and hypotension.
6. Reduced respiratory function e.g. decreased vital capacity.
7. General weakness.
8. Loss of body weight and negative nitrogen balance.
9. Reduced power of regeneration.
10. Decreased resistance to infection.

II- Metabolic effect:

General metabolism:

1. B. M. R is decreased due to decreased hormonal secretion.
2. Body temperature is decreased.
3. RQ is decreased.
4. Mechanical efficiency is decreased.

III. Blood changes:

1. **The blood volume**, RBCs count and H.V. are normal at first, but decrease later.
2. The plasma **proteins** are decreased leading to edema.
3. Blood **glucose** level is kept at fasting state (70 - 110 mg/dl) by gluconeogenesis.
4. **Amino acids** are kept at fasting state 5-7 mg/dl as it is derived from tissue protein.
5. **Fat** content is increased.
6. **Ketonemia**.
7. **Alkali reserve** is decreased as it used for neutralization of ketone bodies.
8. **pH** remains constant as long as respiratory system and kidney function are normal. Level of blood **minerals** are normal as long as the kidney and endocrine system are normal.

IV. Urine changes:

1. Urine **volume** and specific gravity are variable according to water intake.
2. **N₂** excretion depends on stage of protein catabolism.
3. Increase **creatin** due to muscle catabolism (creatinuria).
4. **Urea** is decreased to half it's normal value.
5. **Ketonuria**
6. **pH** of urine is decreased due to presence of keto acids.
7. **Minerals** in urine:

- ✓ Na^+ and Cl^- excretion is decreased till they nearly disappear.
- ✓ K^+ , Mg^{++} and SO_4 excretion in urine are increased, they derived from tissue autolysis.
- ✓ Ca^{++} and ph^- are continuously lost in urine, they are derived from bones.

Starvation & adaptive mechanisms

Simple (non-stress) starvation:

-Short term starvation (< 72 hours) -Prolonged starvation (> 72 hours)

Stress starvation: Starvation plus stress condition.

- Development of adaptive mechanisms to food shortage was necessary for survival.
- Adaptive changes allow healthy subjects of normal initial body composition to survive more than two months of total starvation.

Simple (non-stress) starvation	
<ul style="list-style-type: none"> • Short starvation (< 72 hours) ➤ Diminished insulin and increased glucagon and catecholamine ➤ Increased glycogenolysis and lipolysis. ➤ Hydrolysis of triglycerides in adipose tissue releases fatty acids (FFAs) and glycerol into the circulation. ➤ Increased gluconeogenesis from AA after depletion of glycogen. ➤ Metabolic rate increases initially but begins to decrease after 2 days. 	<ul style="list-style-type: none"> • Prolonged starvation (> 72 hours) ➤ Further decrease in insulin ➤ glycogen stores depletion. ➤ Increased gluconeogenesis <ul style="list-style-type: none"> ➤ increased b-oxidation of fatty acids & ketogenesis in liver ➤ Adaptation of the brain to using ketones as fuel & decline in resting metabolic rate by 10-15% ➤ Leads to reduction in protein catabolism. ➤ Reduction of energy expenditure related to physical activity.

Stress starvation

Stress conditions like:

- Burns
- Necrosis (acute pancreatitis, Ischemic necrosis)
- Severe Infection and Sepsis
- Penetrating and blunt injury
- Tumors

- Radiation
- Exposure to Allergens
- Chronic Inflammatory diseases
- Environmental pollutants
 - normal adaptive responses of simple starvation which conserve body protein are over-ridden by the cytokines (TNF, IL1 and IL6) and hormonal effects

Adaptation to stress starvation

- ❖ Metabolic rate rises rather than falls.
- ❖ ketosis is minimal.
- ❖ protein catabolism accelerates to meet the demands for tissue repair and of gluconeogenesis.
- ❖ hyperglycaemia and glucose intolerance.
- ❖ Salt and water retention is exacerbated.
- ❖ Hypoalbuminemia and edema

Refeeding syndrome

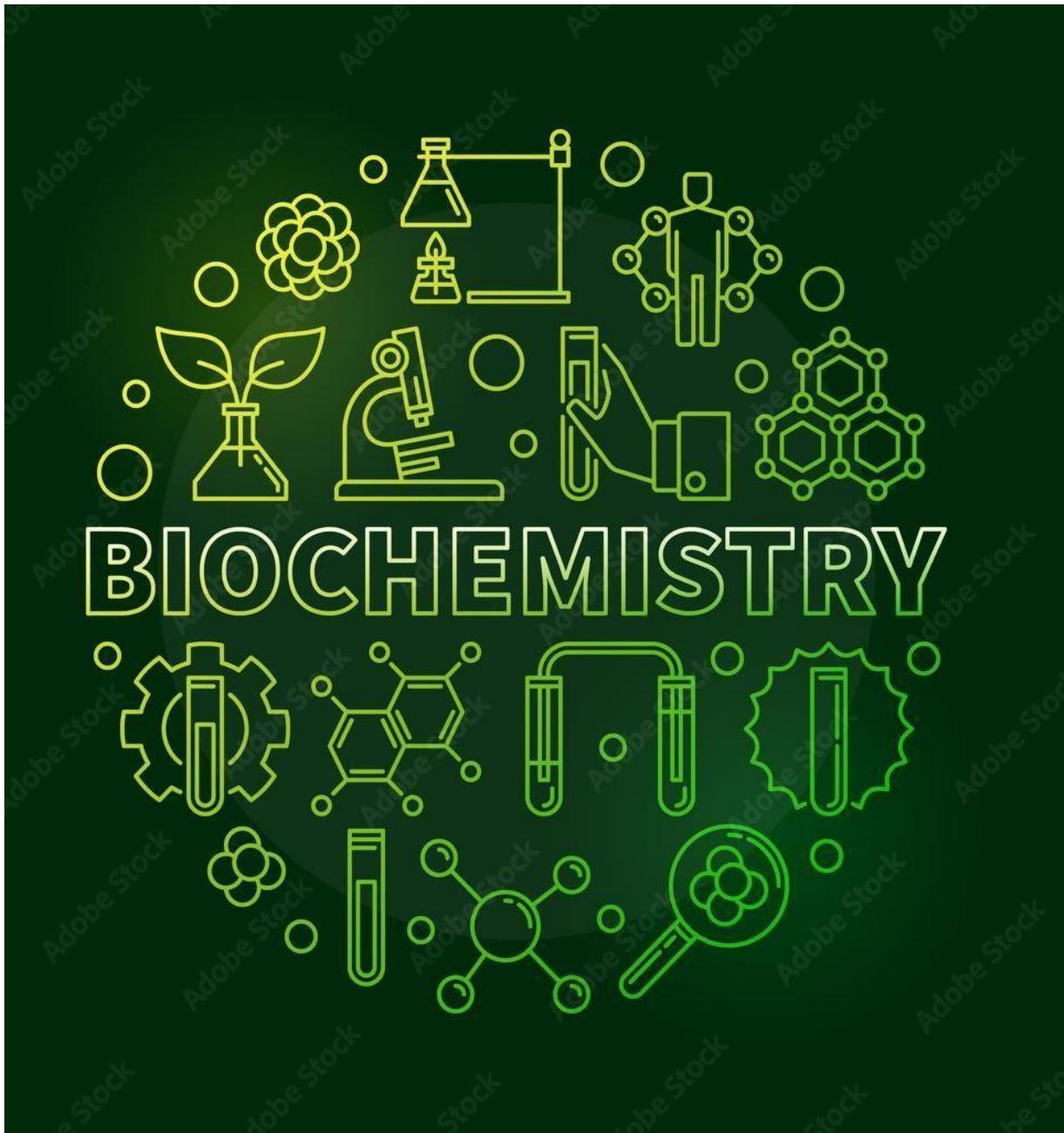
- Fatal or serious disturbances in electrolytes and fluids occurs when severely malnourished or starved patients reintroducing nutrients (oral, enteral or parenteral).
- occurs within the first 2 to 5 days after the start of the nutrition.

Metabolism during refeeding

- Rapid shift from fat to carbohydrate metabolism occurs.
- A glucose load evokes insulin release.
- Insulin stimulates glycogen, fat and protein synthesis.
- This process requires minerals such as phosphate and magnesium and cofactors such as thiamine.
- Insulin stimulates the absorption of potassium into cells through the sodium-potassium ATPase symporter, which also transports glucose.

- Magnesium and phosphate are also taken up into the cells. Water follows by osmosis. These processes result in a decrease of the serum levels of phosphate, potassium, and magnesium.

Biochemistry of Digestion and Absorption



Digestion and Absorption of carbohydrates

Digestion of carbohydrates:

It means hydrolysis of glycosidic linkage and conversion of carbohydrates into monosaccharides.

Steps of digestion include:

1. In the mouth:

Carbohydrates are digested by **salivary amylase**:

- Produced by: Salivary glands.
- Optimum pH: 6.7
- Activated by: Chloride ions.
- Acts on: α 1-4 glycosidic bonds in cooked starch because cooking breaks the amylopectin sheath

2. In the stomach:

- The action of salivary amylase on starch is stopped in the stomach after few minutes due to high acidity of stomach which inactivates the enzyme.

3. In the small intestine:

A. Digestion of carbohydrates by pancreatic amylase:

- Produced by: Pancreas.
- Optimum pH: 7.1
- Activated by: Chloride ions.
- Acts on: α 1-4 glycosidic bonds in cooked and uncooked starch. converting them into maltose and isomaltose.

B. Disaccharidases:

- Produced by the intestinal mucosal cells and remain associated with the brush border.

They include:

- ◆ **Lactase:** Hydrolyses lactose into glucose and galactose.
- ◆ **Maltase:** Hydrolyses maltose into 2 glucose molecules.
- ◆ **Sucrase:** Hydrolyses sucrose into glucose and fructose.

Digestion of cellulose:

- ◆ Cellulose contains β 1-4 bonds between glucose molecules which cannot be digested in humans because of the lack of β 1-4 glucosidase.
- ◆ Cellulose passes as such in stool helping water retention during the passage of food along the intestine → producing larger and softer faeces and **preventing constipation**.

Absorption of carbohydrates

The end products of carbohydrate digestion are monosaccharides (glucose, galactose and fructose).

Site of absorption: Mainly from jejunum.

Rate of absorption: 1 gm/kg body weight /hour. This prevents the occurrence of hyperglycemia after meal.

Route of absorption: Portal circulation.

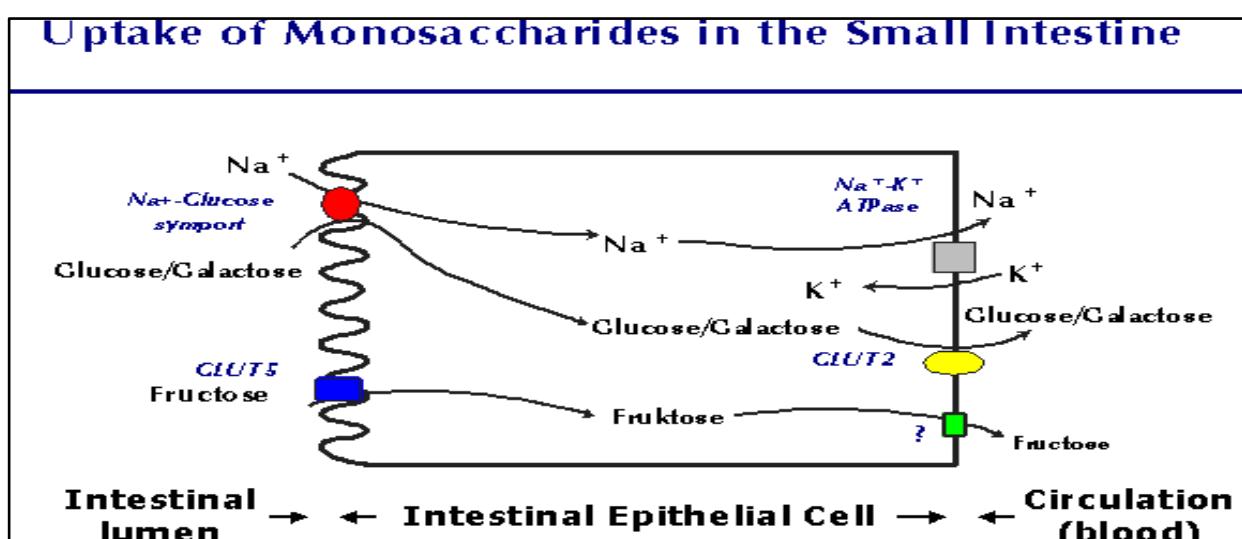
Mechanisms of absorption:

- 1.Active transport.
- 2.Passive transport by facilitated diffusion.

1. Active transport:

Mechanism:

- Sodium-dependent glucose transporter (SGLT-1) is a mobile carrier protein in the cell membrane of intestinal cells.
- It transports glucose inside the cell using energy derived from $\text{Na}^+ - \text{K}^+$ pump using ATP as a source of energy.
- It has two separate sites for sodium and glucose which are transported from intestinal lumen across the membrane to the cytoplasm then the carrier returns for further transport "cargo".
- Sodium is transported with concentration gradient, allowing glucose transport against concentration gradient.
- At the basal border**, all sugars are transported by facilitative transport (GLUT- 2).



2. Passive transport by facilitated diffusion:

- Sugars pass with concentration gradient needing no ATP.
- Fructose and pentoses are slowly absorbed by this mechanism through sodium independent facilitative transporter (GLUT-5).

Inhibitors of monosaccharides absorption:

Ouabain (cardiac glycoside): Inhibits ATPase.

Phlorhizin: Inhibits the binding of glucose in the carrier protein.

Characteristics of Glucose Transporters

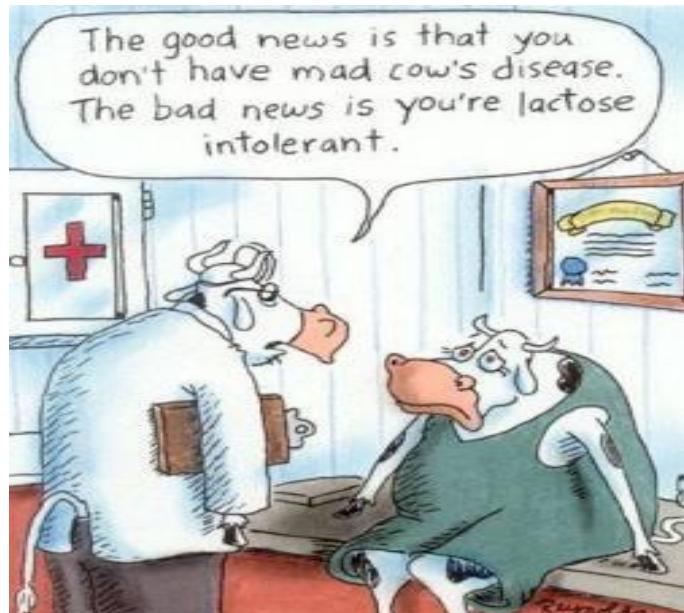
Transporter	Site	Function
SGLT-1	❖ Small intestine. ❖ Renal tubules.	❖ Active transport of glucose. ❖ It is responsible for 10% of glucose reabsorption in kidney.
SGLT -2	❖ Proximal convoluted tubules.	❖ It is responsible for 90% of glucose reabsorption in kidney.
GLUT-1	❖ Red blood cell, Brain, Muscle, Adipose tissue.	❖ Glucose uptake.
GLUT-2	❖ Liver, Pancreatic- β cells.	❖ High Km. ❖ Rapid uptake, and release.
GLUT-3	❖ Brain, Nerve tissue, Placenta.	❖ Glucose uptake.
GLUT-4	❖ Heart, Adipose tissue, Muscle	❖ Insulin-sensitive. ❖ Relatively low Km.
GLUT-5	❖ Small intestine.	❖ Passive uptake for fructose transport.

Defects of carbohydrate digestion and absorption:

Lactase deficiency (lactose intolerance):

Deficiency of lactase enzyme which digests lactose into glucose and galactose.

- **Causes:** Congenital or acquired.
- **Effect:** Accumulation of lactose in the intestine and its fermentation by intestinal bacteria with production of acids and gases with increase in the osmotic pressure.
- **Manifestations:** Distention, abdominal cramps, osmotic diarrhea and dehydration.
- **Treatment:**
 - **For infant:** Prevent the child from taking his mother's milk, and giving him lactose free milk formula.
 - **For adult:** Lactose free diet, yoghurt, green vegetables to ensure adequate calcium intake.



Fate of absorbed sugars:

Monosaccharides (glucose, galactose and fructose) are passed from intestine via portal circulation to the liver where galactose and fructose are converted into glucose.

Glucose passes from the liver to systemic circulation where it undergoes:

1.Uptake by tissues:

- ❖ All tissues take glucose by active transport system using glucose transporters under insulin control except liver, RBCs, intestine and kidney.

2.Glucose utilization by tissues:

A.Oxidation: Through:

- 1.Major pathways (glycolysis and Kreb's cycle): Mainly for production of energy
- 2.Pentose phosphate pathway: For production of pentoses and NADPH+H.

B.Conversion to other significant biological intermediates:

-Ribose → RNA and DNA..

-Glucosamine and galactosamine → Mucopolysaccharides.

-Glucuronic acid → Mucopolysaccharides.

- Fructose → Sugar of semen.

-Galactose → For lactose biosynthesis

3.Storage:

Excess glucose is converted into:

- Glycogen in liver and muscles (Glycogenesis).
- Lipids in adipose tissue by lipogenesis.

4.Excretion in urine:

When blood glucose level exceeds glucose renal threshold (180 mg/dl).

Glycolysis

(Anaerobic oxidation of glucose)

Definition:

Glycolysis is the process by which **glucose** is broken down to **pyruvate** in order to obtain **energy** stored in the glucose molecule for use by the body.

Site:

Cytoplasm of each cell, if a cell has mitochondria and oxygen, glycolysis is aerobic. If either mitochondria or oxygen is lacking (mature RBCs, cornea and lens), glycolysis may occur anaerobically.

End product: in presence of oxygen ,pyruvic acid will be the end product,while lactic acid appears as end product under anaerobic condition.

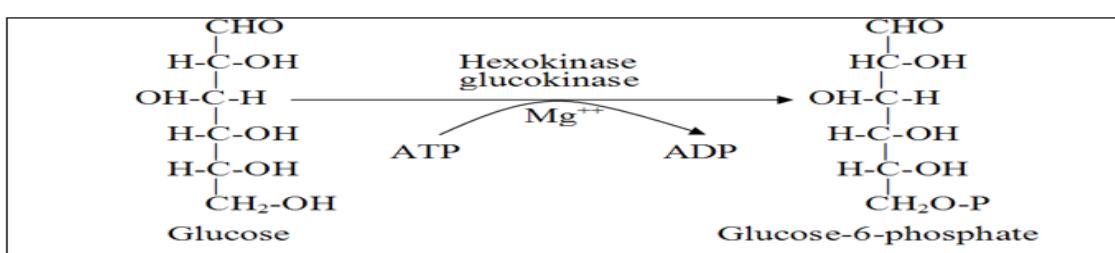
Steps:

The steps can be summarized as follow:

I. First phase (energy consuming) (Energy investment):

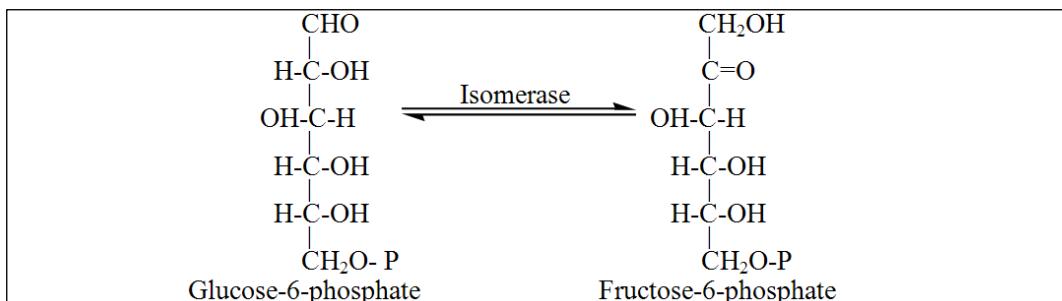
Step 1:

- Glucose is converted to glucose-6-phosphate by hexokinase mainly or glucokinase enzyme.
- Glucose is phosphorylated to trap the glucose inside the cell.
- This reaction is irreversible. One ATP is consumed.

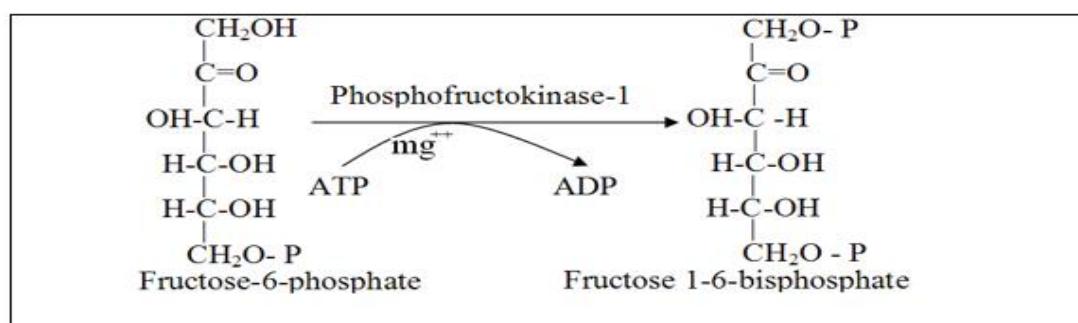


Step 2:

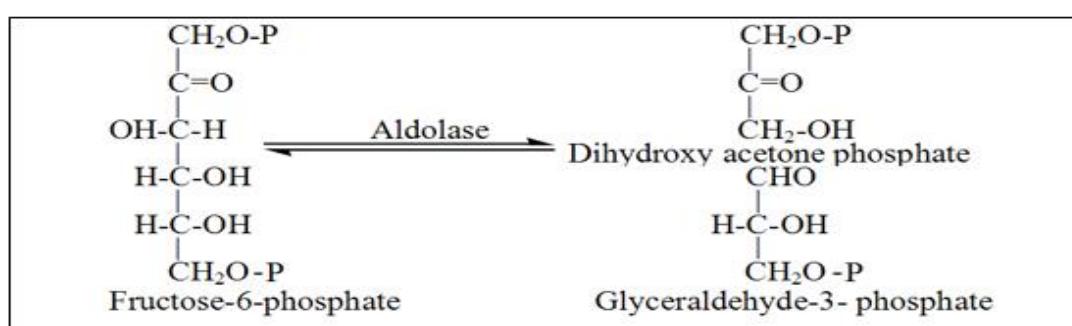
- Glucose-6-phosphate is converted to fructose-6-phosphate by phosphohexose isomerase.

**Step 3:**

Fructose-6-phosphate is converted into fructose-1-6-bisphosphate by phosphofructokinase 1 (PFK.1). This reaction is irreversible. Another ATP molecule was consumed.

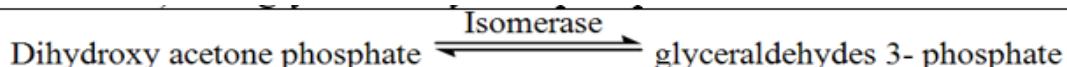
**Step 4:**

Fructose-1-6-bisphosphate is splitted by aldolase (fructose-1-6-bisphosphate aldolase) into glyceraldehyde-3-phosphate and dihydroxy acetone phosphate.

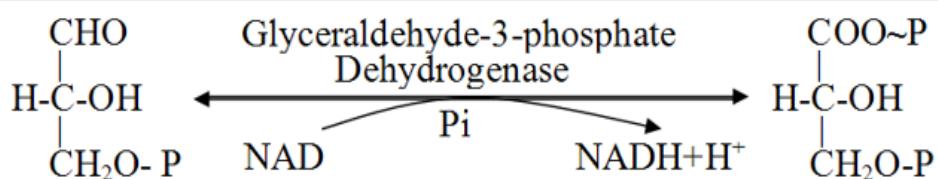


Step 5:

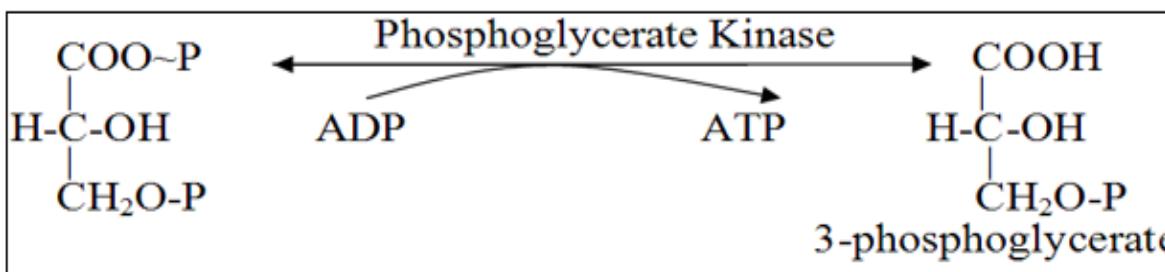
Dihydroxyacetone phosphate is converted by isomerase (phosphotriose isomerase) into glyceraldehyde-3-phosphate.

**II. Second phase (energy-generating)****Step 6:**

- This step includes two processes **oxidation** and **phosphorylation**. Glyceraldehyde-3-phosphate dehydrogenase enzyme catalyzes an oxidation and addition of inorganic phosphate (Pi) to glyceraldehyde-3-phosphate.
- This results in the production of a high-energy intermediate 1,3 bisphosphoglycerate and the reduction of NAD to NADH+H⁺.

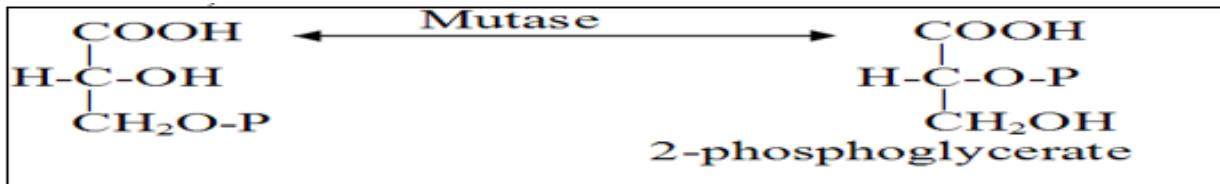
**Step 7:**

- The 1, 3-bisphosphoglycerate gives its high energy phosphate (~P) in carbon 1 to ADP, producing ATP.
- This is an example of **substrate-level phosphorylation**, i.e., the creation of a high-energy phosphate bond through a chemical reaction.

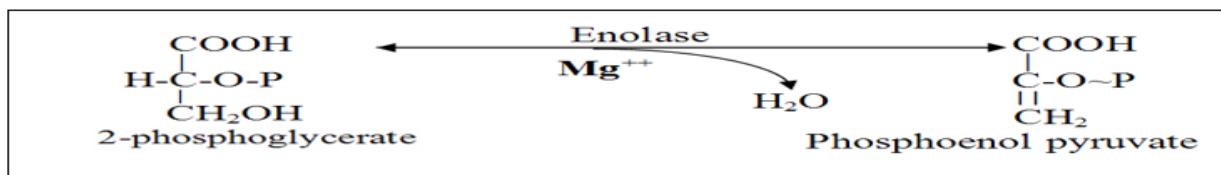


Step 8:

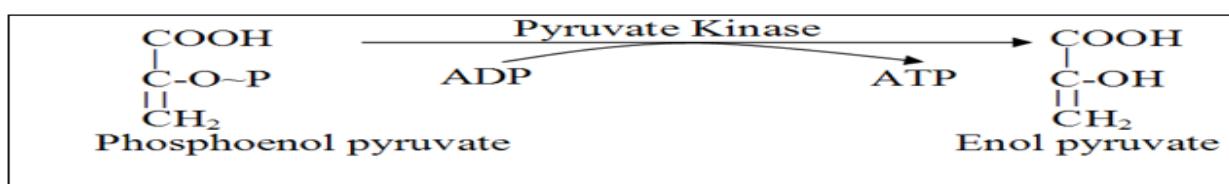
- 3-phosphoglycerate is converted to 2-phosphoglycerate by mutase (phosphoglycerate mutase).

**Step 9:**

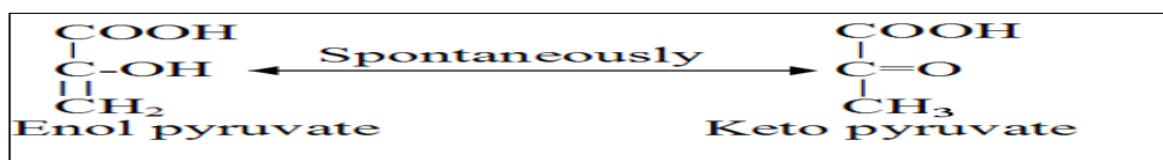
- In this step, there is (1) Dehydration and (2) Redistribution of energy within the molecule, raising the phosphate in position 2 to high energy state, thus forming phosphoenol pyruvate. The reaction is catalysed by enolase enzyme.

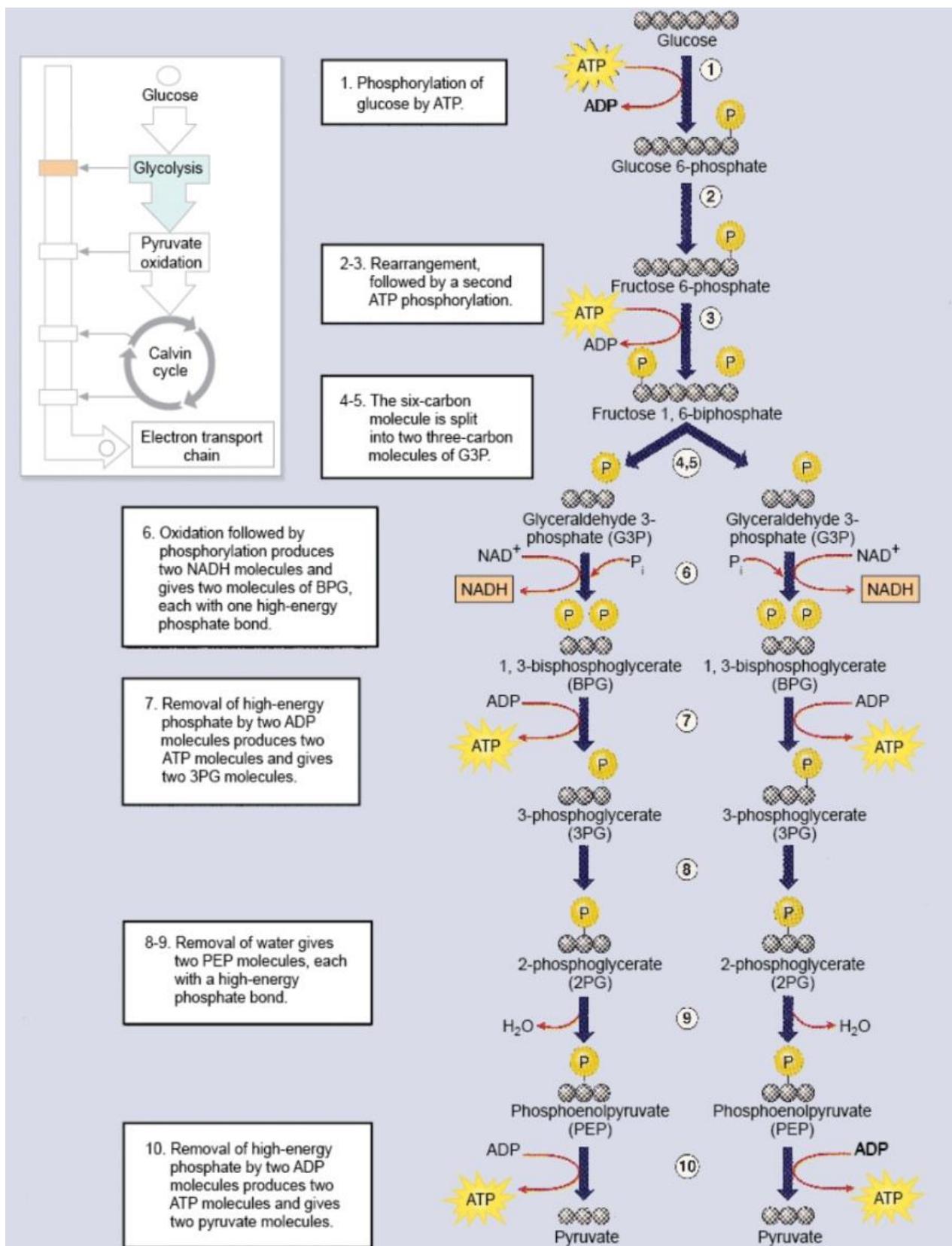
**Step 10:**

- Phosphoenol pyruvate gives its phosphate to ADP forming ATP and enol pyruvate. This is the third irreversible reaction. This is an example of **substrate-level phosphorylation**, i.e., the creation of a high-energy phosphate bond through a chemical reaction.

**Step 11:**

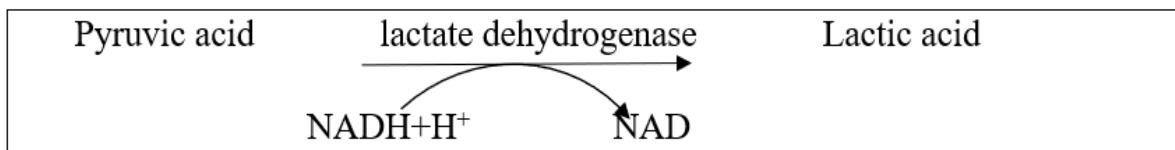
- Enol pyruvate is changed spontaneously into more stable form, pyruvate or pyruvic acid.





In anaerobic glycolysis:

- In cells that are unable to transfer electrons to oxygen due to lack of mitochondria, e.g., RBCs, or in vigorously exercising muscle cells (**anaerobic conditions**), NAD is regenerated by giving its hydrogen to pyruvic acid to form lactic acid.



- In muscle tissue under hypoxic conditions, the energy needs of the tissue may be partially supplied by anaerobic glycolysis:
- **Lactate** build-up during anaerobic glycolysis limits the extent to which muscle can obtain energy by this means.
- **Accumulation** of lactic acid causes a decrease in muscle cell pH.
- **Decreased pH** interferes with function of the contractile machinery of the muscle.
- **Elevated** muscle lactate accounts for fatigue and pain induced by strenuous exercise.

Lactic acidosis:

- Conditions that cause decreased oxygenation of tissues force **excessive** dependence on **anaerobic glycolysis** for energy production, with **lactic acid buildup** in tissues and spillover into the blood.
- Convulsions, **shock**, uncontrolled hemorrhage or conditions that interfere with circulatory function can cause **lactic acidosis**.

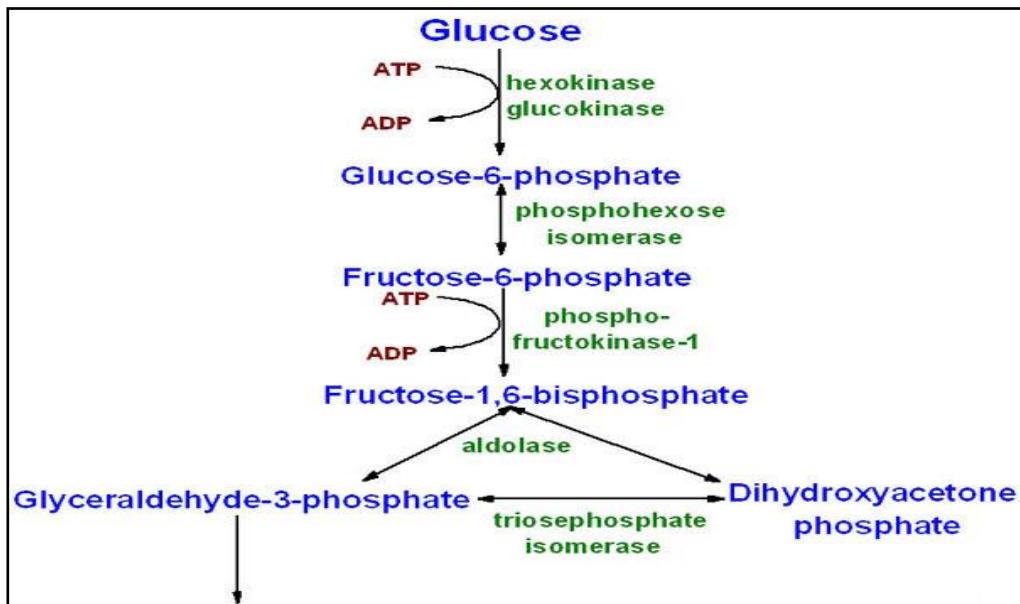
In aerobic glycolysis:

- In the presence of oxygen, $\text{NADH}+\text{H}^+$ is oxidized in the electron transport chain in the mitochondria to produce ATP.

Generally, glycolysis can be divided into two main phases or stages:

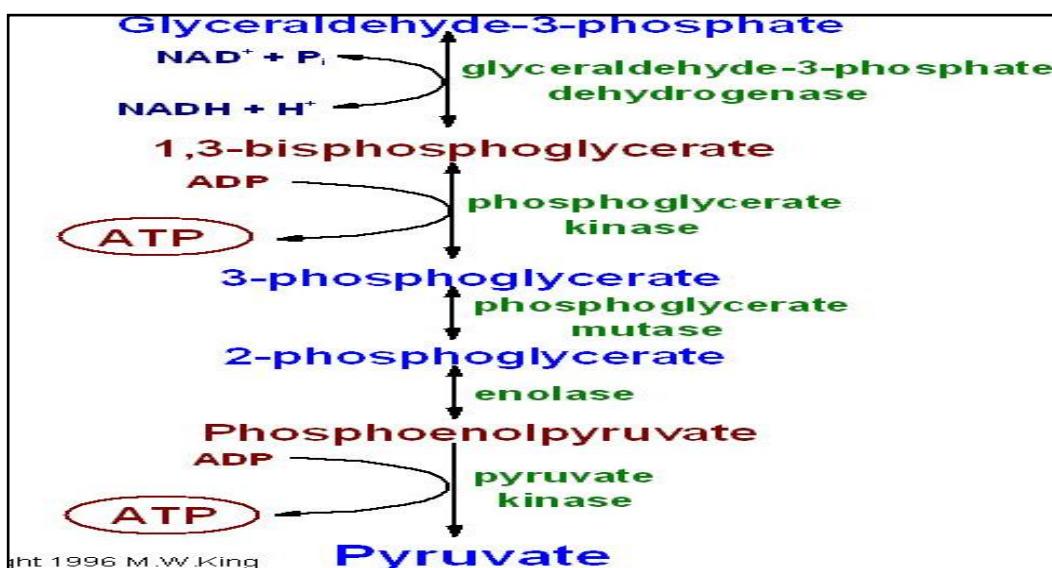
1st phase: “Priming” (Energy requiring) phase:

- ❖ It includes the first 5 reactions. Glucose is converted into two molecules of glyceraldehyde 3-phosphates. It uses **two molecules of ATP**.



2nd phase: (Energy producing) phase:

- ❖ It includes second set of 5 reactions. Each glyceraldehyde 3-phosphate is converted to pyruvate (aerobic) or lactate (anaerobic). It releases 4 ATP molecules. Net gain of energy 2 ATP.

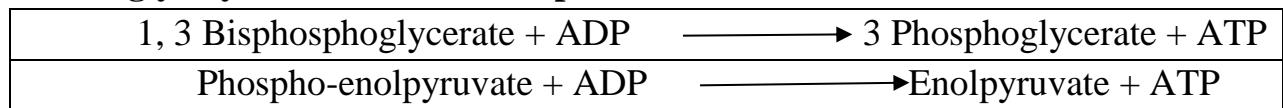


Differences between glucokinase and hexokinase:

	Glucokinase	Hexokinase
1. Site	➤ Liver and pancreatic β islet cells.	➤ All tissue.
2. Affinity to glucose	➤ Low affinity (high km) i.e. it acts only in the presence of high blood glucose concentration.	➤ High affinity (low km) i.e. it acts even in the presence of low blood glucose concentration.
3. Substrate	➤ Glucose only.	➤ Glucose, galactose and fructose.
4. Effect of insulin	➤ Induces synthesis of glucokinase.	➤ No effect.
5. Effect of glucose-6-p	➤ No effect.	➤ Allosterically inhibits hexokinase.

Substrate level phosphorylation in glycolysis:

- ❖ This means phosphorylation of ADP to ATP at the reaction itself.
- ❖ In glycolysis there are 2 examples:



Glycolysis Is Irreversible

- ❖ Three enzymes in the pathway catalyze reactions that are irreversible. When the liver produces glucose, different reactions and therefore different enzymes must be used at these **three points**:
 - Glucokinase/hexokinase.
 - PFK-1 phosphofructo kinase-1.
 - Pyruvate kinase.

Regulation of glycolysis:

By controlling of the three irreversible enzymes (key regulatory enzymes). These enzymes are; **glucokinase (hexokinase)**, **phosphofructokinase (PFK-1)** and **pyruvate kinase**.

1. Hormonal regulation:

- a) **Insulin:** **Stimulates** synthesis of all key enzymes of glycolysis. It is secreted after meal (in response to high blood glucose level).
- b) **Glucagon:** **Inhibits** the activity of all key enzymes of glycolysis. It is secreted in response to low blood glucose level (starvation).

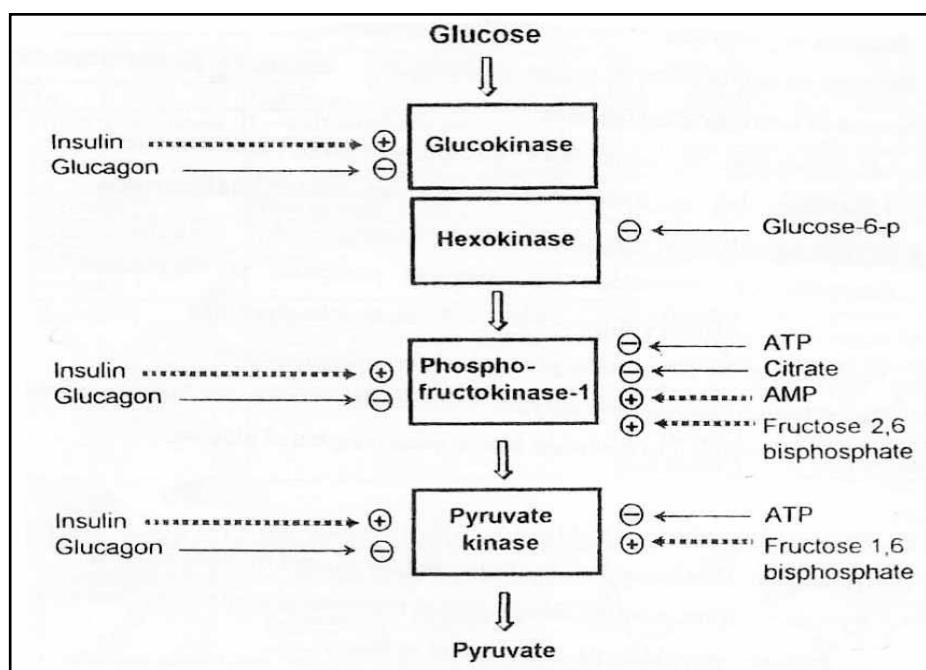
2. Energy regulation:

- a) High level of **ATP** inhibits PFK-1 and pyruvate kinase.

- b) High level of **ADP** and **AMP** stimulate PFK-1.

3. Substrate regulation:

- a) Glucose-6-phosphate inhibits hexokinase (and not glucokinase).
- b) Fructose 2,6 bisphosphate stimulates phosphofructokinase-1.
- c) Citrate inhibits phosphofructokinase-1.
- d) Fructose 1,6 bisphosphate stimulates pyruvate kinase.



Biological importance of glycolysis:

1. Energy production:

- **In Aerobic condition:** $2 \times 2 \text{ ATP} - 2 \text{ ATP} (\text{of activation}) = 2 \text{ ATP}$.
- $2 \text{ NADH} \rightarrow \text{enter electron transport chain (ETC)} \rightarrow \text{each NAD produces } 3 \text{ ATP}$ ($2 \times 3 = 6 \text{ ATP}$) [$2 + 6 = 8 \text{ ATP}$ (Aerobic)]. So, in this case, glycolysis is a preparatory pathway for complete glucose oxidation by TCA cycle.
- **Anaerobic glycolysis:**
- $2 \times 2 \text{ ATP}$ in glycolysis = 4
- $4 - 2 \text{ (ATP of activation)} = 2 \text{ ATP}$ only. So, in this case, glycolysis is the only source of energy for anaerobic tissues.

2. Synthetic functions:

- Some intermediates of glycolysis have synthetic function as:

- 3 phosphoglycerate can form serine
- Dihydroxy acetone- p provides glycerol – 3 – p for triacylglycerol synthesis in adipose tissue.

Clinical correlations of glycolysis:

There are many diseases associated with impaired glycolysis. They include:

1. Pyruvate kinase (PK) deficiency:

- ✓ Genetic deficiency of PK enzyme causes decrease in the rate of glycolysis and decreased production of ATP.
- ✓ ATP is required for $\text{Na}^+ - \text{K}^+$ - ATPase which is important for stability of RBCs.
- ✓ This leads to excessive hemolysis of RBCs → leading to hemolytic anaemia.
- ✓ Treated with transfusions and/or splenectomies.

2. Hexokinase deficiency:

- ❖ It leads to hemolytic anemia due to decrease ATP production.

In vitro inhibition of glycolysis

1. Arsenate:

By competing with inorganic phosphate in the reaction:
 $\text{Glyceraldehyde-3-P} \rightarrow 1,3 \text{ bisphosphoglycerate}$

2. Iodoacetate:

By inhibiting glyceraldehyde-3-P dehydrogenase.

3. Fluoride:

Inhibits **enolase** enzyme. Fluoride-containing tubes are used to reduce glycolysis, in blood samples used for estimation of blood glucose.

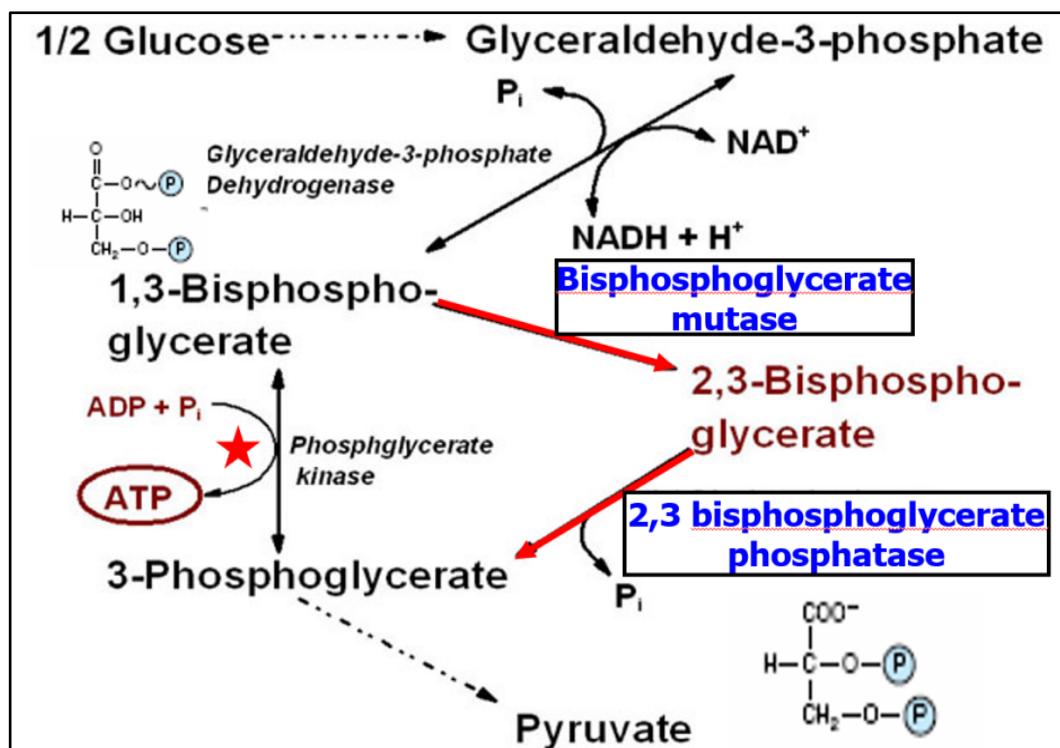
Glycolysis in Red cells (Rapaport - Lubering cycle)

Synthesis of 2,3 BPG in RBCs:

- Some of the 1, 3 BPG is converted to (2,3-BPG) by the action of bisphosphoglycerate mutase.
- 2,3-BPG, is found in only trace amounts in most cells, & in high concentration in RBCs.

Importance of 2,3 BPG in RBCs:

- Oxygen binding to hemoglobin is regulated by 2,3-BPG the interaction of 2,3-BPG with hemoglobin leads to ↓ the affinity of hemoglobin for O₂ → facilitate the release of O₂ to the tissues (protect against hypoxia).
- It binds with the β-chain of Hb and decreases its affinity for O₂, thus helps an easily O₂ release to the tissue cells.
- In high altitudes and other hypoxic states, the O₂ tension is low and this stimulates synthesis of BPG.



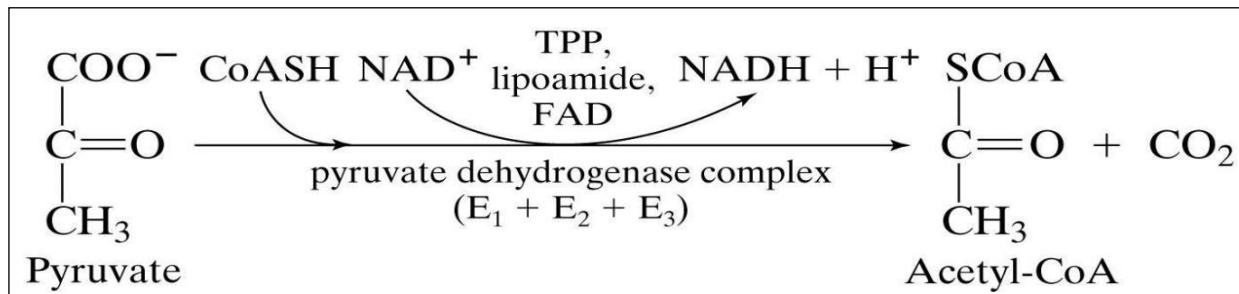
Pyruvate dehydrogenase & Tricarboxylic acid cycle (TCA)

The tricarboxylic acid cycle (TCA) cycle is the final common pathway for the oxidation of the fuel molecules. Also known as the Krebs cycle or the citric acid cycle.

- The reactions of the TCA cycle take place in the mitochondrial matrix.
- Entry point into the TCA cycle is the compound **acetyl-CoA**.

N.B : Glucose \longrightarrow Pyruvic \longrightarrow Acetyl CoA.

Oxidative decarboxylation of pyruvate to acetyl CoA:



Conversion of Pyruvate to Acetyl COA:

- Under aerobic conditions (a plentiful supply of oxygen), pyruvate is oxidized in the mitochondria to form acetyl CoA.
- Pyruvate is converted to acetyl CoA by oxidative decarboxylation.
- This is an irreversible reaction, catalyzed by a multi-enzyme complex, known as pyruvate dehydrogenase complex (PDH), which is found only in the mitochondria.
- The enzyme PDH requires 3 enzymes and five cofactors (coenzymes), namely TPP, FAD, coenzyme A, NAD^+ , and lipoic acid.

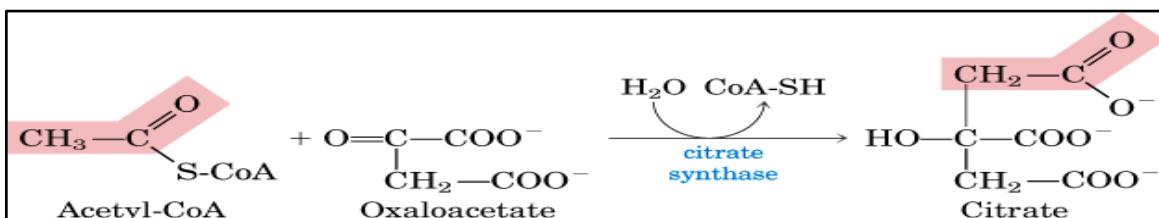
Regulation:

- PDH activity is regulated by its state of phosphorylation, being most active in the dephosphorylated state.
- Phosphorylation of PDH is catalyzed by PDH kinase. The activity of the kinase is enhanced by ATP, NADH and acetyl-CoA. Conversely, an increase in pyruvate, NAD, and coA-SH strongly inhibits PDH kinase.

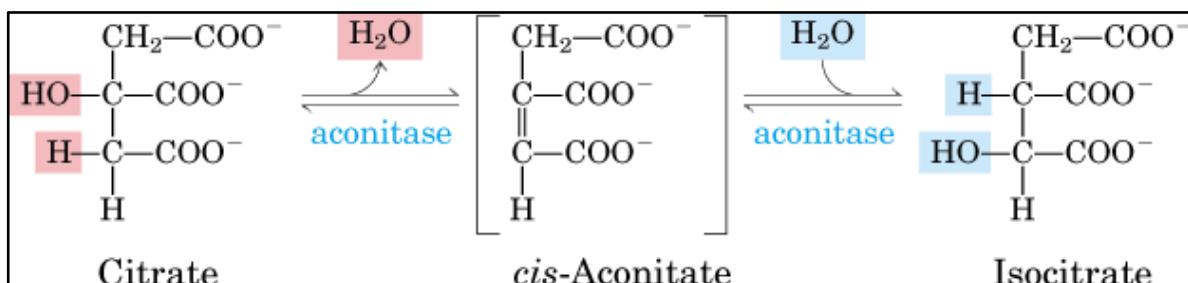
Reactions of the TCA cycle:

1. Formation of Citrate

- Condensation of acetyl CoA and oxaloacetate catalyzed by citrate synthase to form citrate .



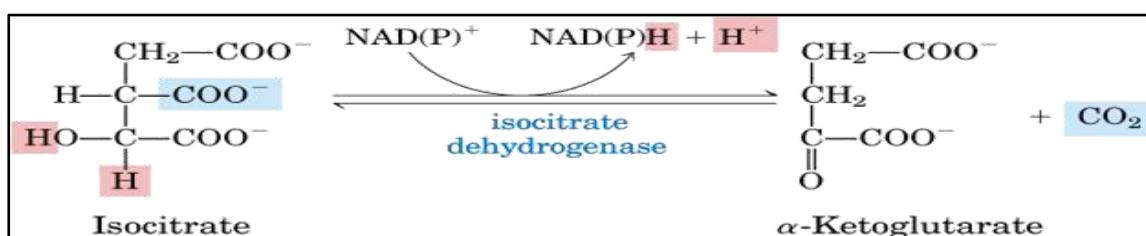
2. Aconitase



- Isomerization of citrate to isocitrate by aconitase

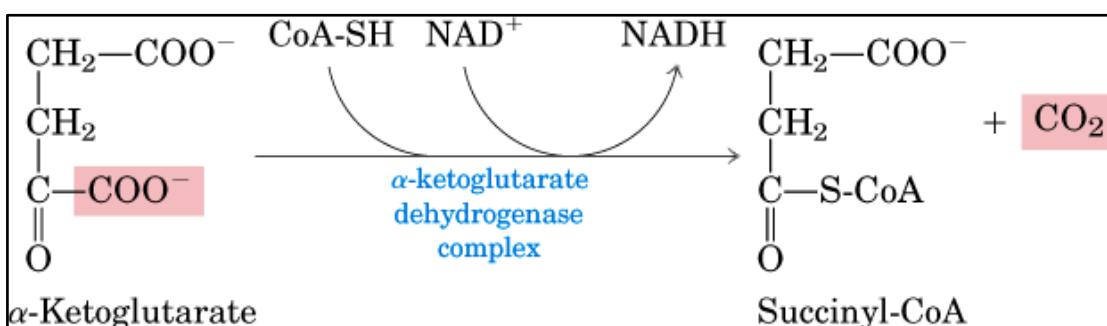
3. Isocitrate Dehydrogenase

- First oxidative decarboxylation of isocitrate to α -ketoglutarate by isocitrate dehydrogenase.
- One of four oxidation-reduction reactions of the cycle.



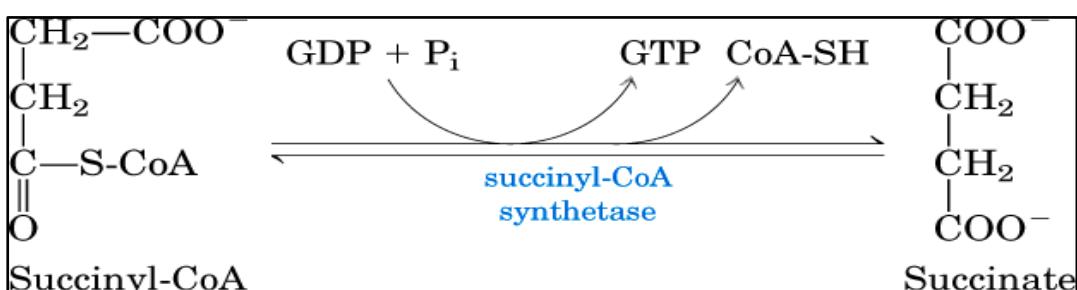
4. α Ketoglutarate dehydrogenase complex-

- α -ketoglutarate is converted to succinyl-CoA. By α Ketoglutarate - dehydrogenase complex.
- Second oxidative decarboxylation reaction. Similar to pyruvate dehydrogenase complex it is composed of 3 enzymes and need 5 coenzymes.
- Succinyl-CoA thioester is very high energy. Generates NADH.



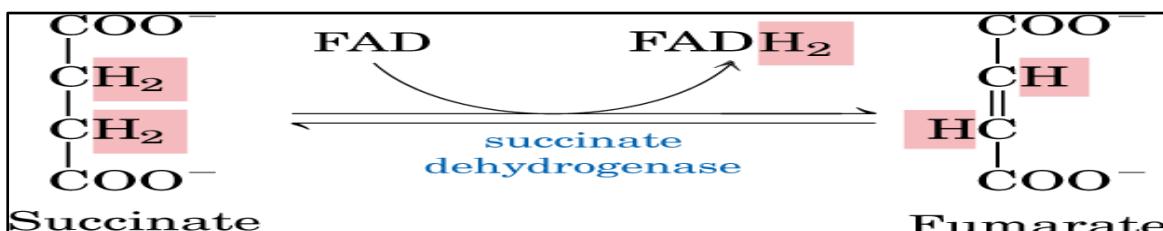
5. Succinyl-CoA Synthetase (Formation of succinate)

- Succinyl COA is converted into succinate by Succinyl-CoA Synthetase.
- Free energy in thioester bond of succinyl CoA is conserved as GTP.
- It is a good example of substrate level phosphorylation.
- Only step where GTP is formed directly in the TCA cycle.



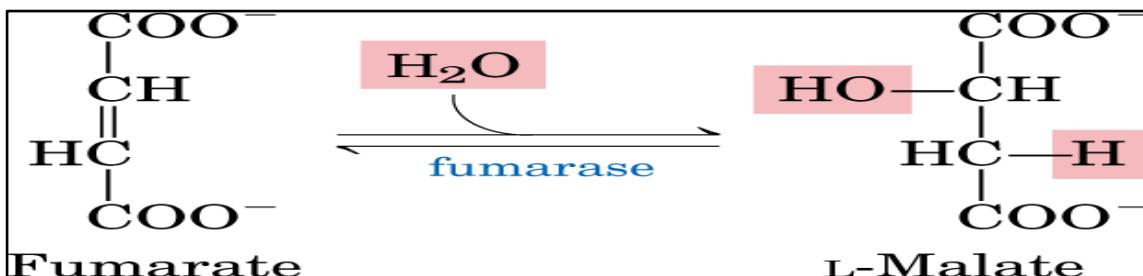
6. The Succinate Dehydrogenase Complex

- Located on the inner mitochondrial membrane.
- Succinate is oxidized to fumarate by succinate dehydrogenase , while FAD is reduced to FADH₂.
- Also known as Complex II of the electron transport chain.



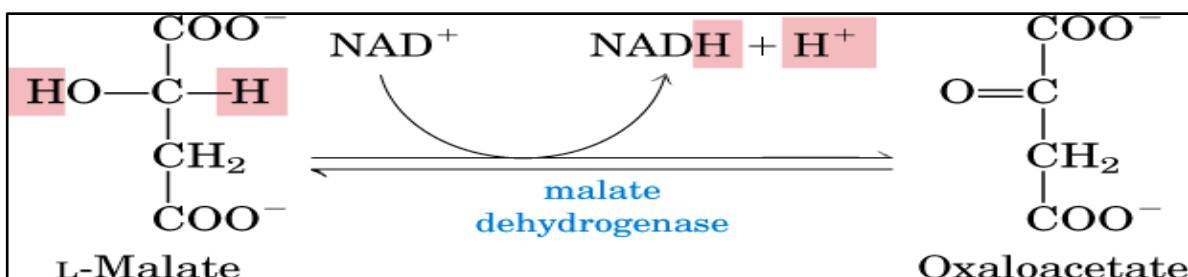
7. Fumarase

- Fumarate is converted to L-malate by hydration (addition of water) to the double bond of fumarate, fumarase catalyzes the reaction.



8. Malate Dehydrogenase

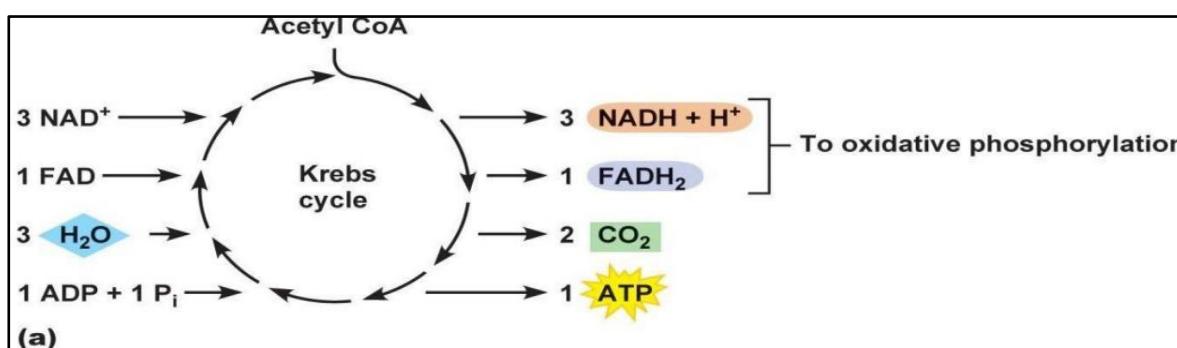
- Regeneration of oxaloacetate from L-malate by malate dehydrogenase with formation of NADH.

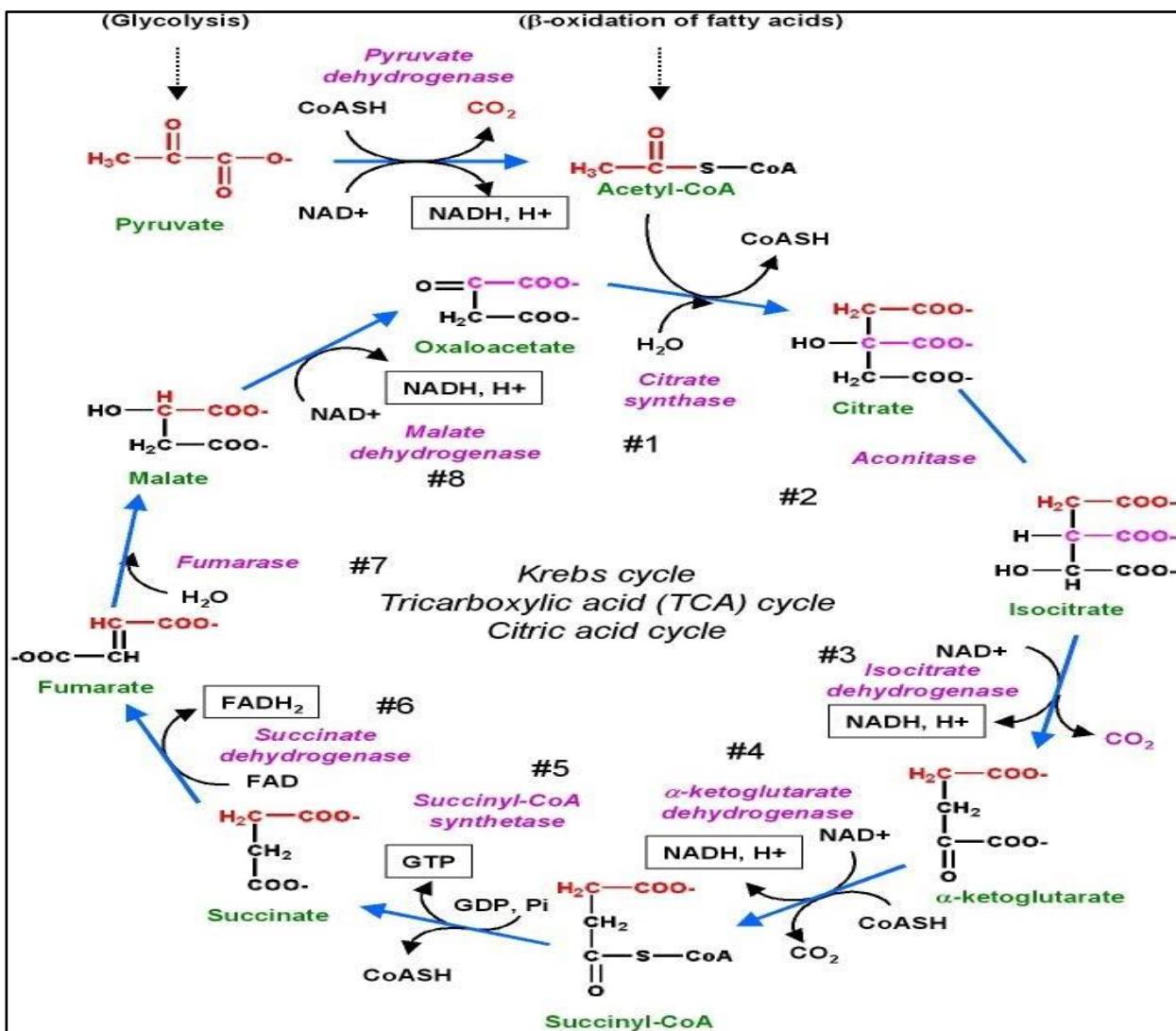


N.B: α -ketoglutarate dehydrogenase complex requires the same cofactors as the pyruvate dehydrogenase complex.

Overall summary of TCA cycle:

The TCA cycle produces 3 NADH, 1 FADH₂, and 1 GTP per acetyl-CoA = 12 ATP/acetyl-CoA (2× everything per glucose)





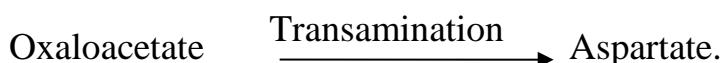
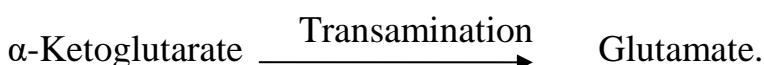
Regulation of TCA cycle:

- In most tissues, the primary function of TCACycle is to provide energy,TCA cycle is therefore inhibited when the cell has no need for further ATP synthesis, and activated when it needs to make more ATP.
- The most likely sites for regulation are citrate synthase,isocitrate dehydrogenase and α -ketoglutarate dehydrogenase.Citrate synyhave is stimulated by acetyl COA,oxaloacetate,ADP and NAD,inhibited by ATP and NADH+H.Isocitrate dehydrogenase (inhibited by ATP,activated by ADP) and α -ketoglutarate dehydrogenase (inhibited by ATP,NADPH and succinyl COA).

Importance of TCA:The cycle is amphibolic i.e. it has catabolic (breakdown) and anabolic (formation) functions.

- A. :**Catabolic function** TCA is the final common pathway for oxidation of carbohydrates, fats and proteins (amino acids), the major source of energy.
- B. :**Anabolic function**Formation of:

1) Amino acids: Are derived from alpha ketoacids



2) Glucose:



3) Heme synthesis: Succinyl COA is important for heme synthesis and for ketolysis (breakdown of ketone bodies)



4) Fatty acid and cholesterol:Citrate diffuses to cytoplasm and converted to oxaloacetate + Acetyl CoA → Fatty acid and cholesterol.

Gluconeogenesis

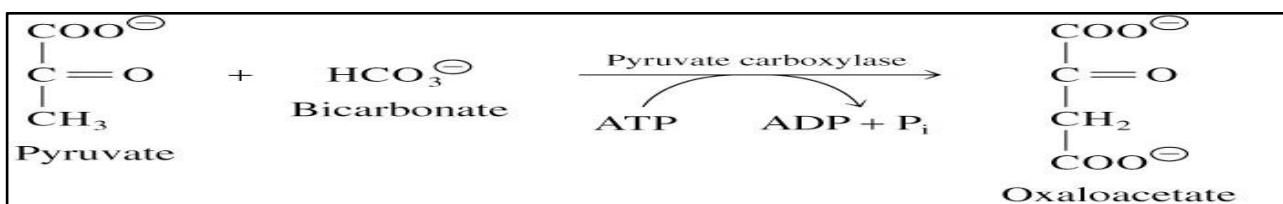
- **Definition:** Biosynthesis of glucose from non-carbohydrate sources.
- **Site:** liver and kidney (Renal cortex contributes about 10%).
- Muscle cannot participate in gluconeogenesis because it lacks glucose-6-phosphatase.
- **Subcellular:** cytosol and mitochondria.
- **Importance:**
 1. Maintain blood glucose levels in case of fasting more than 18 hours (liver glycogen is depleted after 12-18 hours).
 2. Glucose is the source of energy for brain and RBCs.
 3. Clears lactate produced by muscle and RBCs and glycerol produced by adipose tissues from the blood.

Steps:

Are those of reversal of glycolysis, except for the **3** irreversible reactions. The gluconeogenesis pathway is not simply a reversal of glycolysis.

The 3 irreversible reactions can be bypassed as follows:

Bypass I: Pyruvate kinase reaction is reversed by dicarboxylic acid shuttle
 Pyruvate is transported into the mitochondria from cytoplasm as enzyme pyruvate carboxylase is present **only** in mitochondria (mitochondrial matrix). Carboxylation of pyruvate to form oxaloacetate in the presence of biotin as cofactor. Reaction is driven by ATP hydrolysis.



(phosphoenolpyruvate carboxykinase)



- Can occur in either matrix or cytoplasm.
- Reaction is driven by GTP hydrolysis.

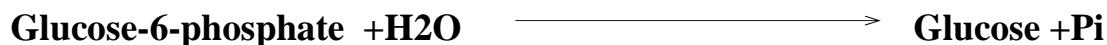
Bypass II: Reversal of phosphofructokinase reaction

This is reversed by fructose 1,6 diphosphatase enzyme.



Bypass III: Reversal of hexokinase (glucokinase)

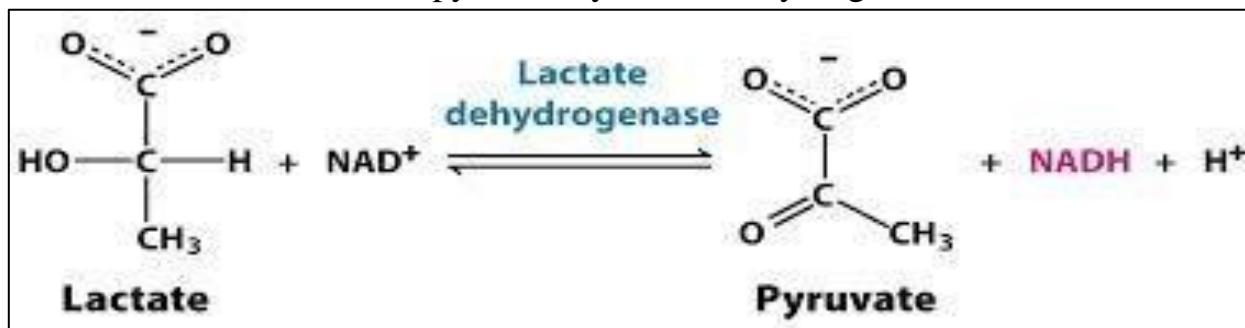
Reversed by glucose-6-phosphatase, which is present in the liver and kidney, but not in the brain and muscles. Thus, glucose produced by gluconeogenesis in the liver, is delivered by the blood stream to the brain and muscles.



• Sources for gluconeogenesis

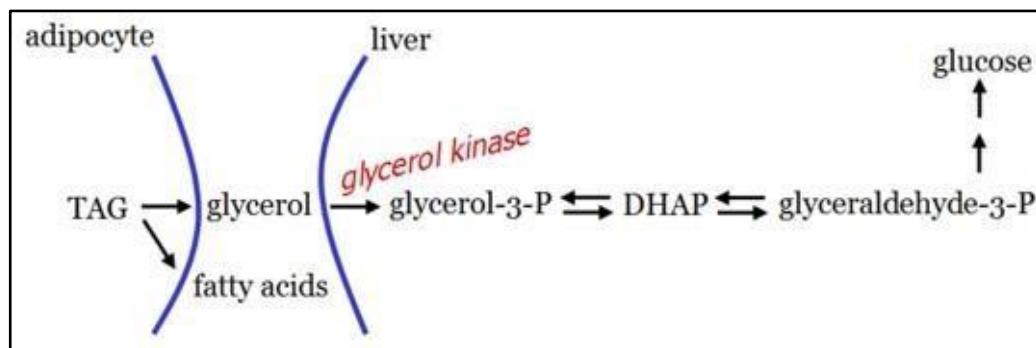
1- Lactate:

Lactate is converted into pyruvate by lactate dehydrogenase.



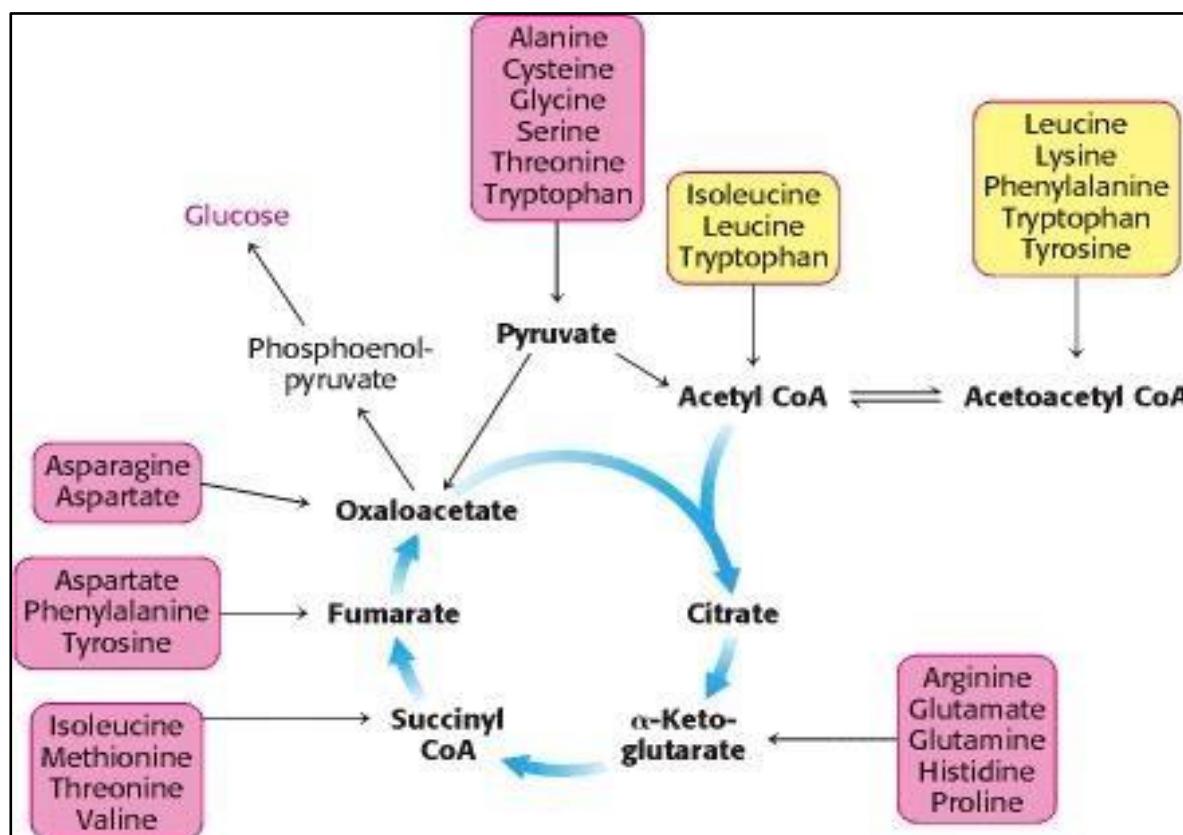
2-Glycerol:

- Glycerol can be generated from hydrolysis of triacylglycerols to yield free fatty acids and glycerol.
- Glycerol is phosphorylated by glycerokinase into glycerol-3 phosphate which is oxidized to dihydroxyacetone phosphate.
- Adipose tissues cannot phosphorylate glycerol because they lack glycerol kinase.

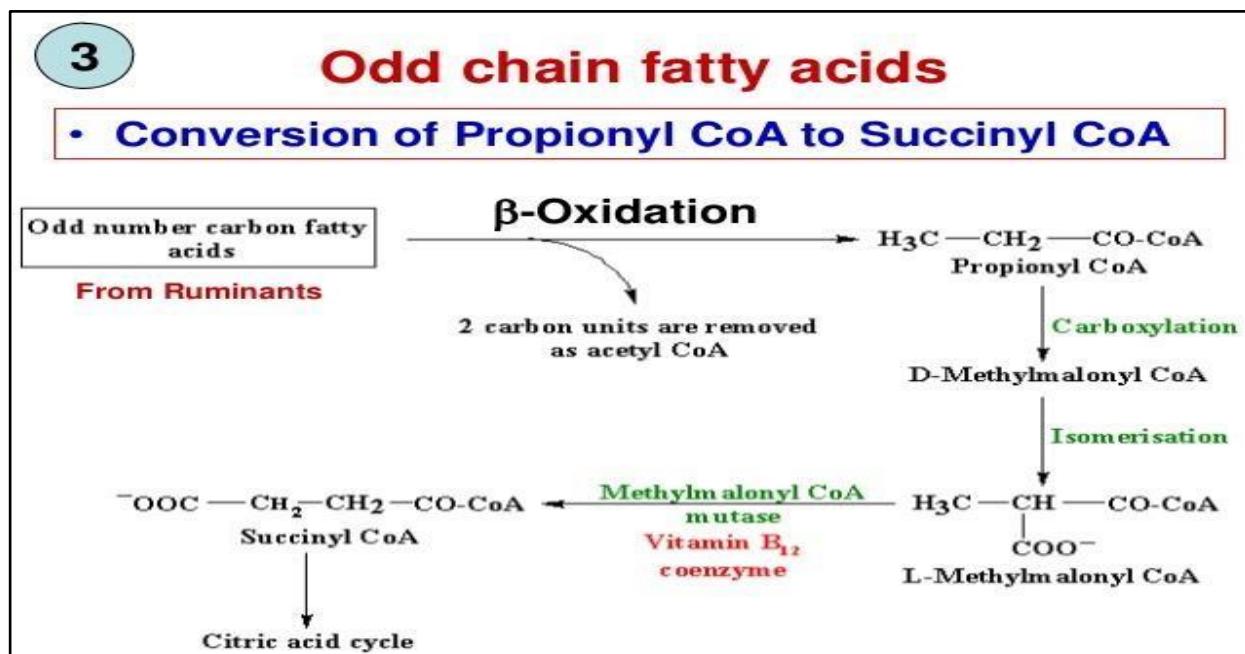


3-Amino acids:

- With exception of leucine, all amino acids are either glucogenic or mixed (glucogenic and ketogenic).
- Amino acids on deamination or transamination give pyruvic acid or intermediates of kreb's cycle (α -keto-glutaric acid, succinyl CoA). Both are converted into oxaloacetate which finally produces glucose.



1. Odd chain fatty acids: The odd chain fatty acids are oxidized in β -oxidation producing acetyl CoA molecules and one molecule of propionyl CoA, converted to succinyl-CoA then fumarate then malate which join the common pathway.



- Propionyl CoA can be derived from the catabolism of some amino acids as methionine, isoleucine and threonine.
- Vitamin B12 deficiency results in excretion of large amounts of methyl malonyl CoA in urine (methyl malonic aciduria).
- Even-chain fatty acids cannot produce new glucose, since they yield only acetyl-CoA equivalents.

Energy cost of gluconeogenesis

- For conversion of 2 molecules of pyruvate to one molecule of glucose, 6 high energy phosphate bonds are hydrolysed (4 ATP and 2 GTP) as follow:

Reaction	Energy cost
Pyruvate \longrightarrow oxaloacetate	2ATP
Oxaloacetate \longrightarrow phosphoenolpyruvate	2GTP
3-phosphoglycerate \longrightarrow 1,3 biphosphoglycerate	2ATP

Regulation of gluconeogenesis

The key regulatory enzymes of gluconeogenesis are pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose 1,6-bisphosphatase and glucose 6 phosphatase.

A. Hormonal regulation

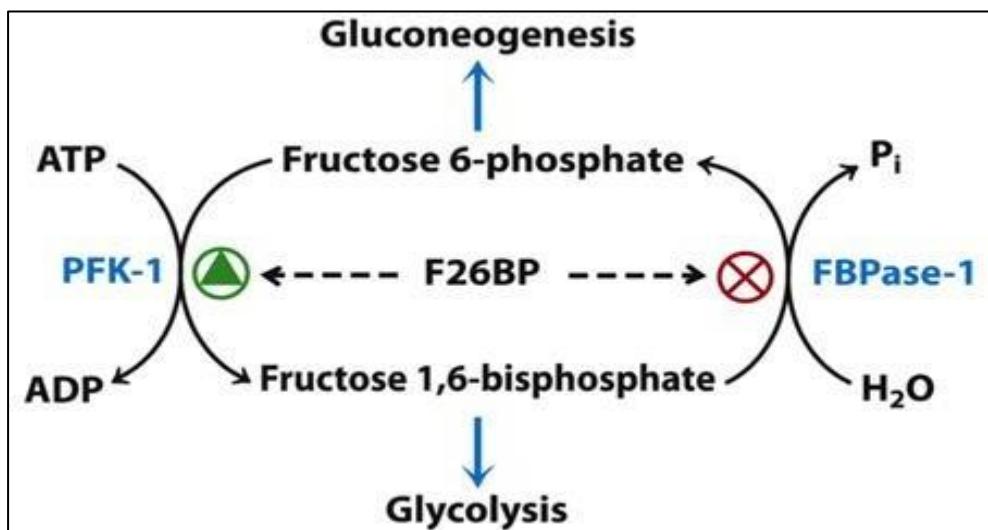
Glucocorticoids: stimulate gluconeogenesis by:

1. They induce the synthesis of the key enzymes.
2. They stimulate protein catabolism, thus increasing glucogenic amino acids available for gluconeogenesis.
3. They induce the expression of transaminases.

Insulin: Inhibits the gluconeogenesis as it represses the synthesis of the key enzymes.

Glucagon: Stimulate gluconeogenesis by inhibiting the formation of fructose 2,6 biphosphate. Low levels of fructose 2,6 biphosphate inhibit phosphofructokinase-1 (glycolysis) and activate fructose 1,6 bisphosphatase (gluconeogenesis).

B. ATP and acetyl CoA:



Fatty acid oxidation is increased during fasting stimulates gluconeogenesis by:

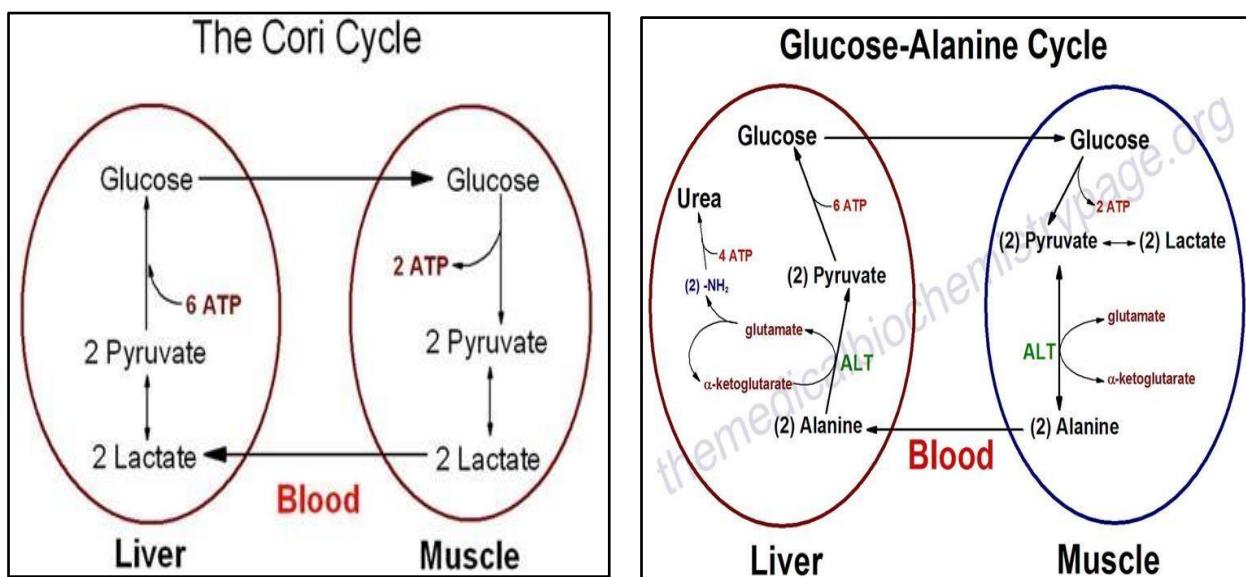
- Production of ATP, which inhibits glycolysis (inhibition of PFK1) and stimulates gluconeogenesis (stimulation of fructose 1,6 bisphosphatase).
- Acetyl CoA production is increased. This stimulates pyruvate carboxylase (gluconeogenesis) and inhibits pyruvate dehydrogenase.

The Cori and alanine cycles

These two important cycles are related to gluconeogenesis.

Cori cycle:

- The lactate produced by skeletal muscles and RBCs diffuses to blood and then taken up by the liver.
- The liver converts lactate into glucose by gluconeogenesis, which returns back to the blood to be utilized by muscles and RBCs for energy production.



Alanine cycle:

- Pyruvate formed from glycolysis in the muscles is converted into alanine by transamination.
- Alanine diffuses to the blood and then taken by the liver.
- In the liver, alanine is converted back to pyruvate.
- Pyruvate is used to produce glucose by gluconeogenesis.

Glycogen Metabolism

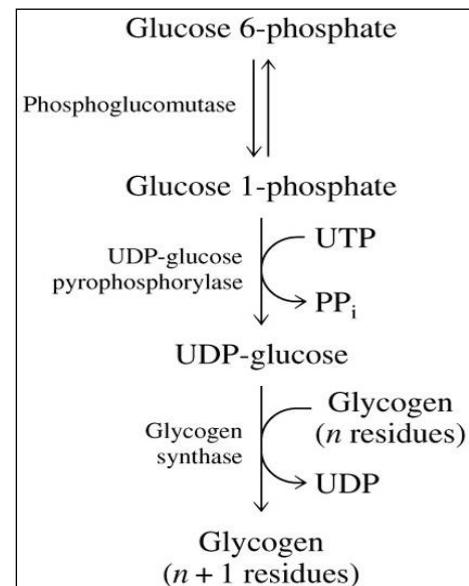
- Glycogen is a highly branched polymer of glucose residues linked by α (1 \rightarrow 4) glycosidic bonds, mainly. Only at the branching point, the chain is attached by α (1 \rightarrow 6) glycosidic bonds.
- Glucose is stored as glycogen predominantly in cytoplasm of **liver** and **muscle** cells.
- Hepatic glycogen is a transient source of glucose, in early fasting, it is exhausted after 10 – 18 hour.
- Muscle glycogen acts as a source of energy within the muscle during muscle contraction.

Glycogen synthesis (glycogenesis)

- **Definition:** It is the formation of glycogen from glucose.
- **Site:** Glycogen synthesis occurs in cytoplasm of all animal tissues, mainly in liver and muscle.
- **Importance:** It stores excess glucose after high carbohydrate meal.
- **Steps:**

1. Formation of UDP-glucose:

- Glucose molecules are first activated to uridine diphosphate glucose (UDP-glucose) as the following:
- Glucose is converted into glucose 6 phosphate by hexokinase in muscle and by glucokinase in the liver.
- Glucose-6-phosphate is converted into glucose-1-phosphate by phosphoglucomutase.
- Glucose-1-phosphate is converted into UDP-glucose by UDP-glucose pyrophosphorylase.



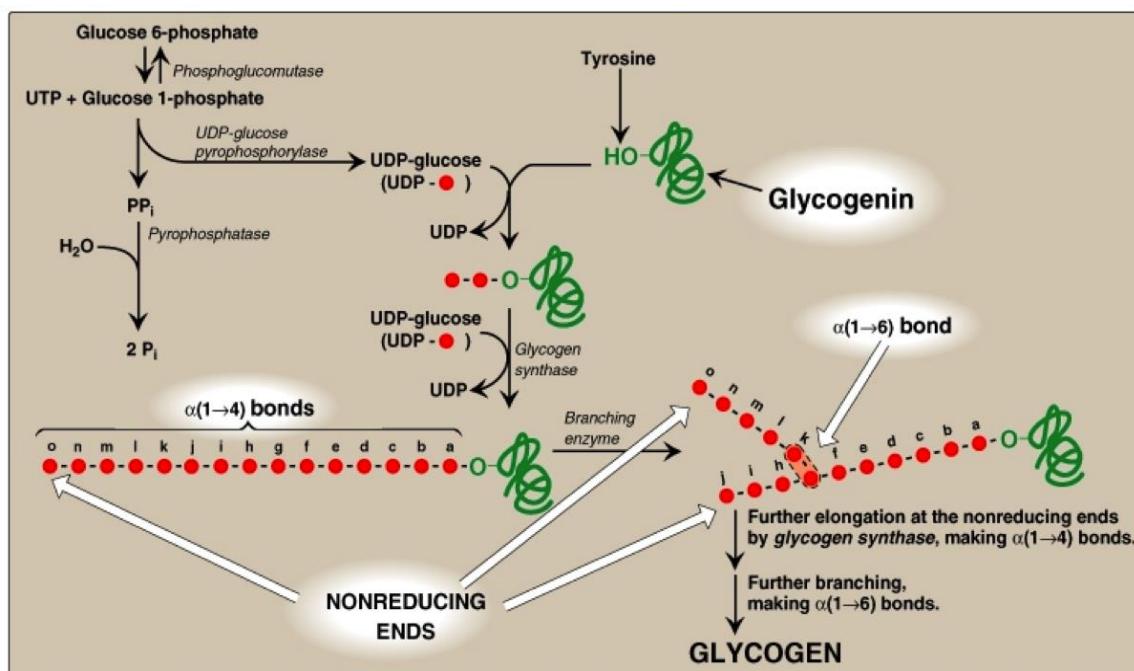
2. Synthesis of the primer:

Glycogen synthase requires a primer for initiation of glycogenesis. This primer may be:

- ❖ At least 4 residues of glucose linked together by $\alpha(1 \rightarrow 4)$ glycosidic bonds (A fragment of glycogen can serve as a primer in cells when glycogen stores are not totally depleted).
- ❖ A protein called glycogenin which is a self-glycosylating enzyme, attaching C-1 of a UDP-glucose to one of its tyrosine residue. The glycosylated glycogenin then serves as the primer required by glycogen synthase to attach additional glucose molecules.

3. Elongation of glycogen chains:

- ❖ By the action of glycogen synthase, C1 of the transferred glucose is attached to C4 of the terminal glucose of an outer branch of glycogen molecule, attached by $\alpha(1 \rightarrow 4)$ glycosidic bonds.
- ❖ This process is repeated many times till the number of glucose residues reaches up to 11 units.
- ❖ Then branching enzyme transfers few glucose residues (around 6) from one branch and attaches them by $\alpha(1 \rightarrow 6)$ linkage in the middle of the adjacent branch, thus creating a new branch point, allowing glycogen synthase to function again.



Glycogenolysis

Definition: It is the breakdown of glycogen into glucose (in the liver) and glucose-6-p (in muscles).

Importance:

- ❖ It is the main source of blood glucose under conditions of fasting for less than 18 hours.
- ❖ The source of energy in muscles during muscle contractions.

Steps:

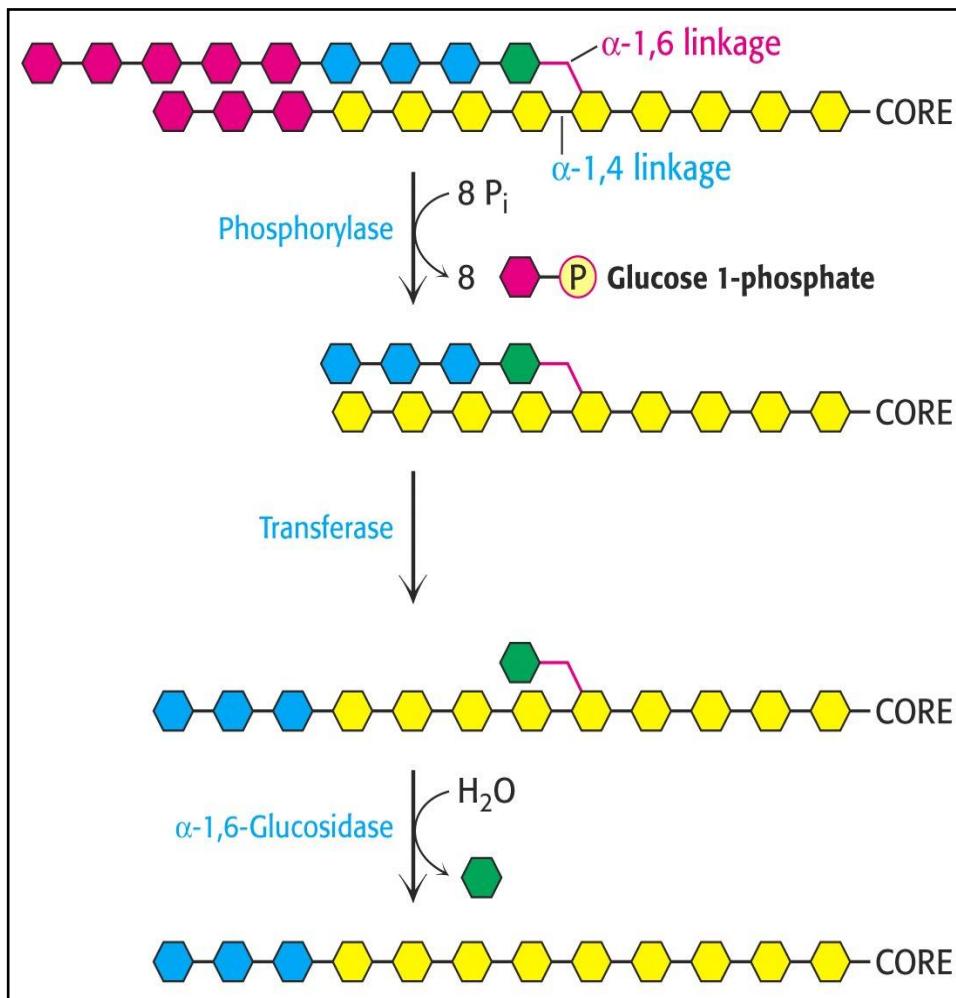
1. Glycogen Phosphorylase catalyzes phosphorolytic cleavage of the α (1 \rightarrow 4) glycosidic linkages of glycogen, releasing glucose-1-phosphate.
2. **Phosphorylase** enzyme acts on the branches containing more than 4 glucose units.
3. When the branch contains 4 glucose units, 3 of them are transferred to a next branch by transferase activity of the **debranching** enzyme, leaving the last one attached by α (1 \rightarrow 6)link.
4. The last glucose unit is removed by the second enzymatic activity of the debranching enzyme, namely α 1 \rightarrow 6 glucosidase activity (by hydrolysis) which release free glucose directly.

N.B: Debranching enzyme is a bifunctional enzyme has two different actions (transferase and glucosidase activities).

5. Glucose-1-phosphate is converted into glucose-6-phosphate by mutase.

6. Fate of glucose-6-phosphate:

- **In liver:** glucose-6-P is converted into glucose by glucose 6 phosphatase.
- **In muscles:** There is no glucose 6 phosphatase, so glucose-6-phosphate enters glycolysis to give lactate.



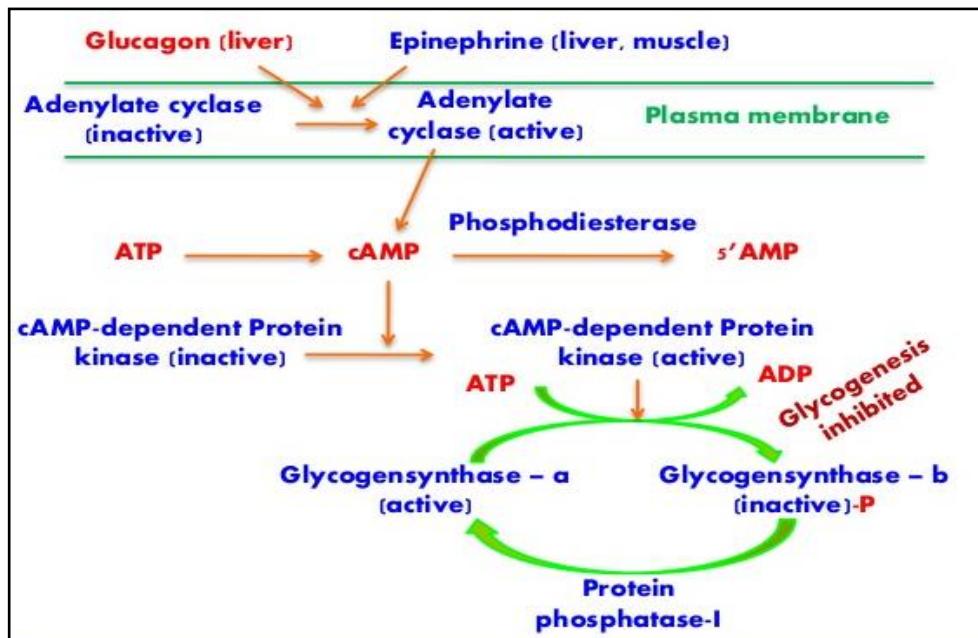
Regulation of glycogen synthesis and glycogenolysis

I-Regulation of glycogenesis

1- Hormonal regulation:

- ❖ Glycogen synthase is the key regulatory enzyme of glycogenesis. It is present in two forms:
 - 1- **Glycogen synthase A** (active form); dephosphorylated.
 - 2- **Glycogen synthase B** (inactive form); phosphorylated.
- ❖ Glycogen synthase A is converted to glycogen synthase B by protein kinase A which is activated by cyclic AMP (cAMP).
- ❖ CAMP is derived from ATP by adenyl cyclase enzyme, whose activity is stimulated by epinephrine and glucagon, and it is inhibited by insulin hormone.

- ❖ CAMP is hydrolyzed to 5' AMP by phosphodiesterase enzyme which is stimulated by insulin.



2-Allosteric regulation:

- Increased concentration of glucose-6-P allosterically stimulates glycogen synthase.
- Increased concentration of glycogen allosterically inhibits glycogen synthase.

II-Regulation of glycogenolysis:

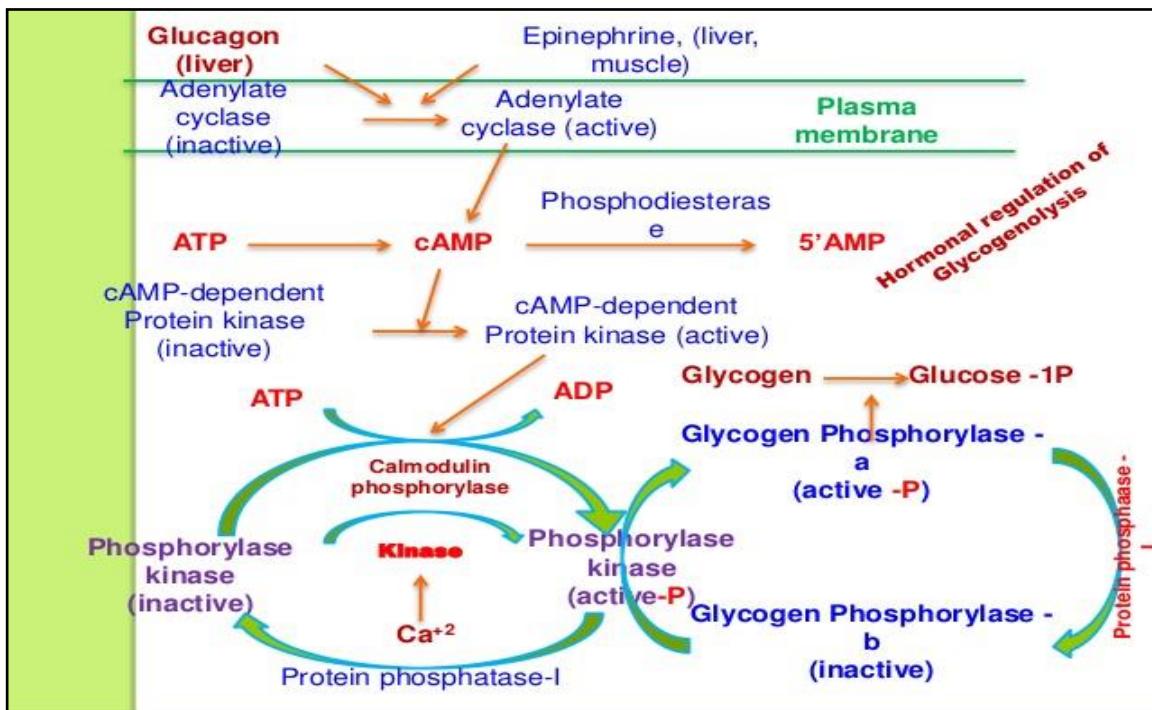
1-Hormonal regulation:

Phosphorylase is the key enzyme for glycogenolysis. It is present in **two forms**:

- **Phosphorylase A (active form); phosphorylated.**

- **Phosphorylase B (inactive form); dephosphorylated.**

- ❖ Phosphorylase B is converted to phosphorylase A by the enzyme phosphorylase A kinase.
- ❖ Phosphorylase kinase B is activated to phosphorylase kinase A by cAMP dependent protein kinase A, that requires cAMP for its activity.
- ❖ CAMP is derived from ATP by adenyl cyclase enzyme, its activity is increased by adrenaline and glucagon and inhibited by insulin.



Glycogenolysis in muscles:

Epinephrine binding to α adrenergic receptors activates phospholipase C leading to hydrolysis of PIP₂ into IP₃ and DAG. IP₃ cause release of Ca⁺² from intracellular structures to cytosol. Ca⁺² ions combine with calmodulin causing its activation. Ca⁺²- calmodulin activate phosphorylase kinase B, so stimulating glycogenolysis.

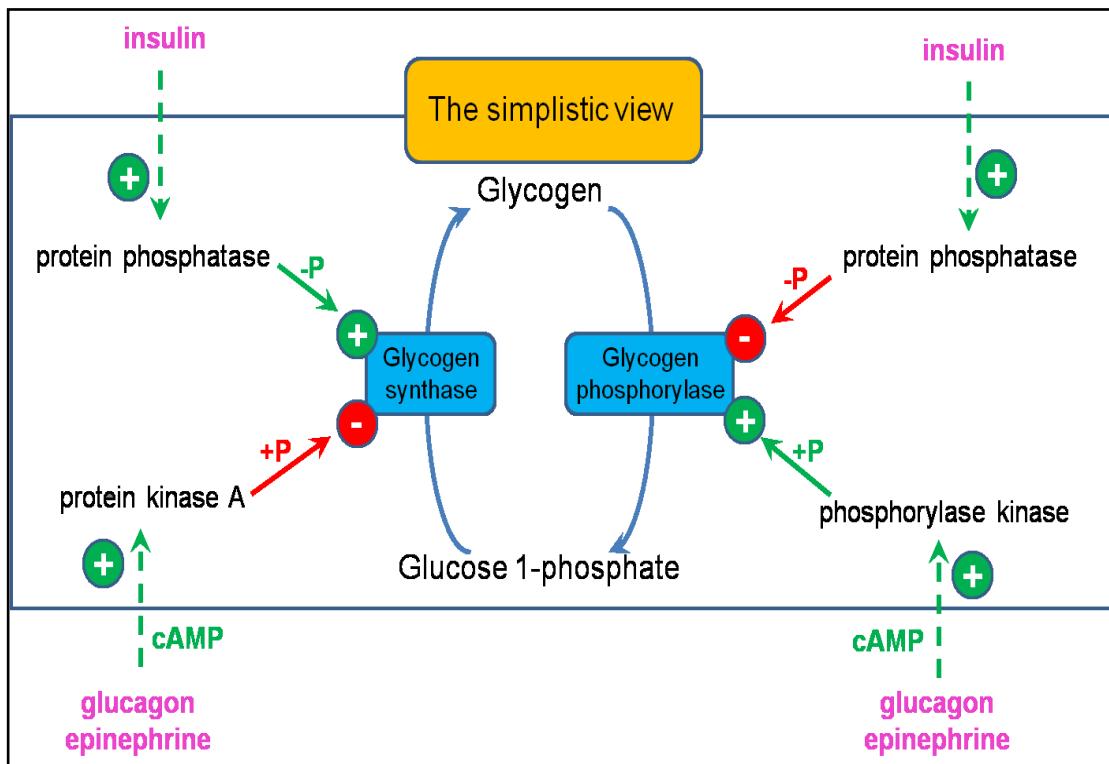
2-Allosteric regulation:

Phosphorylase enzyme is allosterically inhibited by G-6-P and ATP, and activated by AMP in the muscles.

Regulation of glycogenesis and glycogenolysis:

There is a coordinated regulation of glycogenesis and glycogenolysis i.e: conditions lead to stimulation of glycogenesis inhibit at the same time glycogenolysis, and vice versa.

- ✧ **During fasting:** glycogenolysis is stimulated and glycogenesis is inhibited.
- ✧ **After meal,** part of absorbed glucose (40%) goes to the circulation to be utilized by other tissues. The remaining (60%) is converted into glycogen. So after meal, glycogenesis is stimulated and glycogenolysis is inhibited.



Differences between liver and muscle glycogen

	Liver glycogen	Muscle glycogen
-Amount	120 gm (6% of liver weight)	300 gm (1% of muscle weight)
-Source	Hexoses Gluconeogenesis	Blood glucose
-Function	Source of blood glucose	Source of energy to muscle
-Fate	Glucose	Glucose 6-phosphate
-Starvation	Reduces liver glycogen	No effect on muscle glycogen
-Exercise	Has no effect	Reduced
-Insulin	Increase	Increase
-Glucagon	Decrease	Has no effect
-Glucocorticoids	Increase	No effect

Glycogen Storage Diseases (Glycogenosis)

Inborn errors of glycogen metabolism due to deficiency of one of the enzymes of glycogenesis or glycogenolysis.

I- Von Gierke's disease:

It is due to deficiency of glucose 6-phosphatase enzyme in the liver.

The manifestations of Von Gierke's include:

- | | |
|--------------------------|---------------------|
| 1- Fasting hypoglycemia. | 2- Hepatomegaly. |
| 3- Hyperlipidemia. | 4- Lactic acidosis. |
| 5- Hyperuricaemia. | 6- Short stature. |

Pathogenesis (Biochemical basis) of Von Gierke's manifestations:

1. Deficiency of glucose 6-phosphatase has two dual effects, the first, glucose 6-P is not converted to glucose. Glucose 6-P can't pass to the blood leading to hypoglycemia during fasting. Secondly, deficiency of glucose 6-phosphatase affects the last steps of gluconeogenesis leading to more fasting hypoglycemia.
2. Inability to utilize glucose leads to lipolysis and increasing fatty acids oxidation, both are causes of hyperlipidemia.
3. Accumulated glucose 6-P enters glycolysis increasing the formation of lactic acid leading to lactic acidosis. Excretion of lactic acid in urine decreases the excretion of uric acid in urine leading to hyperuricemia .
4. Glucose 6-P is converted to ribose 5-P via HMP-pathway, which in turn stimulate PRPP synthetase enzyme leading to increase in de novo biosynthesis of purine bases and hyperuricemia.

II- Cori's disease:

- It is due to deficiency of debranching enzyme.
- The disease is manifested by mild hypoglycemia and hepatomegaly.

III- Anderson's disease:

- It is due to deficiency of branching enzyme.
- The disease is manifested by accumulation of glycogen with few branches, infantile hypotonia, death by 2 years from heart or liver failure.

IV- McArdle's disease:

- It is due to deficiency of muscle glycogen phosphorylase enzyme leading to muscle cramps and weakness on exercise.
- Blood lactate is very low after exercise.

Pentose phosphate pathway

(Hexose Monophosphate Pathway)

Definition: An alternative pathway for glucose oxidation involving the formation of pentose-5-phosphate as an intermediate.

Site: Cytoplasm

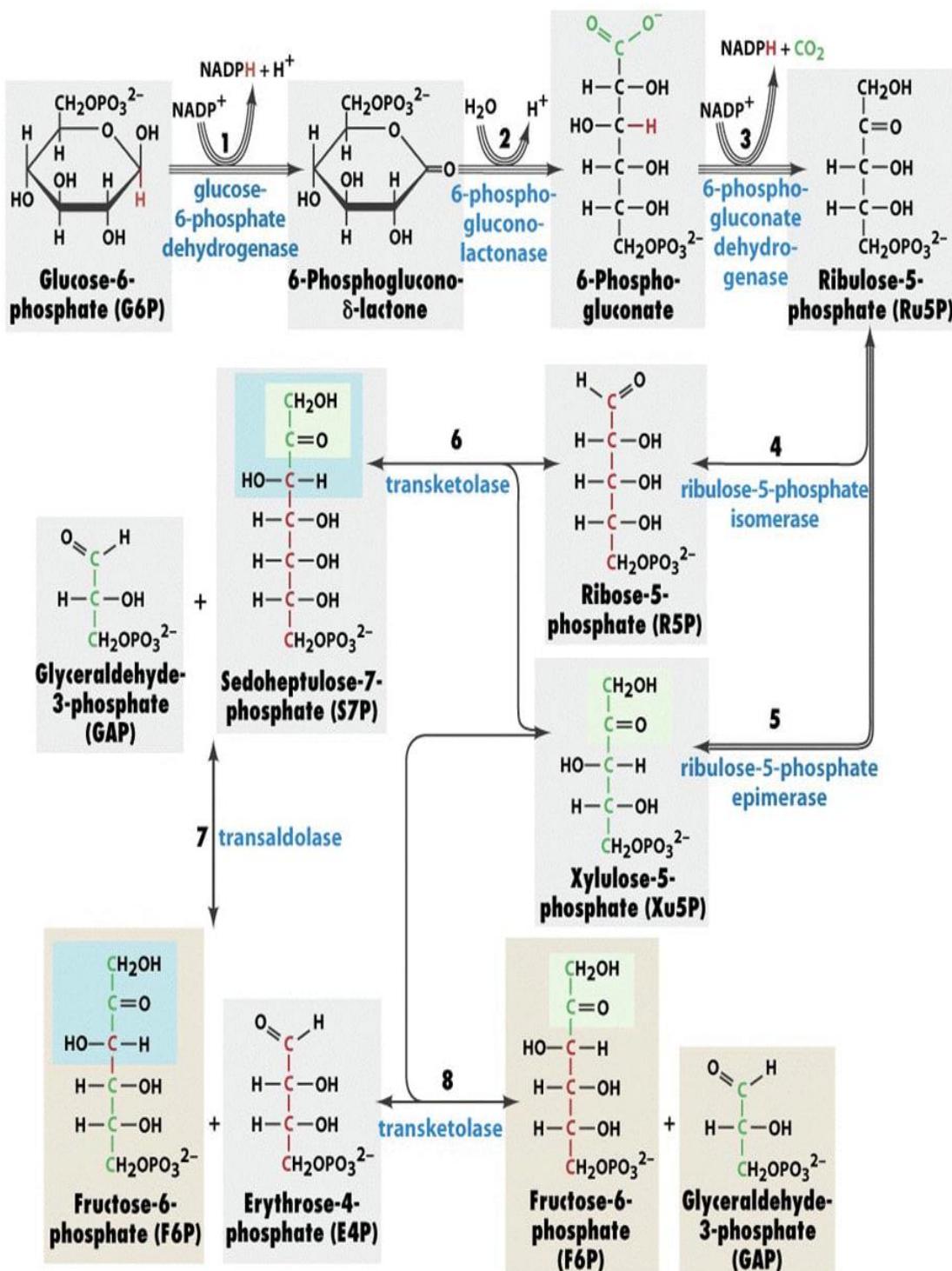
Tissues with active pentose phosphate pathways include:

Tissues	Function
Adrenal gland	Steroid hormones synthesis.
Liver	Fatty acid and cholesterol synthesis.
Testes	Male sex hormones biosynthesis.
Adipose tissue	Fatty acid synthesis.
Ovary	Female sex hormone biosynthesis.
Mammary gland	Fatty acid synthesis.
Red blood cells	Maintenance of reduced glutathione.

The pathway is viewed in two stages:

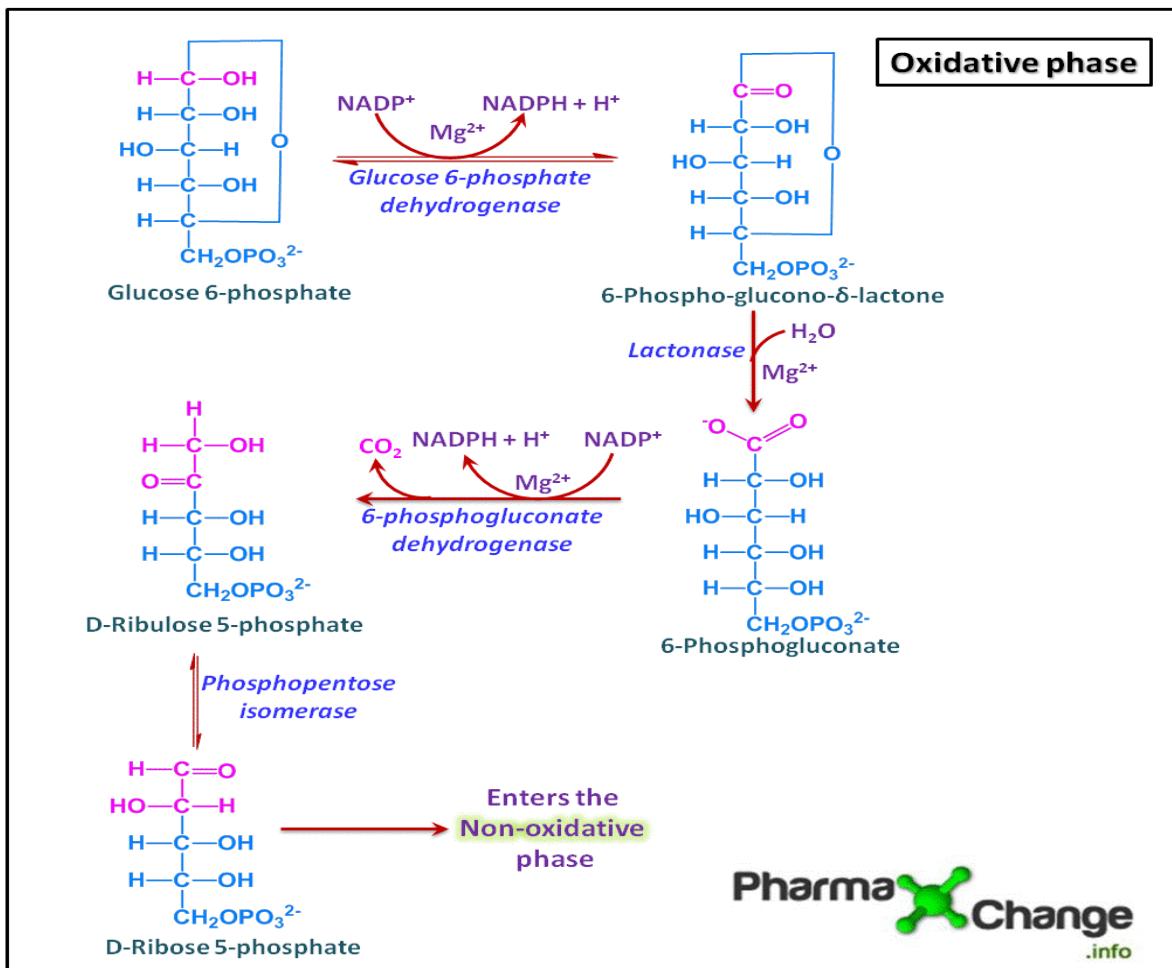
1) **Oxidative pathway:** That produce all the NADPH (6 moles of glucose-6-phosphate ($6 \times C_6 = 36C$) are converted into 6 moles of pentose phosphate ($6 \times C_5 = 30C$) and 6 moles of CO₂.

2) **Non-oxidative pathway:** The 6 moles of pentose phosphate (30C) are converted into 5 moles of hexose phosphate (30C).



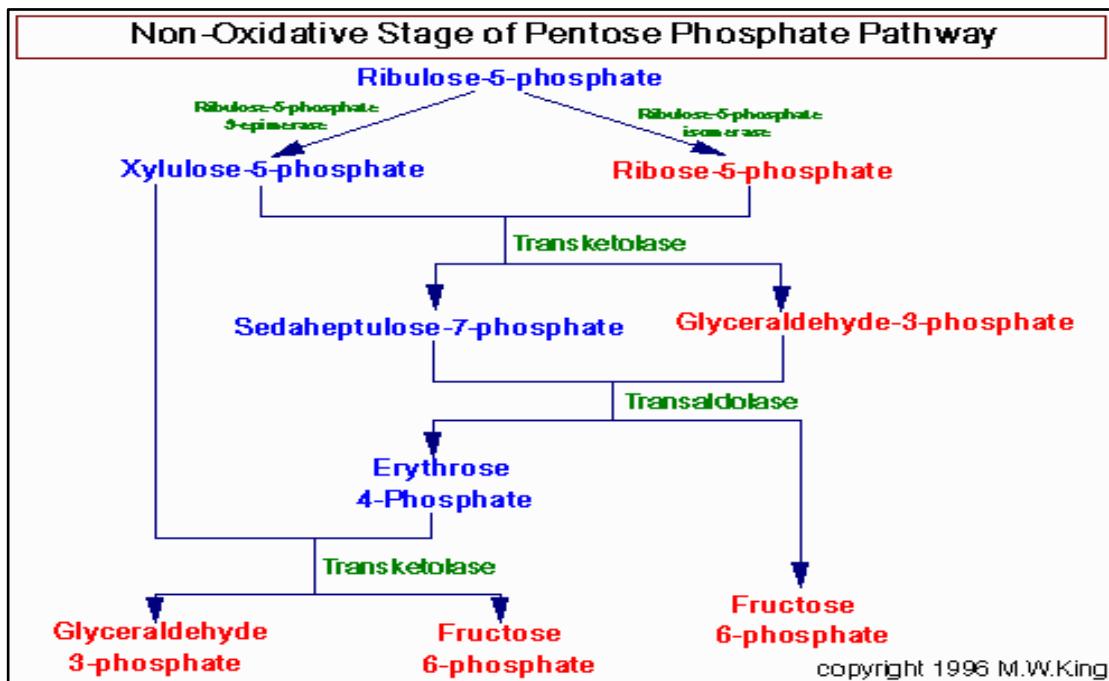
Oxidative pathway of HMP Pathway:

- Glucose 6-P is converted to ribose 5-P with the production of 2 molecules of NADPH+H⁺ and CO₂.
- Glucose 6-P dehydrogenase enzyme is the key enzyme for this pathway. This enzyme is stimulated by NADP and insulin, but inhibited by NADPH+H⁺.



Non-oxidative pathway:

- ❖ Six molecules of ribulose-5-phosphates are converted into 5 molecules of glucose6-phosphates, permitting another oxidative cycle.
- ❖ In addition, some of the sugars made in the shuffling can be used for synthetic purposes, e.g. ribose-5-phosphate is needed for nucleotide synthesis.



- Although glucose can be completely oxidized to CO₂ via this pathway, there is no ATP production.
- Transketolase enzyme needs TPP as coenzyme.

HMP in the muscles:

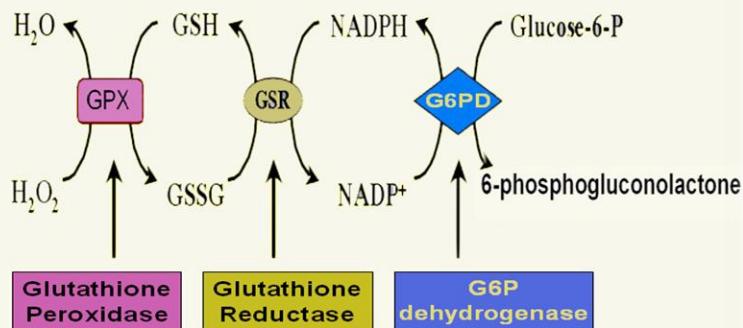
- HMP Shunt is inactive because G6P Dehydrogenase and 6-P Gluconate dehydrogenase are deficient.
- Ribose 5 P synthesized in the way of reverse the non-oxidative pathway of HMP Shunt using fructose 6-P, glyceraldehydes 3-P(produced by glycolysis) and transketolase and transaldolase enzymes.

• Function (Biochemical importance) of the HMP Pathway:

- 1) To supply ribose 5-phosphate for biosynthesis of:
 - A. Nucleic acid DNA, RNA.
 - B. Nucleotide ATP, GTP, UTP and CTP.
 - C. Coenzymes NAD, FAD, CoASH.
- 2) To supply NADPH as hydrogen donor in:
 - A. Cholesterol and steroids synthesis.
 - B. Sphingosine and glycolipids synthesis.
 - C. Keep iron of Hb in reduced state.
 - D. Keep glutathione in reduced state.
 - E. Coenzyme for: Glutathione reductase, hydroxylase and NADPH oxidase.

A. Glutathione reductase:

Glutathione reductase and glutathione peroxidase are important for removal of H₂O₂. H₂O₂ is a powerful oxidant that produces damage of cellular DNA, proteins and phospholipids.

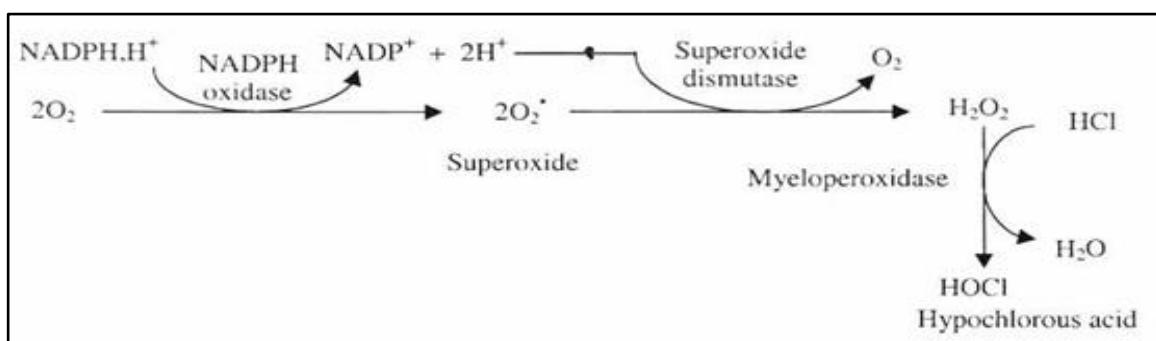


B. Hydroxylases for example:

- 1 -Hydroxylases of steroid synthesis.
- 2 -Phenylalanine hydroxylase.

C. NADPH Oxidase

- ❖ It is present in cell membranes of phagocytic cells, and is responsible for generation of superoxide.
- ❖ Superoxide is converted to H₂O₂ (by superoxide dismutase), which is converted to hypochlorous acid (by myeloperoxidase) that kills the bacteria.
- ❖ Genetic deficiency of NADPH oxidase produces chronic granulomatosis, this disease is characterized by severe and persistent chronic pyogenic infections.



Clinical Importance of HMP pathway (G6PD) deficiency:

It is an inherited disease characterized by hemolytic anemia caused by inability to detoxify oxidized agents. This deficiency affects more than 200 million individual worldwide.

Precipitating factors in G6PD deficiency

Most individuals who have inherited one of many G6PD mutations do not show clinical manifestations. However, some patients develop hemolytic anemia if they are exposed to the following precipitating factors:

- 1) **Oxidant drugs:** Antibiotics (sulfa-methoxazole and chloramphenicol), antimalarials, antipyretics (acetanilide but not acetaminophen).
- 2) **Favism:** Mediterranean forms of G6PD are susceptible to the haemolytic effects of fava bean which contain oxidizing agent (divicine).
- 3) **Infection:** It is the most common precipitating factors of haemeolysis in G6PD deficiency due to generation of more ROS.

Mechanism of haemolysis:

- ❖ G6PD deficiency will lead to decrease in NADPH concentration resulting in deficiency in reduced glutathione, so, ROS accumulate and oxidize the polyunsaturated fatty acids present in the cell membrane phospholipids of RBCs leading to haemolysis.
- ❖ Also, accumulation of H₂O₂ increased rates of oxidation of hemoglobin to methemoglobin.

Diagnosis of G6PD deficiency:

For patient who develops anaemia, jaundice and symptoms of haemolysis, the following tests must be done:

- 1-Complete blood count and reticulocyte count.
- 2-Liver enzymes (to exclude other causes of jaundice).
- 3-Haptoglobin (decreased in haemolysis).
- 4-Direct antiglobulin test “coomb’s test” – should be negative – as haemolysis in G6PD is not immune mediated.
- 5- Estimation of G6PD activity.

The electron transport chain (ETC)

The electron transport chain (ETC) converts the electrons stored as reduced intermediates NADH and FADH₂ into a proton motive force (PMF) across the inner mitochondrial membrane.

Complexes of electron transport chain:

The electron transport chain are organized in 4 complexes; Complex I, Complex II, Complex III, and Complex IV.

Structure of complexes: enzyme and hydrogen or electron carrier.

Complex I:

- ❖ It contains NADH dehydrogenase enzyme, FMN as hydrogen carriers, and iron-sulfur center.
- ❖ It takes 2 hydrogen atoms (2 e and 2 H⁺) from NADH+H⁺, which is then pass to FMN, and lastly the two electrons pass to iron-sulfur center and then to coenzyme Q.

Complex II:

- ❖ It contains FAD, succinate dehydrogenase and iron –sulfur center. Succinate dehydrogenase is the only enzyme of Krebs cycle that is attached to the inner mitochondrial membrane.
- ❖ Electrons move from succinate to FAD, then to iron-sulfur center and finally to coenzyme Q to produce coenzyme QH₂.

Coenzyme Q:

- ❖ It is a lipophilic and mobile electron carriers. It receives electrons from both complex I and complex II. So, link these complexes with cytochrome c₁ of complex III.

Complex III:

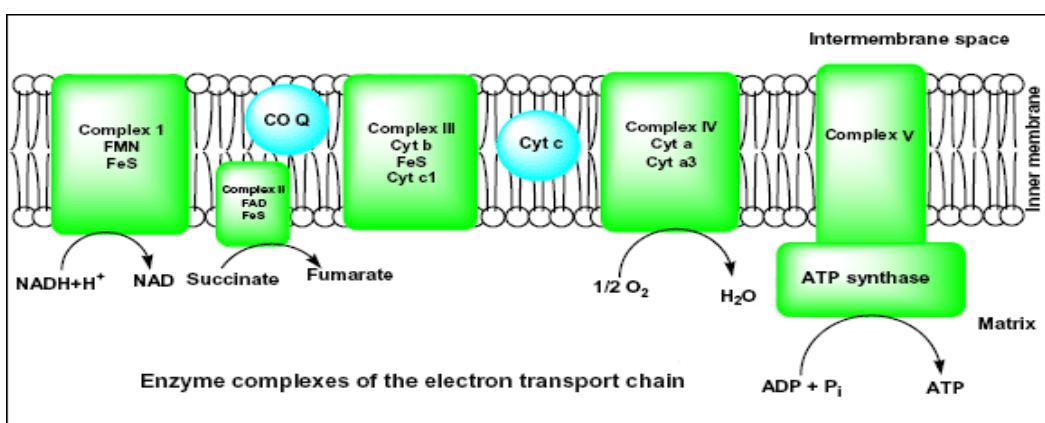
- It contains cytochrome b and cytochrome c₁. The iron of heme is in ferric state.
- Iron acts as electron acceptor and donor by changing its valency. Electrons of cytochrome c₁ are transferred to cytochrome c.

Cytochrome C:

- Is a mobile electron carrier that diffuses through the inner mitochondrial membrane shuttling electrons from c₁ of complex III to Cu_A of complex IV.

Complex IV:

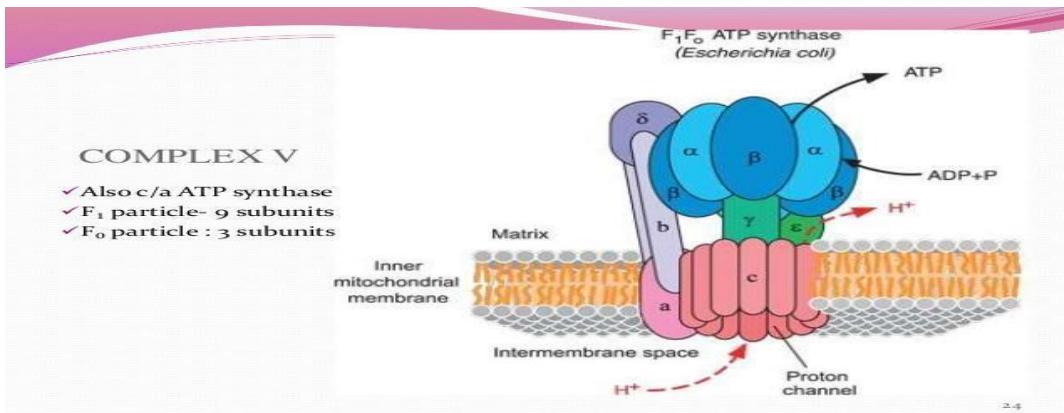
- It contains cytochrome a and cytochrome a₃. It contains copper proteins.
- Electrons are passed from cytochrome c to cytochrome a, a₃ and finally to O₂. Complex IV reacts directly with oxygen, so called cytochrome oxidase.
- At complex IV, the electrons, O₂ and protons are brought together and H₂O is formed.



- Three of the four complexes are also proton pumps: for each pair of electrons, complex I extrudes 4H⁺ from the matrix; complex III, 4H⁺; and complex IV, 2H⁺. Complex II does not pump protons when it transfers electrons from FADH₂ to coenzyme Q.
 - Thus, for each NADH oxidized, 10H⁺ are extruded; and, for each FADH₂, 6H⁺
 - The ultimate electron acceptor is molecular oxygen, which is reduced to water.

Complex V:

- It is the site of biosynthesis of ATP.



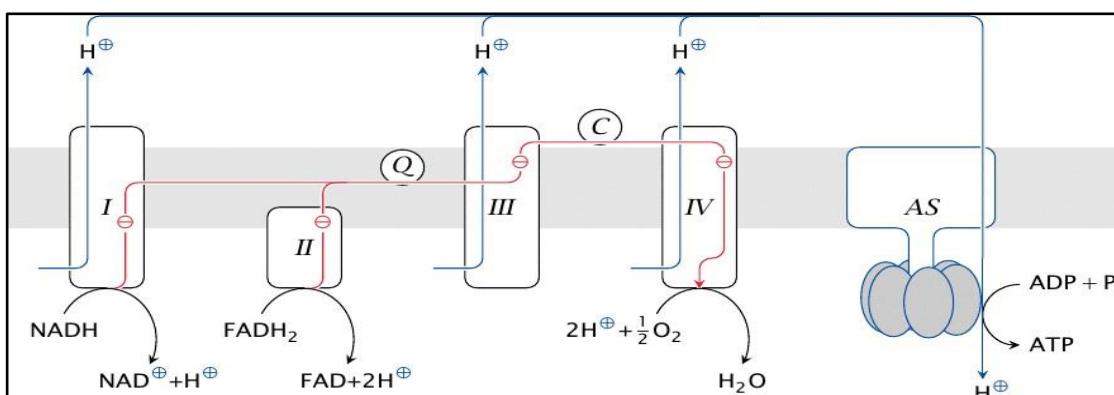
- It contains two subunits, F₀ which span the inner mitochondrial membrane and F₁ which protrude into the mitochondrial matrix. ATP synthase enzyme is a part of this complex.

ATP synthesis: The Chemiosmotic Theory

- Chemiosmotic hypothesis explains how the free energy generated by the transport of electrons by ETC is used to produce energy.

Proton pump:

- Transfer of electrons from one complex to another complex (oxidation) is accompanied by liberation of energy which is used to pump proton from mitochondrial matrix to the inter membrane space.
- Complex I, Complex III, and Complex IV acts as proton pump.



Source of NADH+H⁺ and FADH₂ to ETC:

- The main sources are β -oxidation of fatty acid and Krebs cycle, both occur in mitochondrial matrix adjacent to ETC in the inner mitochondrial membrane.
- **NADH+H⁺** is also formed in the cytoplasm e.g. in glycolysis.
- There is no direct pathway for NADH to cross the inner mitochondrial membrane to enter the ETC.
- NADH can effectively cross the membrane by means of the malate/ aspartate shuttle.
- When cytoplasmic NADH is low, the glycerol-3-phosphate shuttle may be used. Electrons enter the ETC at the level of FADH₂ and so get less ATP per original NADH than with the malate/aspartate shuttle.

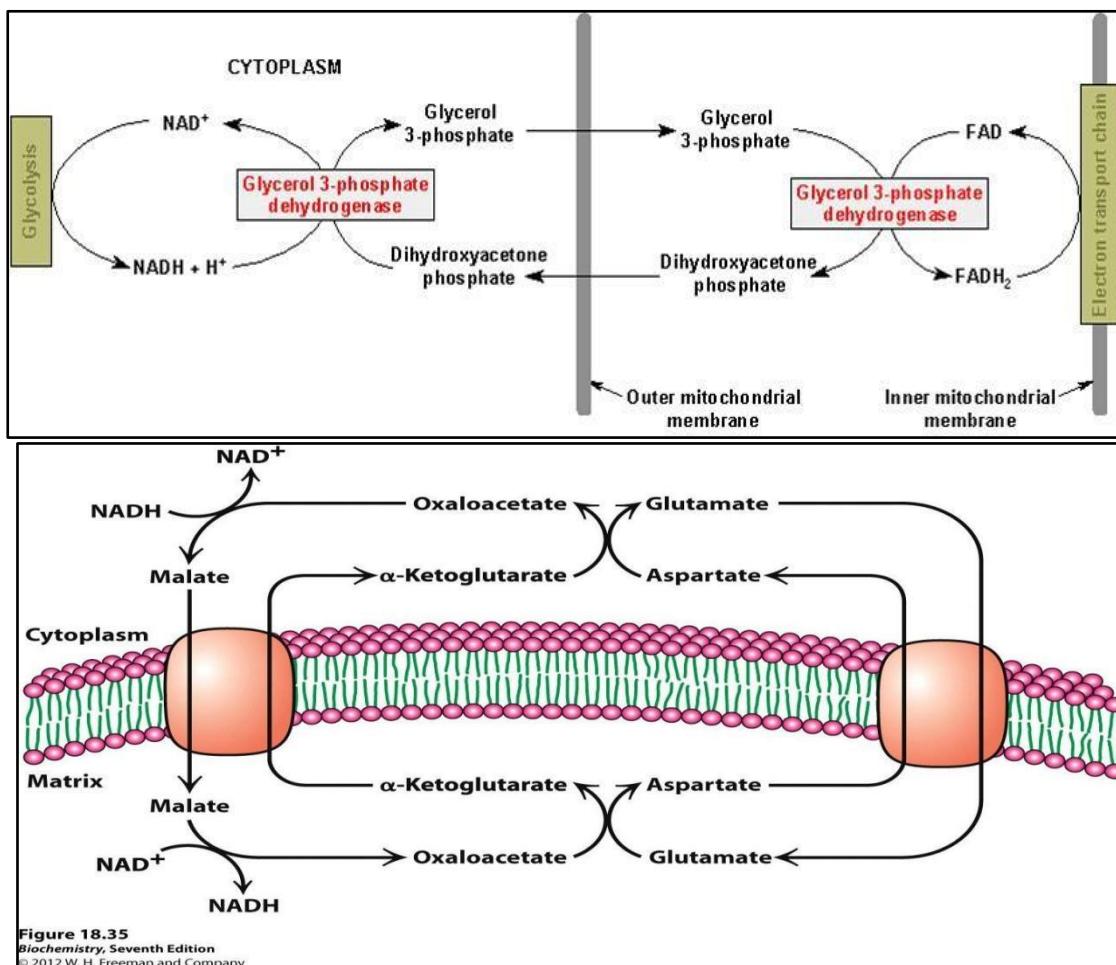


Figure 18.35
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Oxidative-phosphorylation coupling:

- The energy released from oxidation is used to pump protons which accumulate in the inter membrane space creating electrochemical gradient outside the mitochondria.
- The electrochemical gradient drive the protons to reenter the matrix by passing through a proton channel in the F0 driving rotation of F0 and conformational change in F1 and binding of ADP to P to form ATP (phosphorylation).

N.B: For each NADH oxidized, 10H⁺ are extruded; and, for each FADH₂, 6H⁺. Each ATP formed uses four protons. Hence 1 NADH = 2.5 \approx 3 ATP, 1 FADH₂ = 1.5 \approx 2 ATP.

Respiratory control:

- A. Electrons cannot-flow through the ETC unless ADP is simultaneously phosphorylated to ATP.
- B. The most significant controlling factor for electron flow is the availability of ADP for conversion to ATP.

Uncoupler: Is a molecule that disrupts oxidative phosphorylation, prevent coupling between electron transport and phosphorylation reactions.

Thermogenin (uncoupling protein UCP):

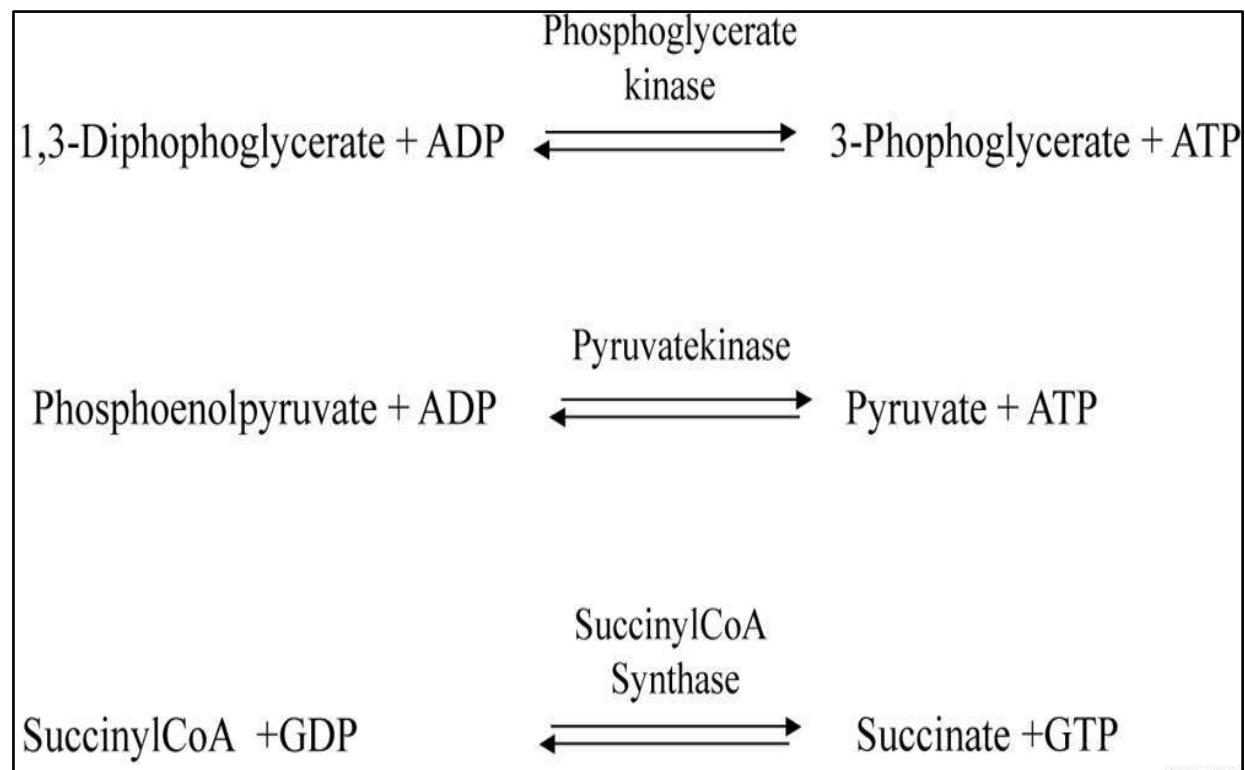
- Physiological uncoupler found in brown adipose tissue that function to generate heat.
- There are different types of UCP: UCP1, UCP2, UCP3, UCP4, and UCP5.
- Green tea polyphenols and UCP: Green tea polyphenols have anti- obesity effects by increasing the expression of UCP2 which enhance thermogenesis.

Oxidative Phosphorylation Inhibitors:

Electron transport inhibitors	*Directly inhibit electron transport, so block ATP synthesis.	Rotenone: complex I inhibitor. Malonate: Competitive inhibitors of succinate dehydrogenase (complex II). Antimycin A: complex III inhibitor. Cyanide, carbon monoxide, azide inhibit complex IV.
ATP synthae inhibits	*Directly inhibit mitochondrial ATP synthase, by blocking the flow of protons through the Fo subunit causing an increase of proton gradient. No ATP is produced because electron transport stops.	Oligomycin
Uncoupling agents	*Increase permeability of membrane, causing a decrease of proton gradient. ATP synthesis stops, but electron transport continues. It allows oxidation to occurs but prevents phosphorylation (ATP formation). The energy is produced in the form of heat giving the sensation of hotness .	2,4-Dinitrophenol (used for weight loss), Aspirin (overdose). Thyroxine in large doses. thermogenin in brown fat (has more mitochondria than white fat).

Levels for ATP production:

1-Substrate levels phosphorylation: The energy which is used for biosynthesis of ATP is derived from substrates containing high energy bonds. There are 3 examples for substrate level phosphorylation:



2-Oxidative phosphorylation: The energy used for formation of ATP is derived from oxidation. This occurs in electron transport chain.

Lipids digestion

- ❖ Triacylglycerol (Glycerol + 3 fatty acid).
- ❖ Cholesterol.
- ❖ Phospholipids.
- ❖ Trans fatty acids.
- ❖ More than 90% of the average daily intake of lipids is normally triacylglycerol (TAG).
- ❖ The remainder of the dietary lipids consists primarily of cholesterol, cholesteroyl esters, phospholipids, and unesterified (free) fatty acid.
- ❖ **Digestion of lipids:**

A. Processing of dietary lipid in the stomach:

The digestion of lipids begins in the stomach, catalyzed by:

Lingual lipase and gastric lipase:

- They act on TAG molecules, particularly those containing fatty acids of short- or medium-chain length (less than 12 carbons, such as milk fat).
- Gastric lipase has a special importance in digestion of milk fats in babies where pH is near neutral.

B. Intestinal phase of lipid digestion:

Emulsification of dietary lipid by

- (1) Bile salts.
- (2) Mechanical mixing due to peristalsis. Emulsification increases the surface area of the hydrophobic lipid droplets for the digestive enzymes to act effectively.

Pancreatic enzymes:

- **Pancreatic lipase** removes the fatty acids at carbons 1 and 3 of TAG.
- **Co-lipase** helps attachment of lipase enzyme to its substrate.
- **Cholesterol esterase**: It hydrolyzes cholesterol ester to cholesterol+FFA.

Phospholipase A2

- It removes one fatty acid from carbon 2 of a phospholipid producing lysophospholipids.
- The remaining fatty acid at carbon 1 can be removed by **lysophospholipase** leaving a glycerylphosphoryl base that may be excreted in the feces, further degraded, or absorbed.

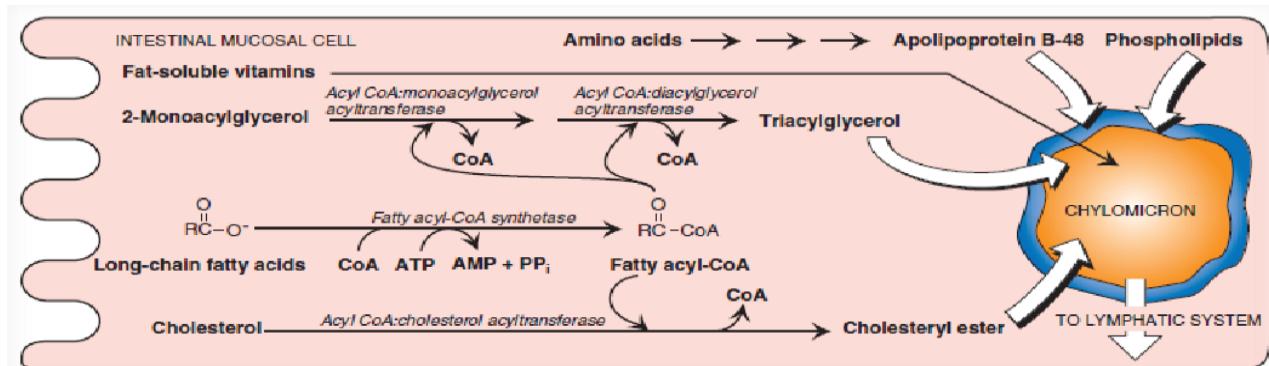
Control of lipid digestion:

Secretion of pancreatic enzymes is hormonally controlled by:

- Cholecystokinin (CCK) produced by duodenum and jejunum mucosa. It stimulates bile release.
- Secretin hormone stimulates the pancreas and the liver to release a solution rich in bicarbonate to neutralize the pH of the gastric contents.

Absorption of Lipids:

1. Short- and medium chain length fatty acids are taken up by enterocytes without the assistance of mixed micelles and released into the portal circulation, where they are carried by serum albumin to the liver.
2. Free fatty acids, free cholesterol, 2-monoacylglycerol, lysophospholipid, bile salts and fat-soluble vitamins (A, D, E, and K), form mixed micelles that facilitate the transport of the hydrophobic lipids through the enterocytes membrane. In the enterocytes, phospholipids, TAG and cholesteryl esters are reformed and secreted into the lymphatic vessels in form of chylomicrons.
3. Because of its large size, chylomicrons pass to the lymphatic system, thoracic duct, superior vena cava, heart, and systemic circulation causing **post-prandial turbidity**. The post-prandial turbidity is cleared by lipoprotein lipase enzyme.



Lipoprotein lipase:

- Secreted from vascular endothelium.
- Released by heparin and activated by insulin and apo C_{II}.
- It acts on triacylglycerol present in chylomicrons into glycerol and fatty acids.
- Lipoprotein lipase is called **clearing factor**.

Inhibitors of fat digestion and absorption:

They act through inhibition of lipase or bile salts e.g.

- 1.Orlistat (lipase inhibitor).
- 2.Green tea extract.
- 3.Grape seed extract inhibits lipase.
- 4.Pectins prevent fat absorption.

Digestion of Proteins

It means breakdown of proteins to amino acids.

1.In mouth: No digestion

2.In stomach:

HCl:

- ❖ Secreted by Parietal cells. Make the pH of stomach highly acidic, so activates pepsinogen.

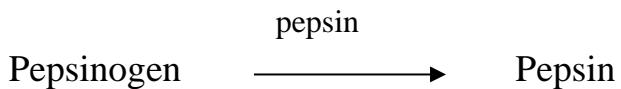


Pepsin:

- Secreted by chief cells.
- PH:1-2 highly acidic.
- Secreted inactive "pepsinogen".

- Activation:





- Pepsin is endopeptidase acting on the peptide linkage in the middle of the polypeptide chain especially between aromatic amino acids "phenylalanine & tyrosine".
- **End Product:** Protein □ Proteoses □ Peptone □ Polypeptide.

Rennin:

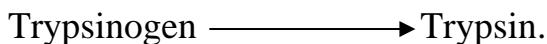
- ❖ Secreted by parietal cells.
 - ❖ pH: 4 so acts in infant because the pH is suitable for its action.
 - ❖ Secreted as pro-rennin which is activated by Ca^{++} into rennin.
 - Rennin acts on casein of milk.
- Casein $\xrightarrow{\text{Rennin}}$ paracasein $\longrightarrow \text{Ca}^{++}$ paracaseinate
- ❖ Ca^{++} paracaseinate is called milk clot. The digestion of Ca^{++} par caseinate is completed by pepsin.
 - ❖ The Formation of **milk clot** is important to prevent rapid passage of milk from the stomach.

1-Pancreatic phase:

The pancreas secretes 4 enzymes to digest proteins: (trypsin- chemotrypsin - carboxypeptidases - Elastase).

Trypsin:

- ❖ pH: 8
- ❖ Secreted as inactive :Trypsinogen



- ❖ Trypsin is endopeptidase acting on peptide linkage between basic amino acids (arginine & lysine).

- ❖ End product: proteins □ proteoses □ peptones □ polypeptide.
- ❖ Trypsin acts as activator for chymotrypsinogen and procarboxypeptidase.

Chymotrypsin:

- ❖ PH: 8
- ❖ Secreted as chymotrypsinogen which is converted into chymotrypsin by help of trypsin.
- ❖ Chymotrypsin is an endopeptidase, acting on peptide linkage between aromatic amino acids.

Elastase:

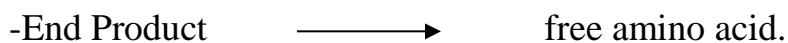
- ❖ Secreted as proelastase.



- ❖ Endopeptidase acting on peptide bonds of small uncharged amino acids e.g .alanine, glycine
- End products \longrightarrow small peptide

Carboxypeptidase:

- ❖ Secreted as procarboxypeptidase.
- ❖ Procarboxypeptidase is activated by trypsin.
- ❖ Exopeptidase acting on peptide linkage on the periphery, it needs free COOH.



2. Intestine:

Three enzymes are secreted by small intestine for digestion of proteins.

Aminopeptidase:

- ❖ Exopeptidase acting on peptide linkage at the free NH₂ of the Polypeptide chain.
- End Product \longrightarrow free amino acid.

Tripeptidase and Dipeptidase:

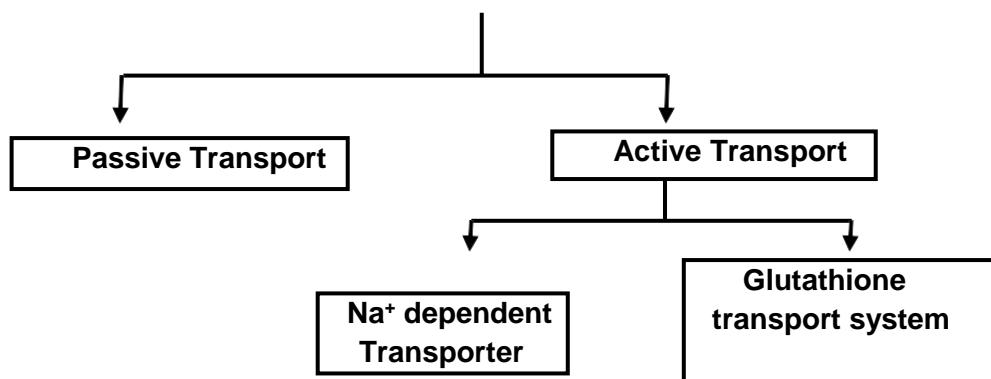
- ❖ They act on tri and dipeptide hydrolyzing it into free amino acid.

N.B: Pepsin, trypsin, chymotrypsin and elastase are endopeptidases.

Carboxypeptidase and aminopeptidase are exopeptidase.

Carboxypeptidase:

- ❖ Secreted as procarboxypeptidase
- ❖ Procarboxypeptidase is activated by trypsin.
- ❖ Exopeptidase acting on peptide linkage on the periphery, it needs free COOH.
- ❖ End Product → free amino acid.

Absorption of Amino Acids

Site of absorption: Jejunum, ileum.

Route of absorption: Portal circulation

Mechanisms of absorption:**1. Passive transport system:**

- Does not need energy.
- Occurs for D-amino Acids.

2- Active transport system:

- Needs energy.
- For absorption of L-amino acids.
- There are **two mechanisms** for active transport system:

A – Na^+ dependent transporters:

- There are specific carriers
- Each carrier has two sites, one for amino acid, the second is for Na^+ .
- Needs energy and vitamin B6.

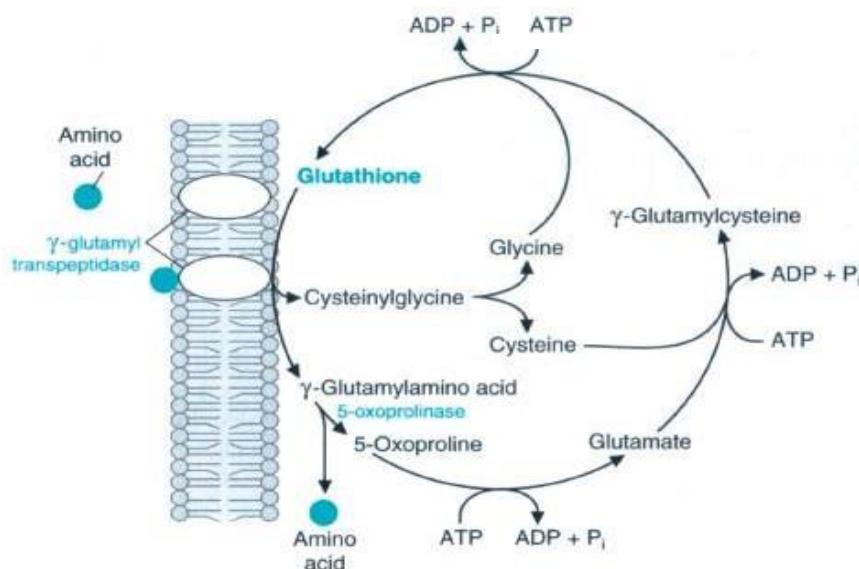
There are 7 carriers for absorption of Amino Acids:

- 1- For small neutral amino acids e.g .alanine.
- 2- for large neutral amino acids e.g. valine.
- 3- For acidic amino acids e.g. aspartic acid.
- 4- For basic amino acids e.g. aragine.
- 5- For imino acid e.g. proline.

B- Glutathione transport system γ . Glutamyl cycle

- ❖ This mechanism is rapid but needs more energy.
- ❖ The enzyme γ . Glutamyl tranpeptidase is located in cell membrane, shuttles glutathione to the cell surface.

γ . Glutamyl Cycle



Defects in Digestion and Absorption

1. Intestinal absorption of proteins:

- ❖ This occurs in newly born infant: Immunoglobulin of milk are absorbed without digestion to provide immunity to infant.
- ❖ Adult: Absorption of proteins in adult lead to food allergy.

2. Celiac Sprue:

- ❖ Gluten "protein of wheat" is digested to large peptide rich in glutamine, these peptides are toxic to intestine fatty diarrhea. This disease is treated by gluten free diet.

Plasma Amino Acids

In post - absorptive state, plasma amino acids level is 4-6 mg/dl, but after protein diet 8 mg/dl.

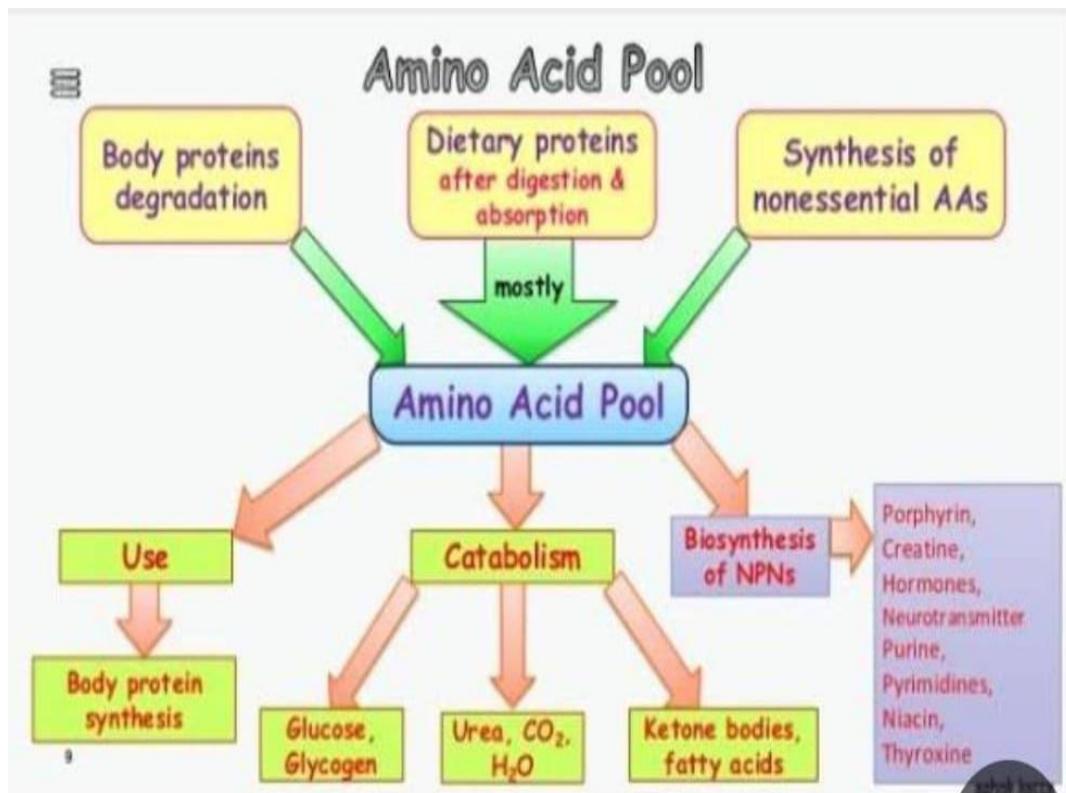
Sources of amino acids pool in the body

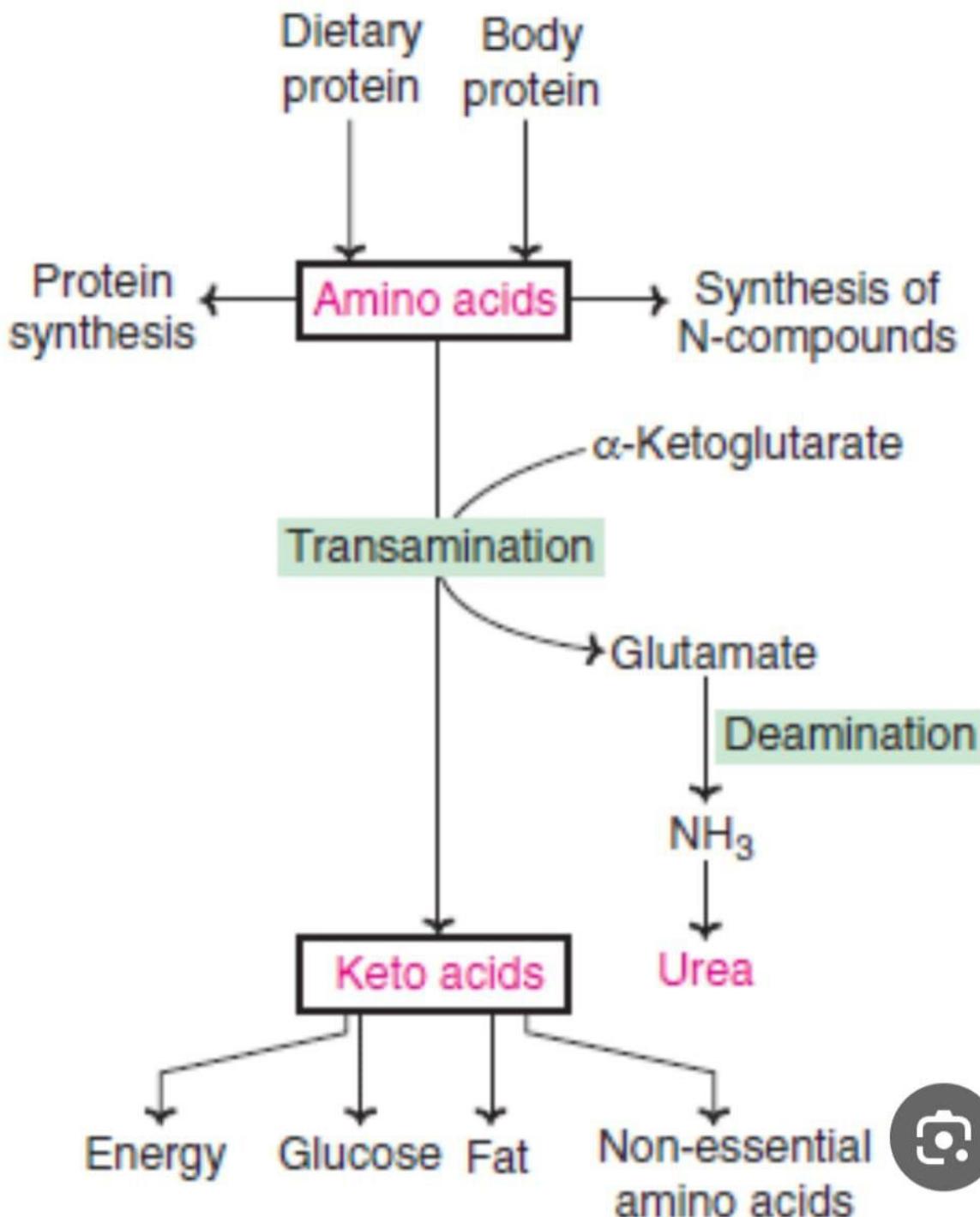
1. Exogenous from diet.
2. Catabolism of tissues protein.
3. Endogenous "biosynthesis of non essential amino acids".

Fate of Absorbed Amino Acids

1- Anabolic pathway

2- Catabolic pathway





Overall Nitrogen Metabolism

I- Nitrogen intake:

- ❖ Protein is the major source for utilizable nitrogen. Each 100 gm proteins of diet contain 16 gm nitrogen. The average daily intake of protein is 90 gm provide the body with 14.5 gm nitrogen.
- ❖ Other minor sources: Phospholipids, nucleic acid, inorganic nitrite and nitrate.

II – Nitrogen output:

It is the nitrogen excreted from the body. It results from protein catabolism.

❖ Routes for nitrogen output :

1.Urine:

Urine is the major route for nitrogen excretion in the form of non protein nitrogenous substances (NPN) e.g.

- Urea: 20-40 gm/ day.
- Uric acid: 0.7 gm/day.
- Ammonia: 0.7 gm/ day.
- Hippuric acid: 0.7 gm /day.
- Creatinine: 1gm/day ♀, 1.5 gm/day ♂.

2.Stool: 1gm/ day. Nitrogen excreted in stool include nitrogen of undigested protein, mucin, digestive enzymes.

3.Sweat → 0.3 gm/day

In sweat nitrogen is excreted in the form of urea.

4.Other routes → milk, hair, menstruation and nails.

Nitrogen balance:

Definition:

It is the balance between nitrogen intake and nitrogen output. It represents the balance between protein anabolism and protein catabolism.

There are 3 states of nitrogen balance:

- A. Nitrogen equilibrium.
- B. Positive nitrogen balance.
- C. Negative nitrogen balance.

Nitrogen Equilibrium:

- Nitrogen intake is equal to nitrogen output.
- This occurs in healthy adult on an adequate diet.

Positive Nitrogen balance:

- Nitrogen intake exceeds nitrogen output.
- It is a state of anabolism
- It occurs in → pregnancy, during growth, muscular training, and convalescence from disease.

Negative nitrogen balance:

- Nitrogen output exceeds nitrogen intake
- It is a state of catabolism "weight loss".

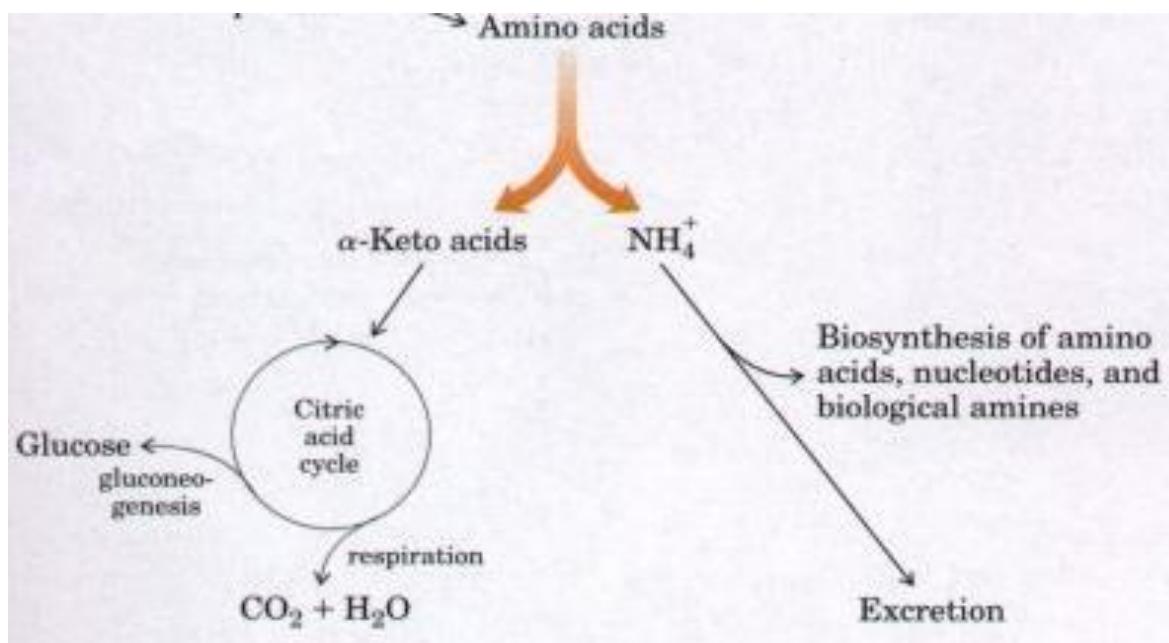
It occurs in:

Catabolic diseases: diabetes mellitus, thyrotoxicosis, cancer, Cushing syndrome, fevers, and infectious diseases.

Inadequate intake of proteins: malnutrition, starvation, and malabsorption.

Loss of proteins: albuminuria, haemorrhage, burns, lactation on an inadequate diet.

Catabolic Pathways of Amino Acids



Deamination

It means removal of amino group NH_2 from amino acid in the form of NH_3

Methods of deamination:

I- General methods:

- ❖ Oxidative deamination.
- ❖ Transamination.
- ❖ Trans deamination.

II- Specific methods for deamination

General method for deamination:

1- Oxidative Deamination

Definition: The removal of amino group is accompanied by oxidation.

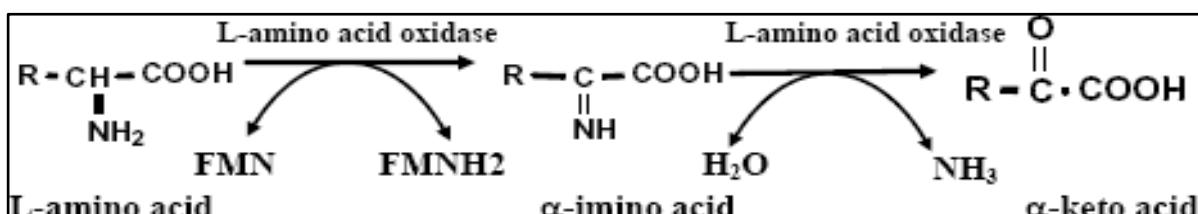
Site: liver, kidney.

There are 3 enzymes concerned with oxidative deamination:

- ❖ L-amino acid oxidase.
 - ❖ D-amino acid oxidase.
 - ❖ L-glutamate dehydrogenase.

A- L-amino acid oxidase:

- ❖ Acts on L-amino acids except glutamic acid.
 - ❖ Not widely distributed in the body.



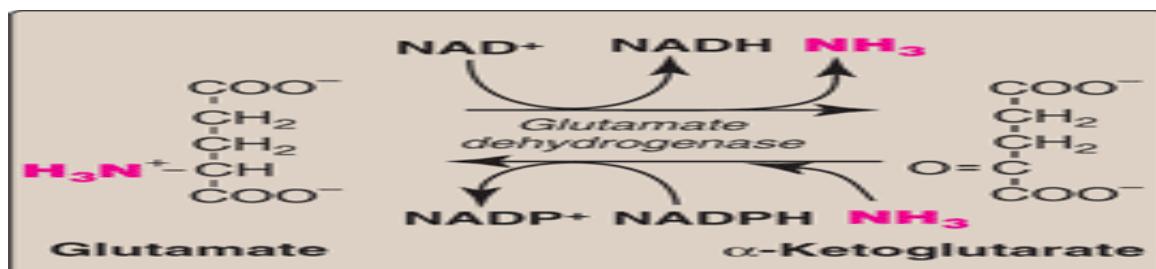
- ❖ Needs FMN as a coenzyme.

B- D- amino acid oxidase

- ❖ Acts on D-amino Acids.
 - ❖ Needs FAD as coenzymes.
 - ❖ Present in animals and bacteria.

C-L-glutamate dehydrogenase

- ❖ Acts on glutamic acid.
 - ❖ Highly active inside the body.
 - ❖ Needs NAD as coenzymes.



2-Transamination:

Definition: it is the transfer of an amino group from α -amino acid to an α - keto acid forming a new amino acid and a new keto acid.

Site: liver, Muscle, heart (Mitochondria, cytoplasm).

All amino acids except lysine, threonine, proline and hydroxyproline may undergo transamination.

Reactions of transamination are reversible.

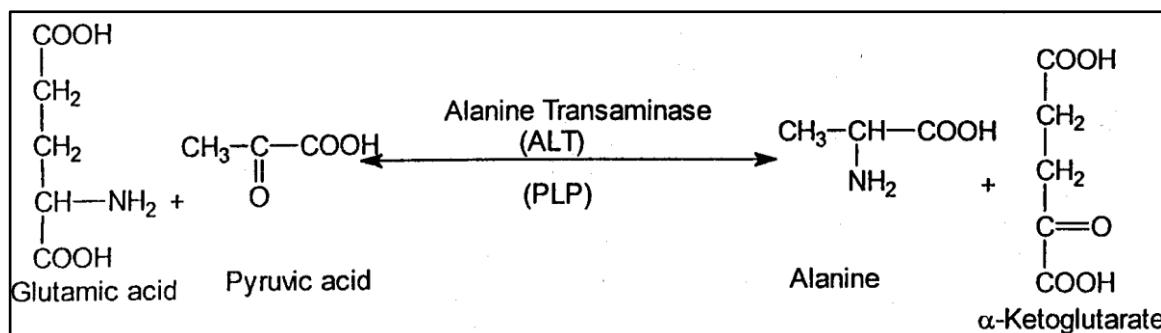
Enzymes: Transaminases.

Coenzymes: vitamin B₆ (PLP).

The biosynthesis of transaminases is induced by glucocorticoids, thyroxine, growth hormone but inhibited by insulin.

Importance: Biosynthesis of non-essential amino acids.

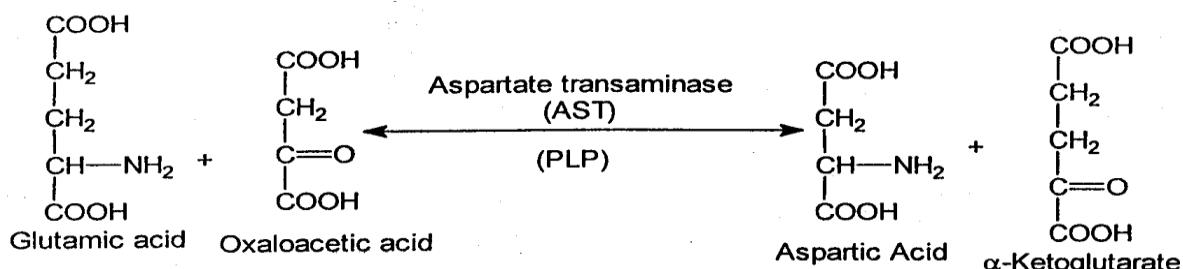
1.Glutamate Pyruvate Transaminase GPT



This enzyme is called Alanine aminotransferase (ALT).

2.Glutamate Oxaloacetate Transaminase GOT

It is called aspartate aminotransferase (AST)



Clinical importance of GOT and GPT:

GOT (AST) → increase in cases of myocardial infarction and liver disease.

GPT (ALT) → increase in liver disease.

3-Transdeamination:

Definition:

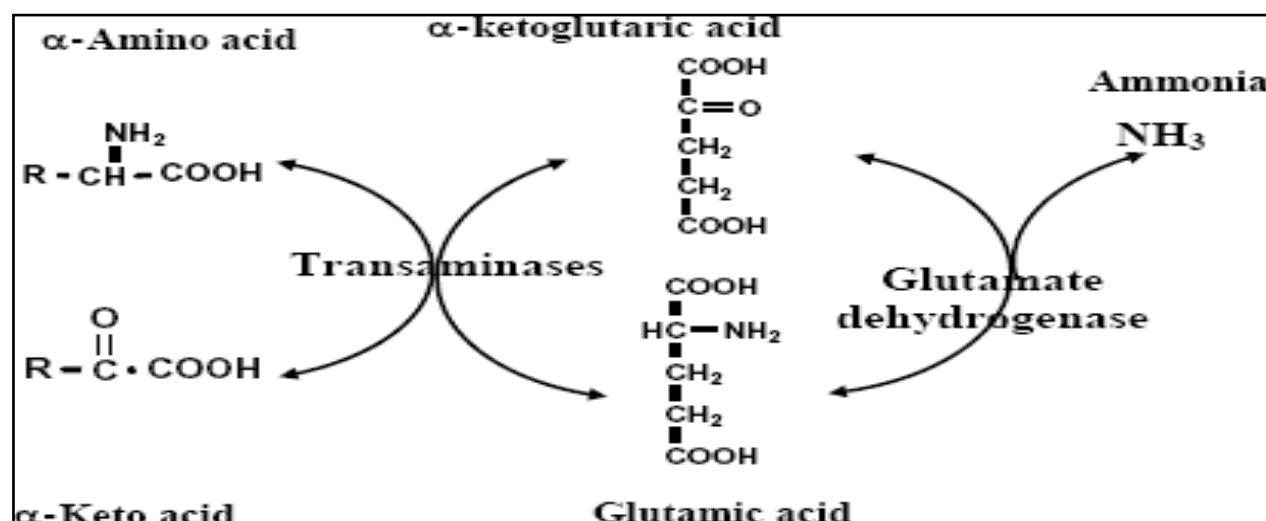
It is a combination of transamination and oxidative deamination. Transamination does not lead to removal of NH₃, L-amino acid oxidase is of low activity, while L-glutamate dehydrogenase which is highly active acts only on L-glutamate. So transdeamination is the only mechanism for deamination of amino acids.

Mechanism:

Amino acid is firstly transaminated with α- Ketoglutaric acid to form glutamic acid which is acted upon by L-glutamate dehydrogenase to release NH₃.

Importance:

This system is widely distributed and highly active. L-glutamate dehydrogenase is responsible indirectly for deamination of all amino acids.



Fate of end product of deamination:

- 1-Fate of NH₃
- 2- Fate of carbon skeleton

Metabolism of Ammonia

Sources of Ammonia:

- Deamination of Amino Acids.
- Ammonia is produced from bacterial action on proteins of diet in GIT.
- Catabolism of purine and pyrimidine bases.

Blood Ammonia:

- 10-20 µgm/dl.
- Ammonia is highly toxic substance because it is highly diffusible substance.

Transport of ammonia in blood

- There are two mechanisms for transport of NH₃ from peripheral tissues to the liver. The first found in most tissue is glutamine pathway, in which NH₃ combines with glutamic acid to form glutamine.
- The second, used primarily by muscle, involves transamination of pyruvate to form alanine. Alanine is transported by the blood to the liver, where it is converted to pyruvate again by transamination.

Fate of Ammonia:

1-Anabolic pathway.

2- Catabolic pathway.

Anabolic pathway of Ammonia

1. Biosynthesis of purine bases and pyrimidine bases which are important for:

- Biosynthesis of RNA, DNA.
- Biosynthesis of coenzymes NAD, FAD, CoASH.
- Biosynthesis of biologically active nucleotides e.g ATP, CTP, UTP, 3',5' CAMP.

2.Biosynthesis of Amino sugars e.g glucosamine which are important for mucopolysaccharides formation.

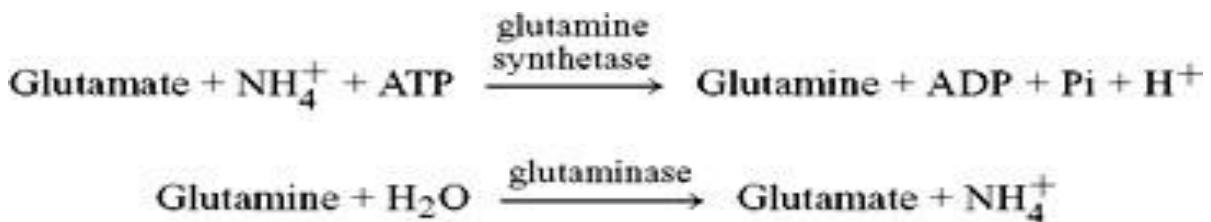
3.Biosynthesis of non essential amino acids.

Catabolic pathway of Ammonia

1- Direct excretion in urine

Ammonia resulting from deamination of amino acids in the kidney are directly excreted in urine, this accounts for about 40% of the urinary ammonia.

2-Glutamine pathway:



Ammonia resulting from deamination of amino acids in extra-renal tissues may form glutamine by glutamine synthetase enzyme which is a mitochondrial enzyme present in the kidney and brain.

In the brain: Glutamine formation is the major mechanism for removal of NH₃.

Glutamine is considered as a storage form of NH₃ inside the body.

In the Kidney: Glutamine by glutaminase is converted to NH₃ and glutamic acid.

NH₃ formed by this way accounts for 60% of urinary ammonia.

N.B: One of the most important roles of NH₃ is regulation of acid base balance.

Urea cycle

This is the main catabolic pathway for NH_3 .

Urea is the main end product of protein catabolism in human.

Site: Liver.

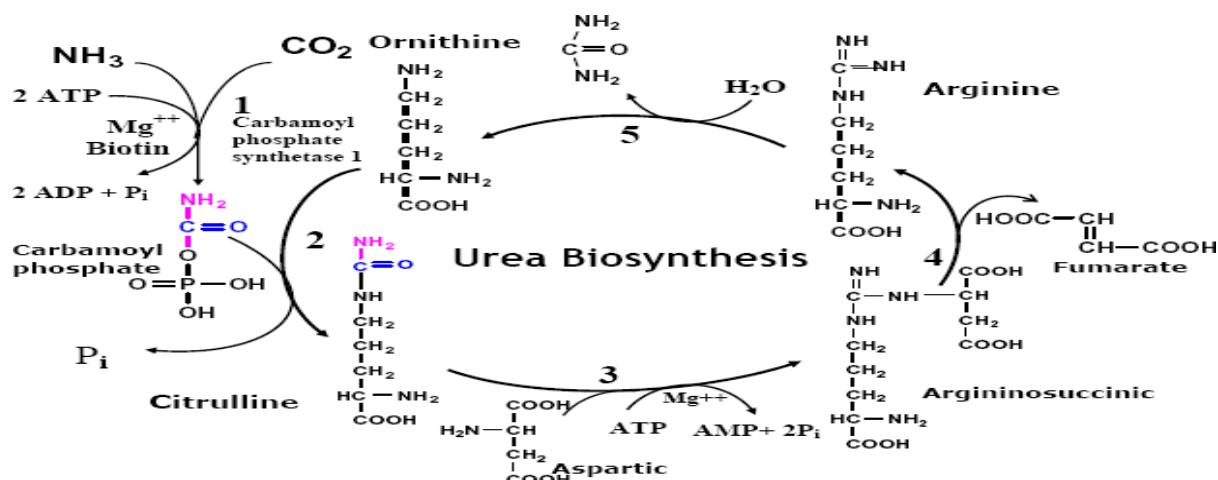
The first two reactions occur in mitochondria, while the subsequent reactions occur in cytoplasm.

Steps:

- This reaction is a good example for CO_2 fixation.
- It needs 2 ATP, one provides energy, the other provides phosphate.
- N-acetyl glutamate ↑ the affinity between carbamoyl phosphate synthetase I and ATP.

Characters of carbamoyl phosphate synthetase I:

- Present in mitochondria of the liver.
- Needs the presence of 2 ATP.
- Needs N-acetyl glutamate as activator.
- This reaction is irreversible.
- Takes NH_3 from deamination of amino acids.



Regulation of urea cycle:

- ❖ Carbamoyl phosphate synthetase-I and L-glutamate dehydrogenase enzyme are the key enzyme for regulation of urea cycle.
- ❖ NH₃ produced from glutamic acid and all other amino acids by L-glutamate dehydrogenase are used by carbamoyl phosphate synthetase-I to form urea.
- ❖ So any factor stimulates L-glutamate dehydrogenase will stimulate at the same time carbamoyl phosphate synthetase-I enzyme.

Urea: It is the main NPN (Non protein nitrogenous compound).

- Synthesized by the **liver** and excreted by the **kidney**.
- Blood urea → 20-40 mg/dl.
- Urinary urea → 20-40 gm/day.

Factors affecting the level of blood urea

1. Protein diet: ↑Protein diet→↑urea formation this is because proteins → Amino Acids → NH₃ → urea.

2. Liver: diseased liver → ↓urea formation→ ↓Blood urea → ↑ Blood NH₃.

3. Kidney: It is the organ which excrete urea so, in cases of renal failure→↑ Blood urea due to ↓ excretion.

High blood urea: Occurs in cases of:

- High protein diet.
- Renal failure.
- Obstruction of urinary tracts by stone.

Low blood urea: occurs in cases of

- Low protein diet.
- Liver disease e.g Bilharzial liver disease, viral hepatitis.

Relations between Kreb's cycle and urea cycle:

- CO₂ used in urea cycle is produced by kreb's cycle.
- ATP needed by urea cycle is produced by Kreb's cycle.
- Fumaric acid produced by urea cycle is oxidized via kreb's cycle.

Inborn errors (Metabolic disorders) of urea cycle

Causes: deficiency of one or more of the 5 enzymes concerned with urea cycle.

Result: NH₃ is not converted to urea → NH₃ intoxication.

Types:**Hyperammonemia type I:****Cause:**

- Due to deficiency of carbamoyl phosphate synthetase-I.
- This disease is manifested by lethargy, convulsions, coma, and death.

Hyper ammonemia type II:**Cause:**

- Due to deficiency of ornithine transcarbamoylase.
- Glutamine levels ↑ in blood due to ↑ levels of NH₃.

Citrullinemia:**Cause:**

- Due to deficiency of arginosuccinate synthetase.
- Excess citrulline is present in plasma, urine.

Argino succinic aciduria:**Cause:**

- Due to deficiency of arginosuccinase.
- Levels of arginosuccinic acid in plasma and urine are increased.

Hyperargininemia:**Cause:**

- Due to deficiency of arginase enzyme.
- Increased arginine levels in blood, urine and increased excretion of lysine and
- cystine in urine due to competition with arginine for renal reabsorption.

Hyperammonemia

The two major types of hyperammonemia are:

1. Acquired hyperammonaemia

- ❖ Liver diseases are the common cause. It includes:
 - Viral hepatitis.
 - Hepatotoxin.
 - Liver cirrhosis caused by alcoholism, hepatitis, and biliary obstruction may result in collateral circulation. So, portal blood is shunted directly to systemic circulation.

2. Hereditary hyperammonaemia:

- It is due to genetic deficiencies of each of the five enzymes of urea cycle with an overall prevalence 1:30,000 live birth.
- Ornithine transcarbamoylase deficiency is the most common of these disorders. Hyperammonaemia occurs during the first weeks following birth leading to mental retardation.

Biochemical bases of NH₃ intoxication:

NH₃ is toxic for many reasons:

1- Inhibition of energy production:

- NH₃ can interfere with energy metabolism through inhibition of Kreb's cycle. Excess blood NH₃ cross the blood brain barrier.
- The defensive mechanism in the brain against NH₃ is glutamic acid which is present in high concentration in the brain. NH₃ combines with glutamic acid converting it into glutamine.
- After that excess NH₃ combines with α-ketoglutaric acid of kreb's cycle converting it → glutamic acid → inhibition of kreb's cycle → ↓ ATP production in the brain.

2- Brain oedema:

- Excess NH₃ increases glutamine synthesis and accumulation resulting in astrocytes swelling and cerebral oedema.

Symptoms of NH₃ intoxication

- *Flapping tremors.
- * Slurring of speech.
- *Blurring of vision.
- * Disturbance in sleep.
- *Vomiting in infancy.
- * Coma in late cases.

Management of NH₃ Intoxication:

- ❖ The main strategies in treatment of NH₃ intoxication is to lower NH₃ production. This is done through **two** parallel lines:

1- Dietary management:

- ❖ Adequate protein intake is necessary to maintain an adequate nitrogen balance.
- ❖ Dietary supplementation with BCAA.
- ❖ Vegetable based protein is advised as it contain high fiber content which increases colonic motility and enhance intestinal NH₃ clearance. Also, vegetable proteins reduces colonic PH, which prevents NH₃ from being absorbed in gut.
- ❖ Administration of probiotics.

2- Drugs:

- ❖ Non-absorbable disaccharides such as **lactulose** and lactitol. They decrease NH₃ production by bacteria, render the NH₃ inabsorbable by converting it to NH₄, and increase transit of bowel content through the gut.
- ❖ **Antibiotic:**
 - ❖ Neomycin and Metronidozol inhibit NH₃ production by bacteria.
 - ❖ Rifaximin is a nonabsorbable antibiotic, more safer than neomycin. L-ornithine and L-aspartate (LOLA) convert NH₃ to urea.

Fate of Carbon skeleton of amino acids

1- Reamination

α - Keto acid + NH₃ → Non essential amino acids

2- Glucogenic Pathways

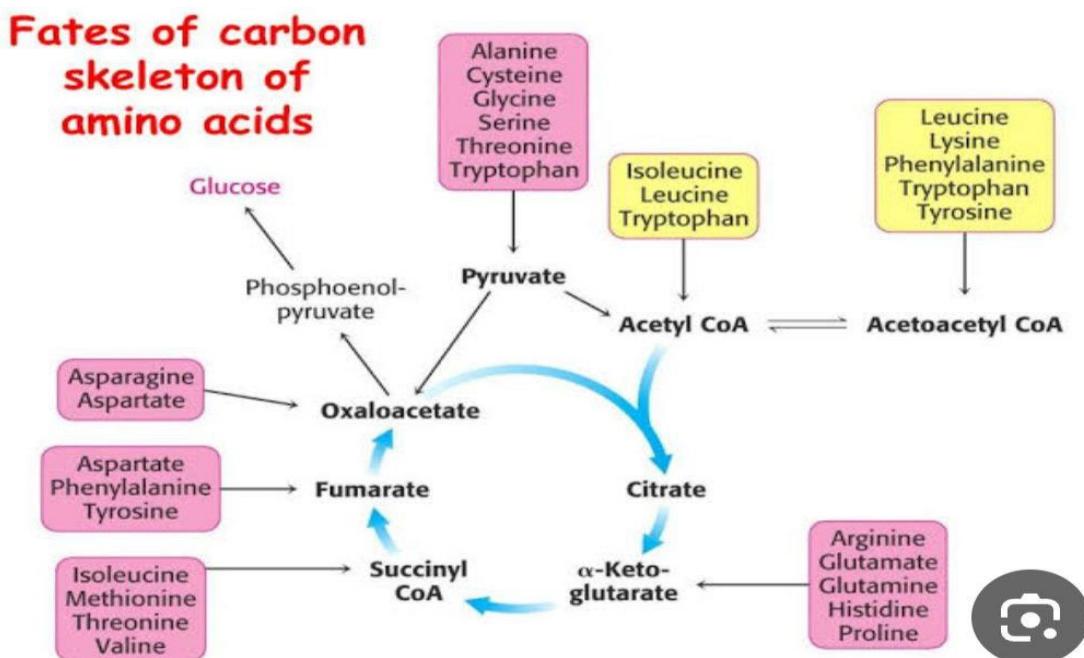
- Glucogenic amino acids give pyruvates or oxaloacetate, α -keto glutarate, succinyl CoA which can give glucose by gluconeogenesis.
- Glucogenic Amino Acids include all amino acids except leucine.

3- Ketogenic Amino acids " Ketogenic pathways"

- Ketogenic amino acid does not give pyruvate but it gives acetoacetyl CoA → ketone bodies.

4- Glucogenic and ketogenic pathways

Glucogenic and ketogenic amino acids give both glucose and ketone bodies.



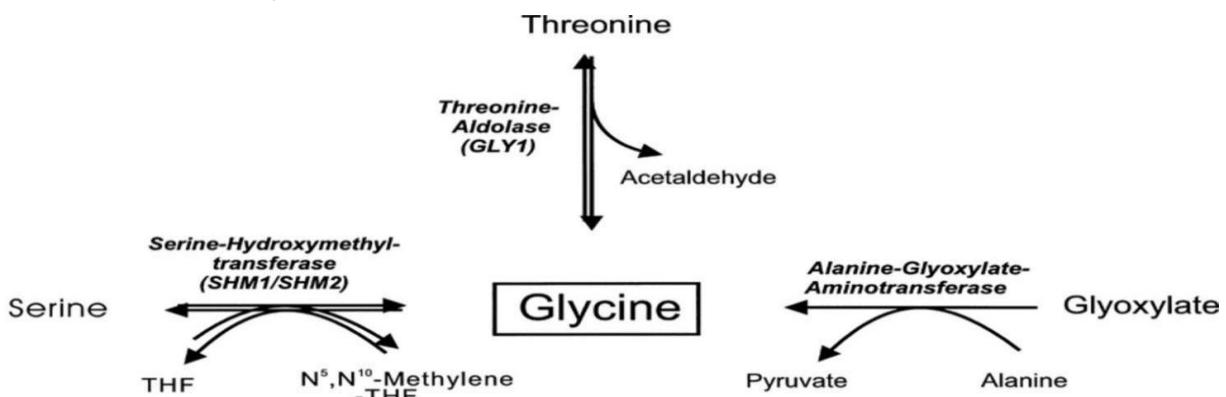
Metabolism of Amino Acids

Glycine Metabolism

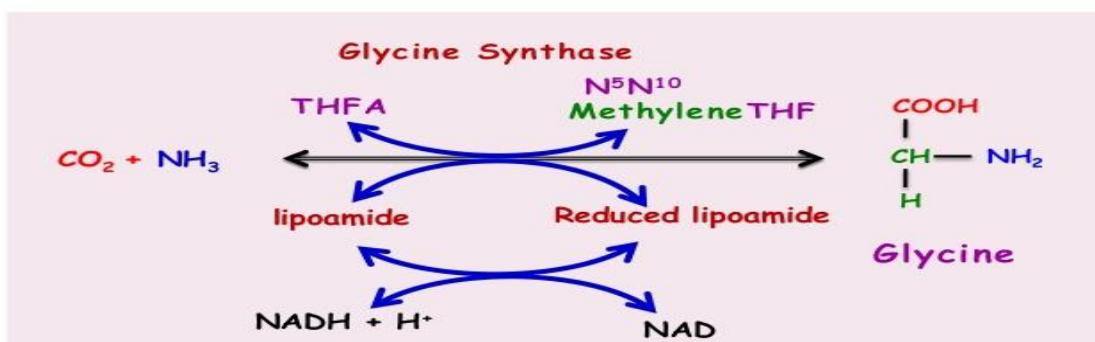
Glycine Biosynthesis

Glycine is not essential, as it is synthesized in the body from:

- 1- Serine, by serine hydroxy methyltransferase.
- 2- Threonine by threonine aldolase.



- 3-By glycine synthase enzyme .



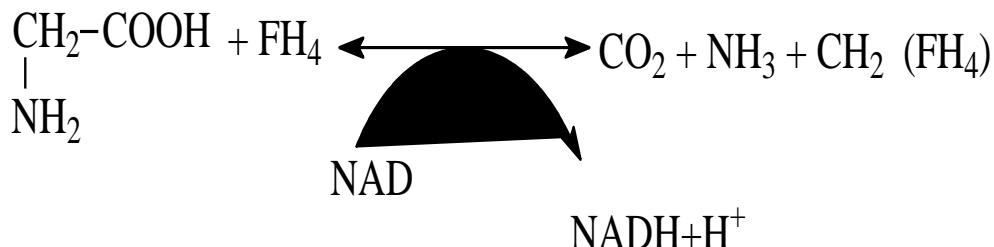
Importance of Glycine:

1. Formation of purine bases that enter in DNA and RNA structure.
2. Formation of bile salts.
3. Formation of creatine: formed from three amino acids glycine, arginine and methionine and in two organs liver and muscle.
4. Formation of other amino acids as serine (see serine biosynthesis).
6. Glycine itself acts as a neurochemical transmitter in spinal cord and medulla and exerts its action through the glycine receptor.

7. Glutathione formation (glutamic acid + cysteine + glycine).
8. Heme production: Glycine shares in the first step in heme synthesis
9. Collagen formation: glycine is one-third of amino acid content of the collagen.

Glycine catabolism :

1-By glycine cleavage system, glycine gives NH₃, CO₂, and CH₂.



2-Glycine oxidase.:Glyoxylic acid has produced and has two pathways:

- ❖ Re transamination back into glycine.
- ❖ Oxidative decarboxylation into formate .

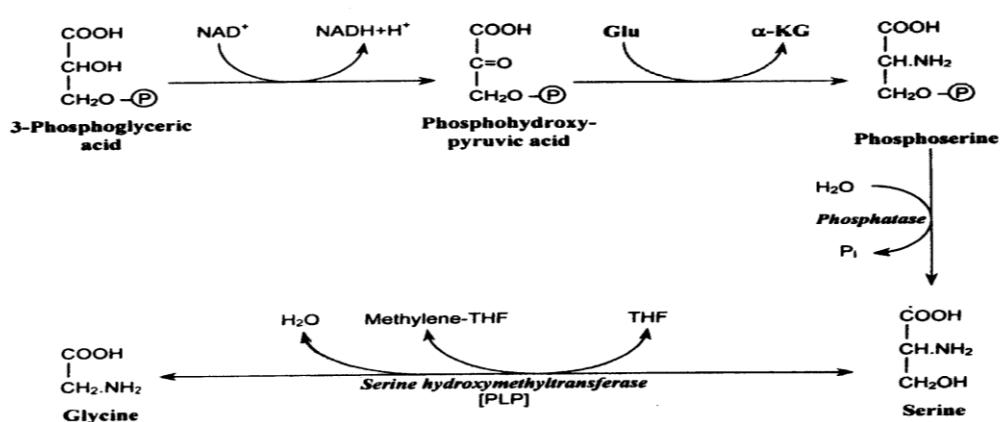
In born error of glycine metabolism:

- 1. Primary hyperoxaluria:** excessive conversion of glyoxylic acid to oxalic acid by oxidation leads to increase synthesis of oxalate and oxaluria, this condition named primary hyperoxaluria not related to diet, Ca oxalate stone and hypertension.
- 2. Glycinuria** due to defect in renal tubular reabsorption of glycine, the condition with tendency to oxalate stone formation.

Serine

- **Glucogenic** amino acid because it gives pyruvic acid
- **Non-essential** amino acid because it can be synthesized from glycine and 3-phosphoglycerate

Serine biosynthesis:



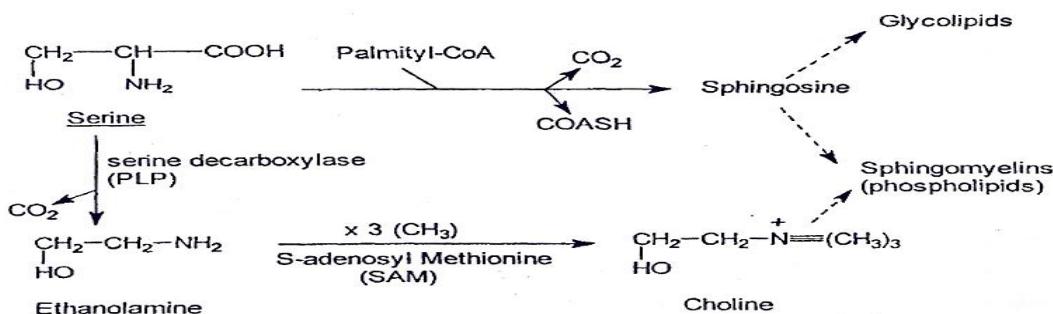
Importance of serine:

1) Synthesis of cysteine.

2) Ethanolamine and choline synthesis.



3) Formation of sphingosine base.



4) Formation C2 and C8 of purine.

Methionine

- ❖ Essential amino acid -Sulphur-containing amino acid
- ❖ Glucogenic amino acid because it gives succinyl CoA

Activation of methionine:

- ❖ Methionine is activated to S-adenosyl methionine (SAM).

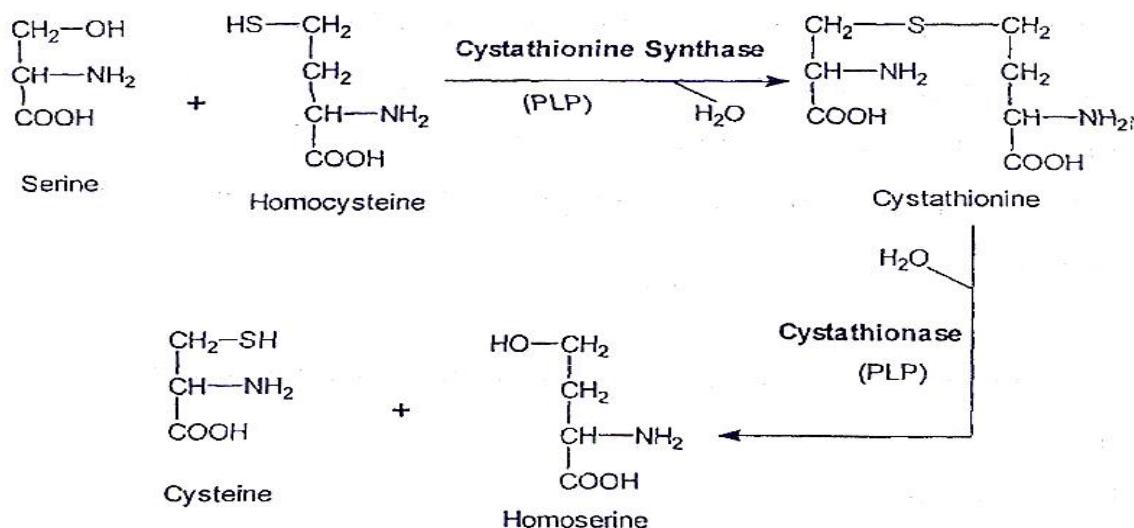
Importance of methionine :

Formation of S-adenosyl methionine (**SAM**) which act as methyl donor in many reaction as:

- Conversion of N-acetyl serotonin → Melatonin.
- Conversion of ethanolamine to choline.
- Conversion of Carnosine into Anserine .
- Conversion of nor-epinephrine into epinephrine.
- Synthesis of thymine from uracil.

Cysteine

- ❖ Glucogenic amino acid because it gives pyruvic acid.
- ❖ Non essential because it can be synthesized from homocysteine and serine as shown in the following reaction.



Homocystinuria:

Homocystinuria is excretion of homocysteine in urine.

Cause: Deficiency of cystathione synthase enzyme.

Manifestations: Thrombosis, osteoporosis, dislocation of eye lens and mental retardation.

- There are two forms of homocystinuria : vitamin B6 responsive, and vitamin B6 unresponsive.
- Infants with this disorder are normal at birth. Dislocation of the lens of the eye, causing severely decreased vision, usually begin after 3 years of age.
- Homocystinuria makes the blood more likely to clot spontaneously, resulting in strokes, high blood pressure, and many other serious problems.

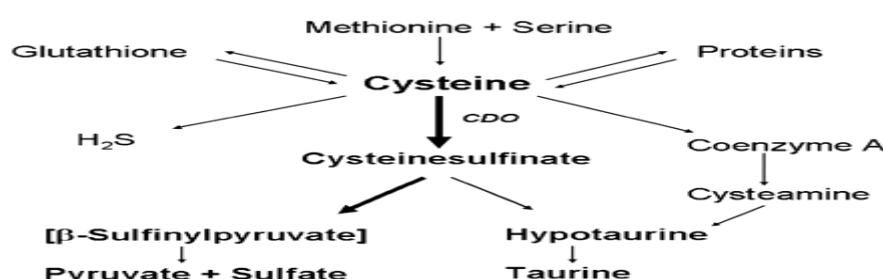
Treatment: Diet low methionine and high in cysteine prevent development of complication.

Importance of cysteine:

1-Enter in glutathione formation.

2-Synthesis of thio-ethanolamine that enter CoASH and acyl carrier protein (ACP), so it plays important role in fatty acid synthesis and oxidation.

3-Synthesis of taurine that binds with bile acid to form bile salt.



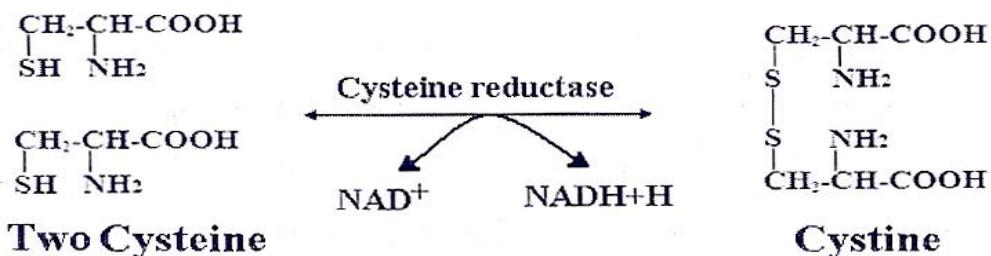
4.Plays a role in the detoxification of bromobenzene.

5.Formation of S_2O_3 thiosulfate and sulfite SO_3 . SO_3 is converted to SO_4 that can be activated into PAPS 3-phosphoadenosine 5-phosphosulphate (PAPS) which acts as active sulphate donor.



Cystine

- ❖ Non essential because it can be synthesized from 2 molecules of cysteine.



Cystinosis (cystine storage disease): is lysosomal disorder caused by defective carrier –mediated transport of cystine lead to deposition of cystine stone in RES; reticuloendothelial system, that lead to renal failure later.

Cystinuria:

It is a genetic disease characterized by excretion of cystine and dibasic amino acids lysine, arginine, ornithine in urine.

Cause:

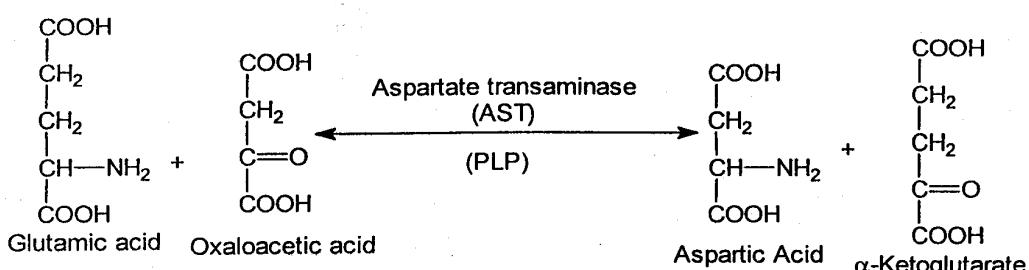
Defect in renal tubular reabsorption of dibasic amino acids.

Manifestations:

- Formation of renal stone due to low solubility of cystine.
- Cystine stones are often not visible on most x-rays, CT's, and ultrasounds.
- Urine odor in cystinuria has a smell of rotten eggs due to the increase in cystine.

Aspartic Acid

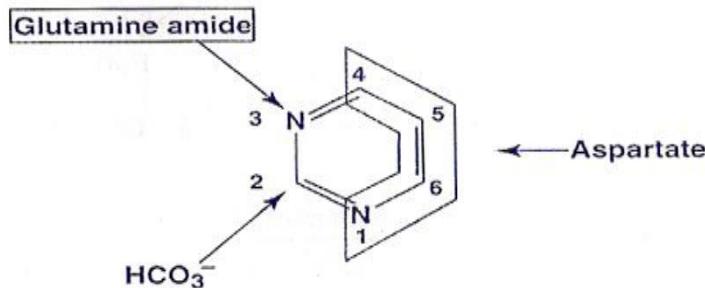
- Non essential because it can be synthesized from oxaloacetic acid.



- Glucogenic amino acid because it gives oxaloacetate.

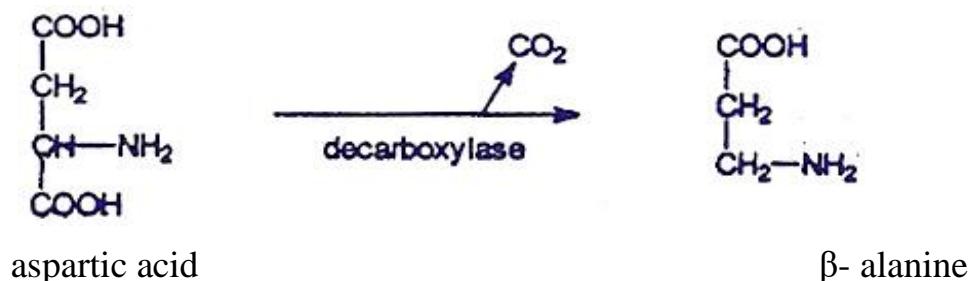
Importance of aspartic acid:

- 1) Synthesis of pyrimidine (N_1 , $C_{4,5,6}$).



- 2) Formation of urea.

- 3) By decarboxylation , aspartic acid \rightarrow β alanine \rightarrow formation of CoASH. So, cysteine and aspartic \rightarrow CoASH synthesis.



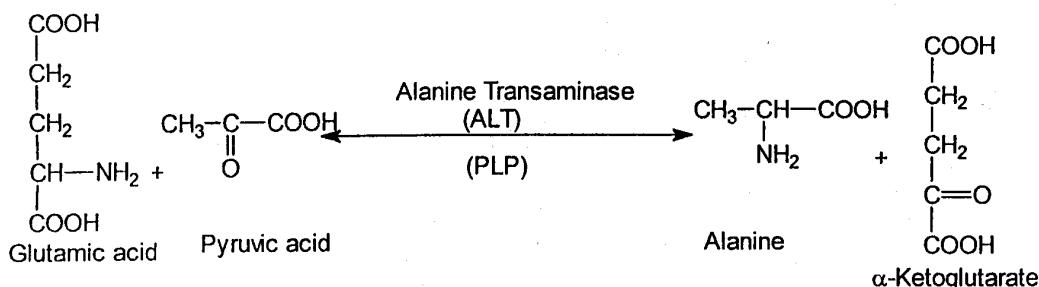
β -alanine, ornithine ,and citrulline are non-protein amino acids e.g. they don't enter into the formation of tissue proteins. β -alanine enters the formation of carnosine, anserine and pantothenic acid. Ornithine and citrulline are intermediates of the urea cycle.

- 5) Synthesis of a purine base (N_1).

Glutamic Acid

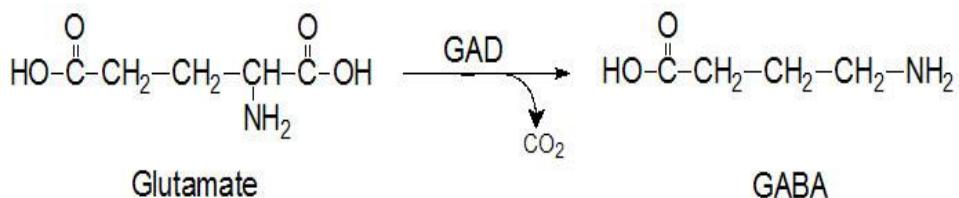
Non essential amino acid as it is formed from α -ketoglutaric acid.

Glucogenic amino acid because it gives α -ketoglutaric acid .



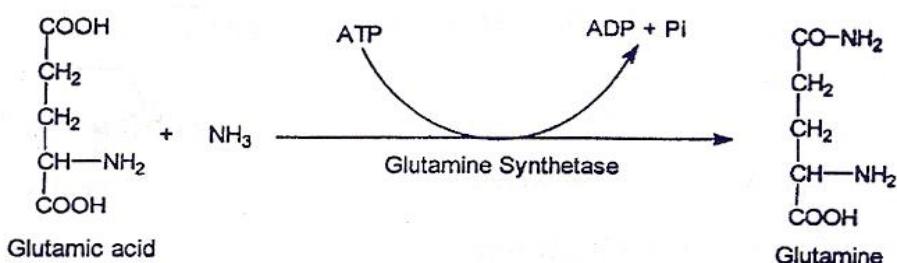
Importance of glutamic acid:

- 1-Glutamic acid enters in protein structure.
 - 2-It acts as excitatory neurotransmitter.
 - 3-Formation of γ aminobutyric acid (GABA) which is inhibitory neurotransmitter .



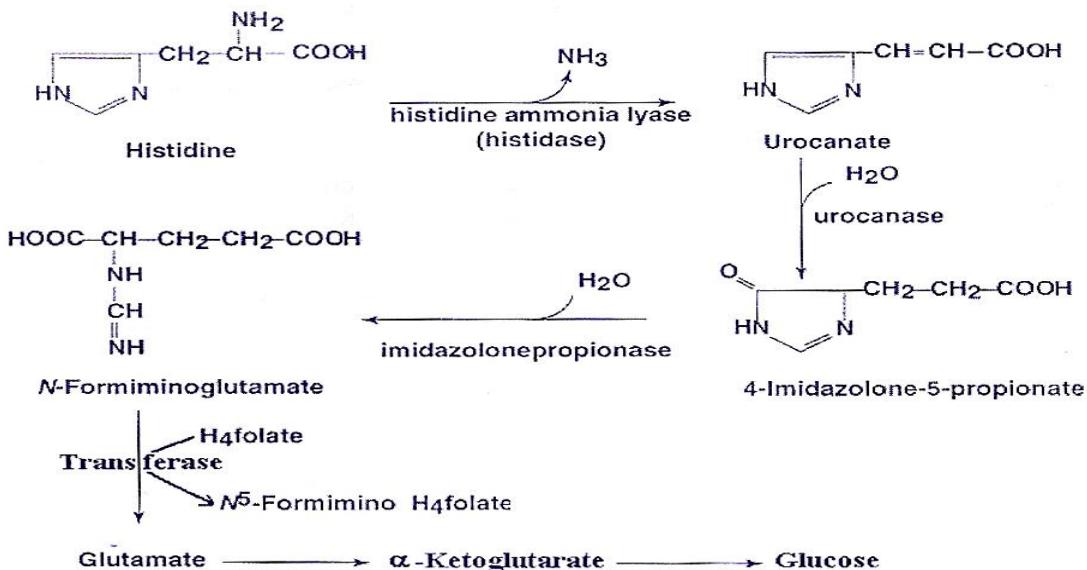
In case of vitamin B₆ deficiency, GABA formation is inhibited, which leads to convulsion especially in infant after stress stimuli.

- 4- Glutathione formation.
 - 5-Its N-acetyl glutamate acts as a coenzyme activator for carbamoyl phosphate synthetase I in urea formation.
 - 6-Formation of non-protein amino acid → ornithine→ arginine in urea cycle
 - 7-Formation of glutamine (Gln), so it helps in the removal of excess NH₃ the from brain in case of NH₃ intoxication. Glutamine in kidney is hydrolyzed by glutaminase → glutamic and NH₃ →excreted as NH₄



Histidine

- **Semi-essential** amino acid .
 - **Glucogenic** because it gives glutamic acid.

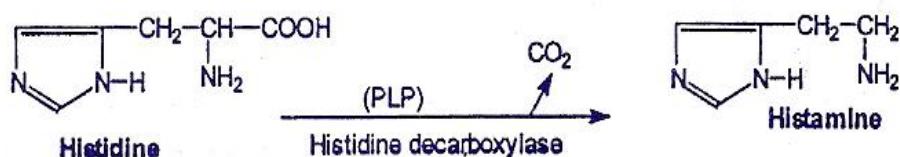


During histidine catabolism, formoimino glutamate (FIGLU) is formed. In case of folic acid deficiency there are increased amounts of FIGLU in urine.

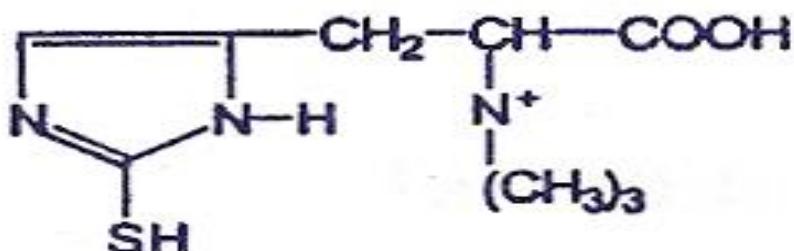
Specialized product of Histidine

1-Histamine formed by decarboxylation and act as

- Vasodilator
- Neurotransmitter



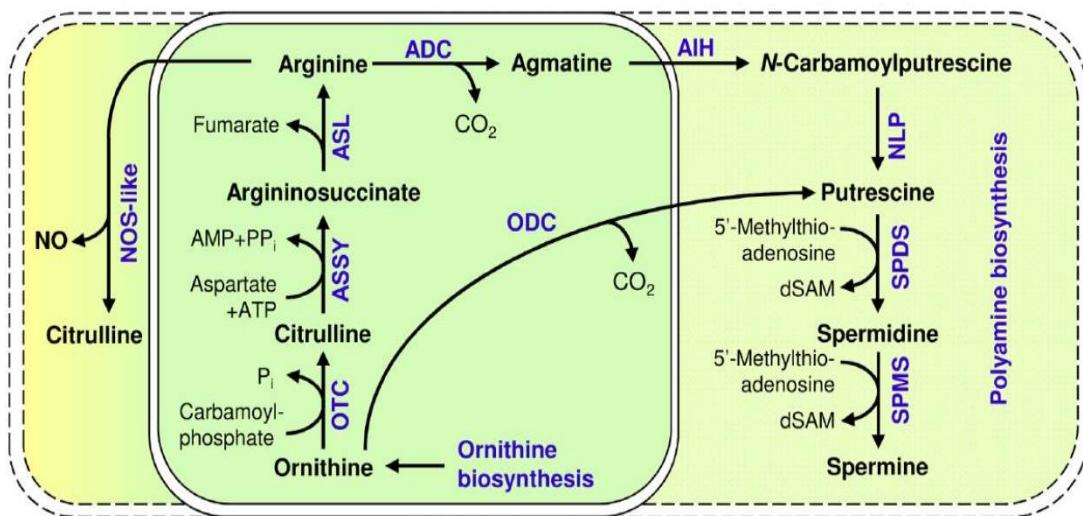
2- Ergothioneine is named betaine of thiohistidine present in RBCs, liver, and semen. Ergothioneine acts as antioxidant , it protects liver and RBCs from effect of free radicals.



Arginine

- ❖ Basic semi-essential amino acid.
- ❖ Glucogenic amino acid because it gives ornithine → Glutamate semialdehyde → glutamic acid α-ketoglutaric acid.

Importance of arginine:



1-Formation of creatine and creatinine.

2-Intermediate in urea cycle.

3-Formation of nitric oxide NO.

- ❖ NO is a neurochemical transmitter doing its action through cGMP causing vasodilatation and smooth muscle relaxation.

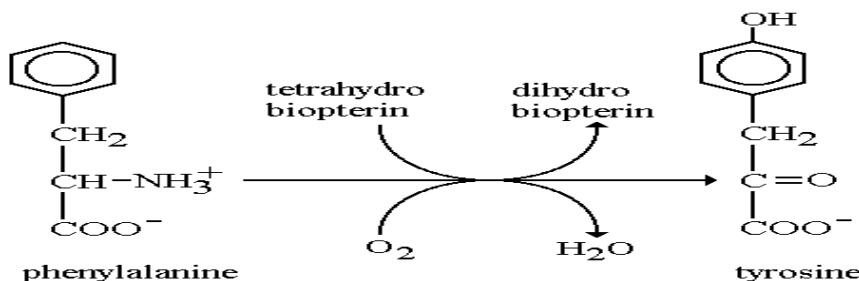
4-Synthesis of agmatine by arginine decarboxylation .

Agmatine has been suggested as a novel neurotransmitter and/or neuromodulator in mammalian brain, as it is synthesised in the brain and also in the spinal cord. Also, agmatine inhibits NO synthesis.

Aromatic amino acid

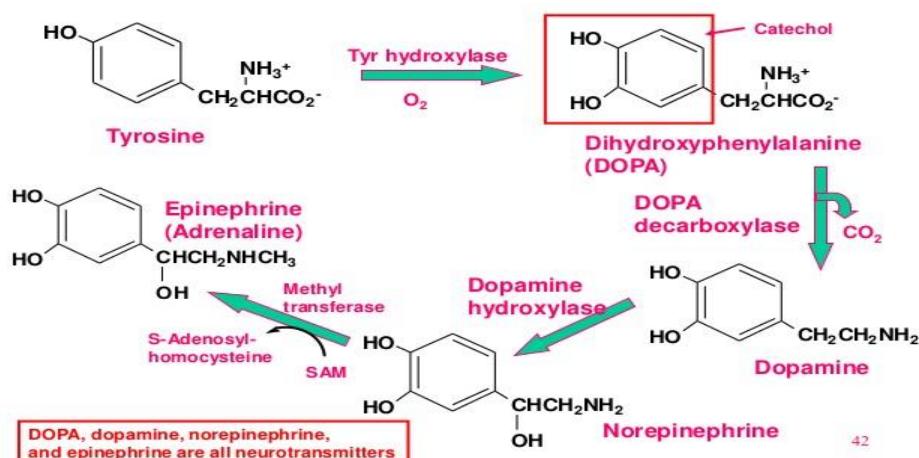
Phenyl Alanine and Tyrosine

- ❖ Phenylalanine is essential amino acid.
 - ❖ Phenylalanine and tyrosine are **glucogenic** and **ketogenic** amino acids because both give fumaric acid and acetoacetic acid.
 - ❖ Tyrosine is **non-essential amino** acid because it can be formed from phenylalanine by phenylalanine hydroxylase enzyme.

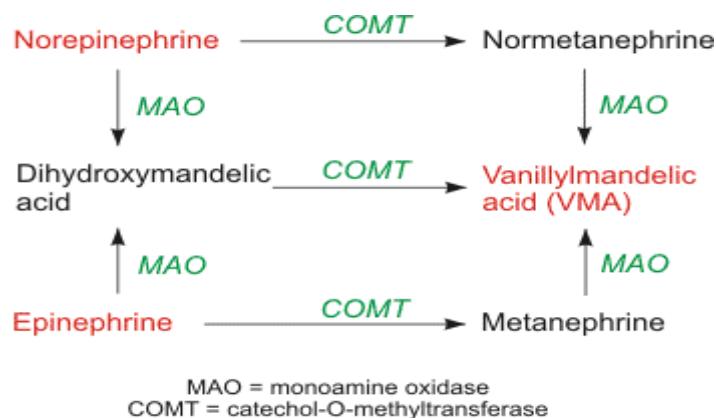


Importance of tyrosine:

- 1) Biosynthesis of thyroid hormones:** Occurs in follicular cells of thyroid gland from two molecules of tyrosine and four molecules of organic iodine. Three forms of thyroxine are synthesized T₃, T₄ and reverse T₃(rT₃) the first is more active than T₄, on the other hand reverse rT₃ is not active.
 - 2) Adrenaline and nor adrenaline:** These hormones are synthesized in adrenal medulla and nerve endings, methylation of noradrenaline in presence of SAM leads to adrenaline formation.

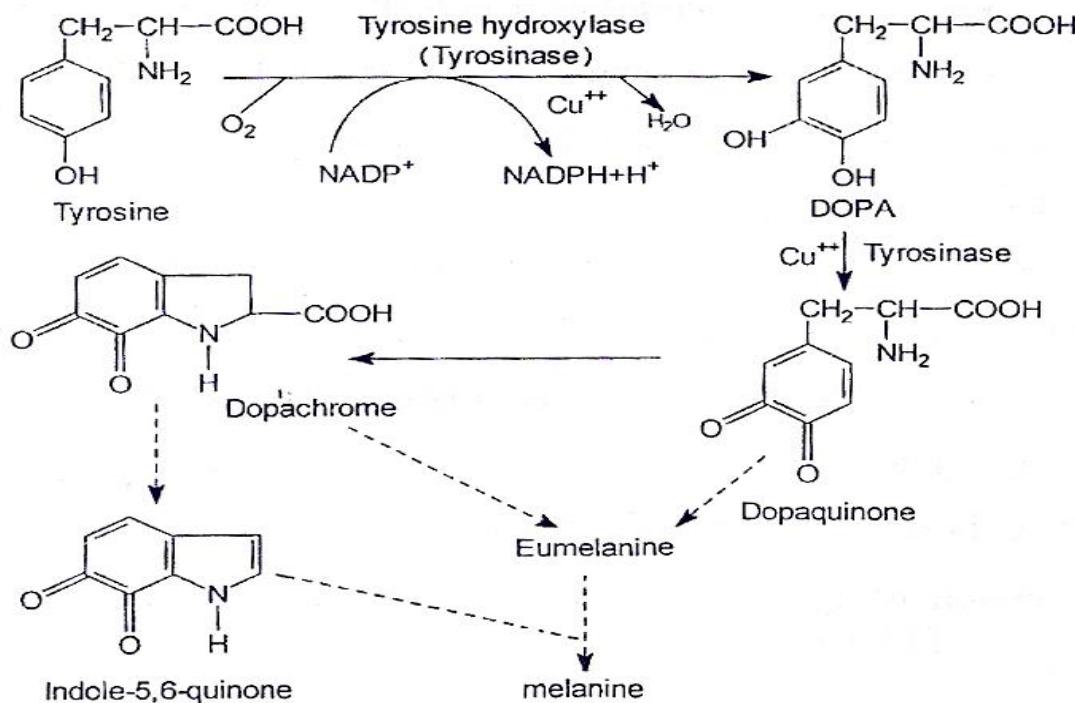


Catabolism of catecholamine:



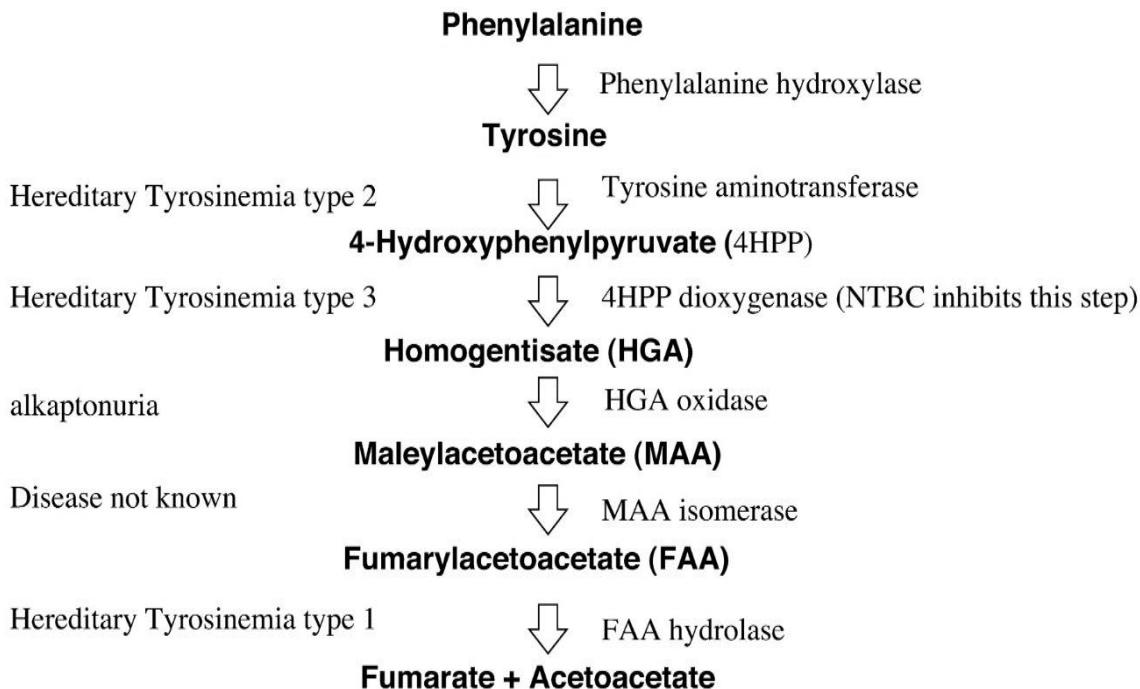
Both hormones are catabolized by monoamino oxidase (MAO) enzyme with formation of 3-methoxy 4-hydroxymandilic acid (vinyl mandilic acid, VMA), the latter is increased in urine in case of tumors of adrenal medulla called **pheochromocytoma**.

3) Melanin pigment: in melanocyte, tyrosinase enzyme also convert tyrosine to DOPA then by another oxidation dopaquinone is formed and converted by series of reactions into different types of pigment as shown in the figure.



Catabolism of tyrosine

Phenylalanine and tyrosine act as ketogenic and glucogenic during degradation ,the end product is fumaric and acetoacetyl COA.



Inborn error of tyrosine metabolism:

1-Phenylketonuria:

It is due to deficiency in phenylalanine hydroxylase enzyme which is necessary to metabolize phenylalanine to tyrosine.

Characteristics of phenyl ketonuria:

- 1.Elevated blood levels of phenylpyruvate, phenyl-lactate and phenylacetate in tissues, plasma and urine.
- 2.CNS symptoms: mental retardation, failure to walk, or to talk, seizures, hyperactivity, tremors, microcephaly and failure to grow.
- 3.Hypopigmentation: It is due to inhibition of tyrosinase enzyme "necessary for melanin pigment formation" by high levels of phenylalanine.

Neonatal screening and diagnosis:

Early diagnosis of phenylketonuria is important because the disease is treatable by dietary means. Laboratory testing for elevated levels of phenylalanine in urine must be done 24 – 48 hours after birth to avoid false negative results.

Treatment of phenylketonuria:

- Diet formula low in phenylalanine and rich in tyrosine. It must be started during the first seven or ten days of life to prevent mental retardation.
- The sweetener aspartame, present in many diet foods and soft drink, must be avoided, as aspartame contains phenylalanine.
- Gene therapy is under investigation

2-Alkaptonuria:

It is a rare disease due to deficiency of homogentisic acid oxidase responsible for degradation of phenylalanine and tyrosine.

Characteristic symptoms include:

- Homogentisic aciduria (the urine becomes black on standing).
- Large joint arthritis.
- Black ochronotic pigmentation of cartilage.
- Formation of renal stones and deterioration of cardiac valves.

Treatment:

- Low protein diet.
- Vitamin C reduces ochronosis.
- Nitisinone is a drug used to suppress homogentisic acid production

3-Hypertyrosinemia: deficiency of tyrosine aminotransferase (TAT) leads to hypertyrosinemia and the urinary excretion of tyrosine.

4-Albinism:

It is due to deficiency of tyrosinase enzyme activity in melanocytes resulting in complete absence of melanin pigmentation of skin, hair and eyes.

The disease is manifested by:

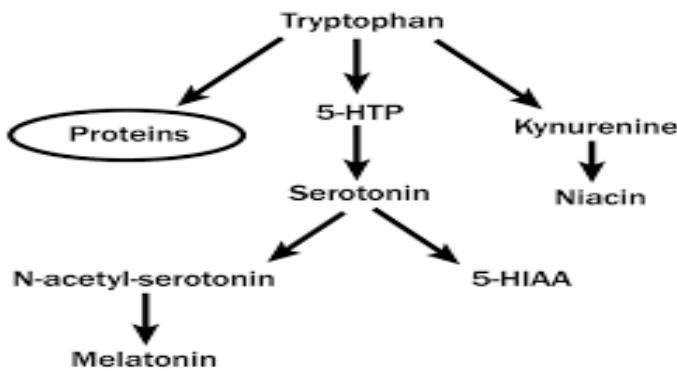
- Hypopigmentation.
- Photophobia
- Increased risk for skin cancer.

Tryptophan

- ❖ Essential amino acid.-Glucogenic and ketogenic amino acid because it gives alanine and Acetocetate.

Importance of tryptophan :

- Tryptophan is converted into various types of important biological substance as vitamin (Nicotinic acid), hormone (melatonin) and neurotransmitter (serotonin).



1-Serotonin synthesis:

- ❖ **Serotonin** is formed from tryptophan in two steps hydroxylation and decarboxylation
- ❖ **Serotonin:** acts as vasoconstrictor and neurotransmitter. Serotonin is present at highest concentrations in platelets and in the gastrointestinal tract. Lesser amounts are found in the brain. 5 hydroxy indol acetic acid is a catabolic product of serotonin and increased in urine in cases of carcinoid tumor of intestine .

2-Melatonin:

- ❖ Melatonin is a hormone formed from serotonin by acetylation followed by methylation within the pineal gland and the retina, where the necessary N-acetyltransferase enzyme is found. Synthesis and secretion of melatonin increase during the dark period of the day and are maintained at a low level.

3-Formation of Nicotinic acid:

- ❖ 60 mg of tryptophan is converted into 1mg of nicotinic acid ,so in case of tryptophan deficiency or deficiency of B6, nicotinic acid synthesis is impaired. Deficiency of tryptophan and niacin leads to **pellagra**.

Inborn error of tryptophan metabolism:

Hartnup disease is a hereditary disorder of tryptophan metabolism resulted from impaired renal tubular reabsorption of tryptophan and basic amino acid histidine and lysine (aminoaciduria).

- The condition is associated also pellagra skin rash, and improved with nicotinic acid administration.

Putrefaction of tryptophan :

Indo and skatol: these products are formed and excreted by urine and stool respectively, they give them characteristic odour and color.

Lysine

- Essential-ketogenic amino acid because it gives acetoacetate.
- Formation of hydroxylysine.

Importance of lysine and hydroxylysine:

- 1- Formation of collagen and elastin.
- 2- Lysine is also important as a precursor for the synthesis of carnitine, required for the transport of fatty acids into the mitochondria for oxidation. .

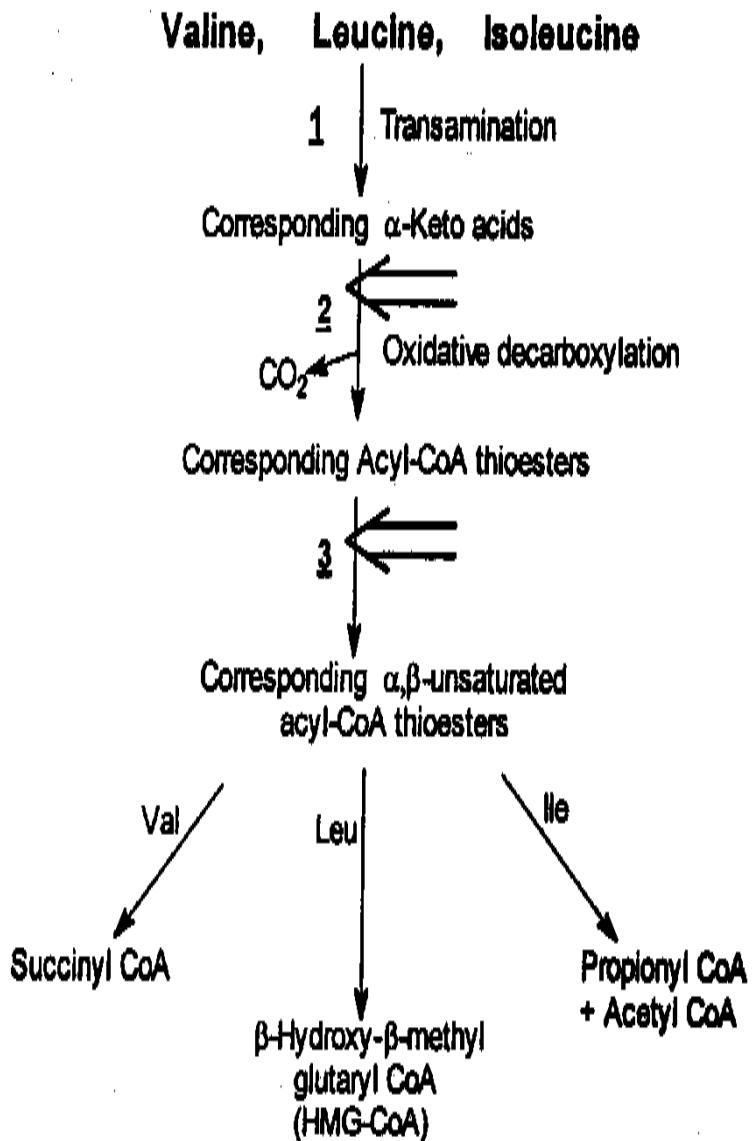
Branched Chain Amino Acids (BCAA)

These amino acids are essential mainly metabolized in muscle, brain and adipose tissue. Liver is not involved in their metabolism since liver is deficient in transaminases required for these amino acids.

- **Valine** is glucogenic amino acid → it gives succinyl CoA.
- **Leucine** is ketogenic amino acid → it gives acetoacetate.
- **Isoleucine** is glucogenic and ketogenic amino acid → it gives succinyl CoA and acetyl CoA.

Catabolism of branched chain amino acids:

- 1- Transamination to give corresponding β -keto acids.
- 2- Oxidative decarboxylation to yield corresponding acyl CoA.
- 3- Then the pathway proceeds to give succinyl CoA, acetoacetate, succinyl CoA and acetyl CoA .



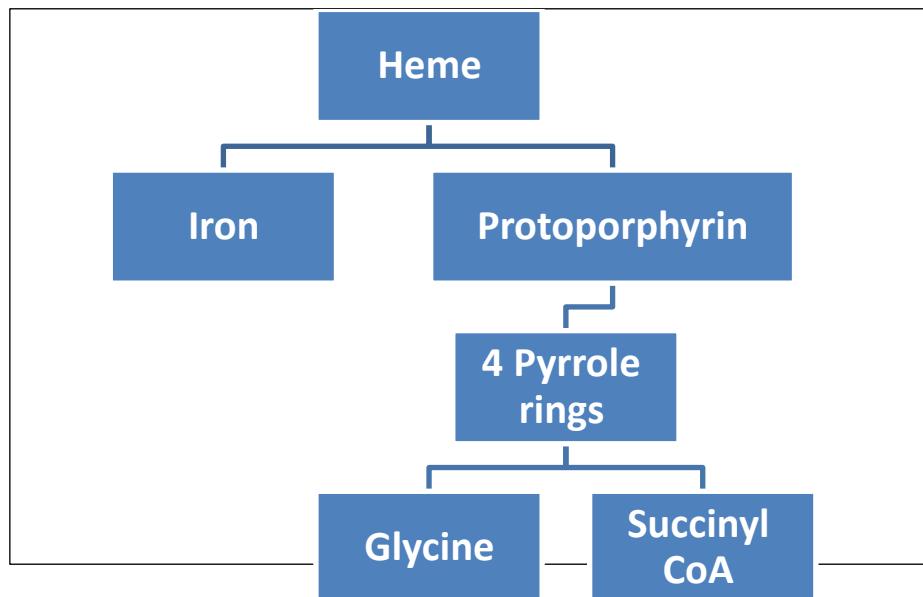
• Maple Syrup Urine Disease:

It is caused by lack of the decarboxylase enzymes needed to metabolize α -ketoacids produced from branched-chain amino acids after their transamination.

• Accumulation of these keto acids leads to:

- 1- Maple syrup odour or burnt sugar due to the rise in leucine.
- 2- Ketoacidosis.
- 3- Mental retardation.
- 4- Death after 1 year of age if no treatment

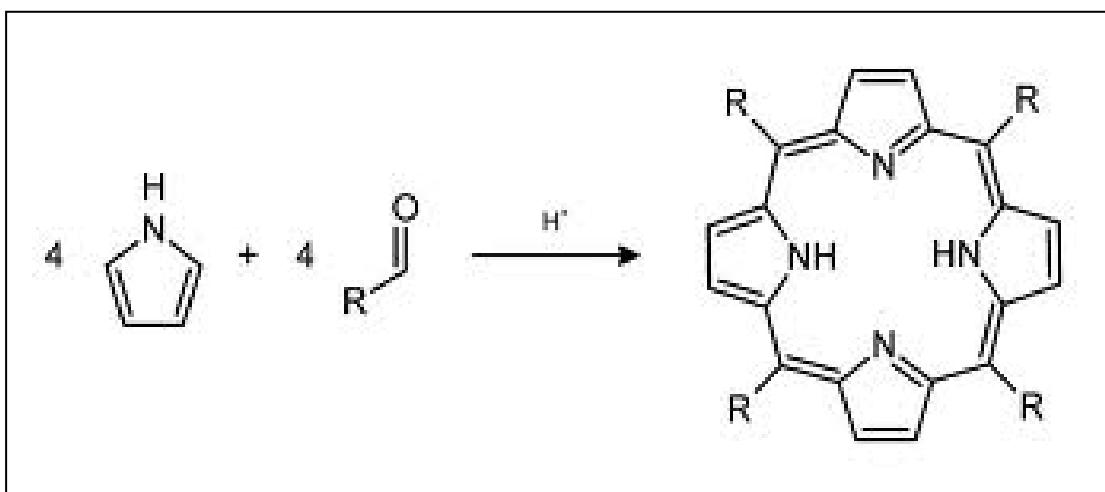
Heme Synthesis



Biosynthesis of heme occurs in 3 stages:

- 1- Biosynthesis of pyrrole ring.
- 2- Biosynthesis of protoporphyrin.
- 3- Biosynthesis of heme.

Site: Heme is synthesized in the bone marrow for immature red blood cells, and in the liver for cytochrome and other proteins



Location within cell:

It occurs in mitochondria and cytoplasm.

Stage (1): Biosynthesis of pyrrole ring

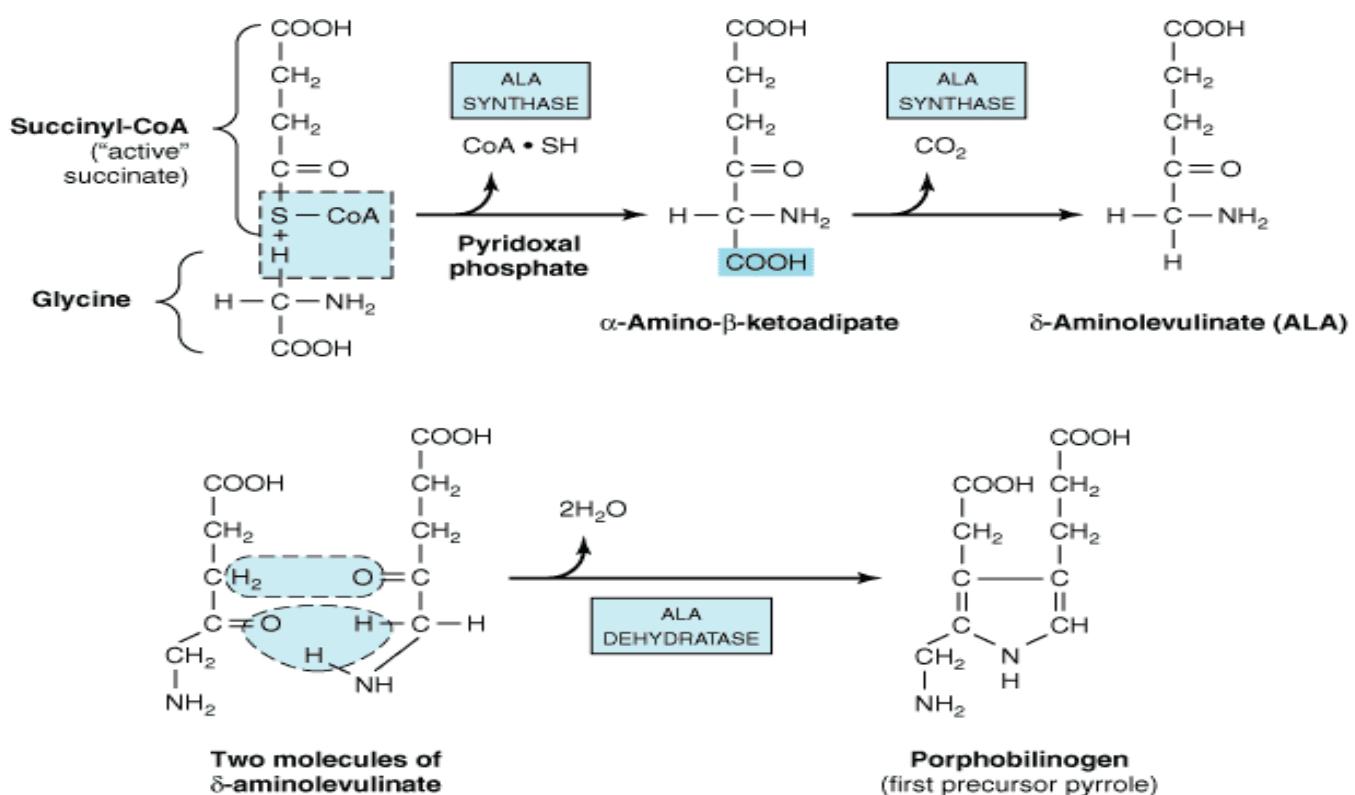
Step 1:

- Succinyl CoA condenses with glycine to form α -amino β -ketoadipic acid, which is decarboxylated into δ -amino levulinate (δ -ALA).
- The reaction needs ALA synthase enzyme and pyridoxal phosphate (PLP) as coenzyme.

Step 2:

- The δ -amino levulinate (δ -ALA) comes out of the mitochondria to cytoplasm, where 2 molecules condense to form porphobilinogen, which is the first precursor of pyrrole ring.
- The reaction is catalyzed by ALA dehydratase enzyme which needs Cu^{+2} as cofactor.
- **N.B:** Porphobilinogen is a pyrrole ring to which propionate (P) (CH_2CH_2COOH) and acetate (A) (CH_3COOH) groups are attached.

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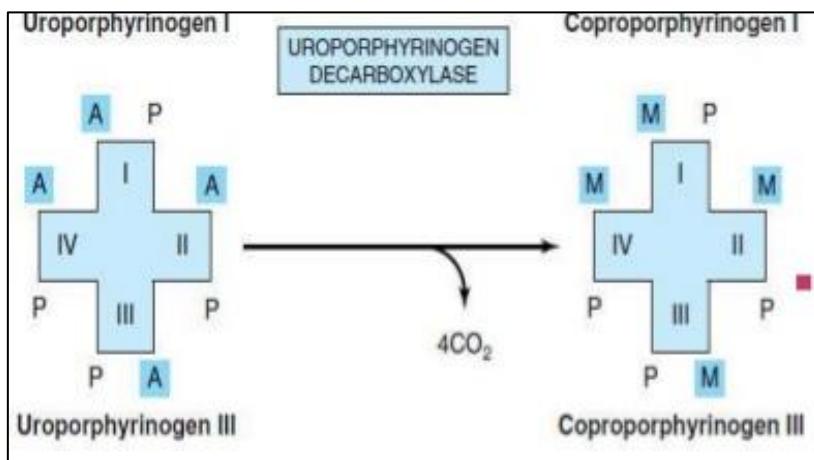
Stage (2): Biosynthesis of Protoporphyrin

Step 3:

- 4 molecules of porphobilinogen by Uroporphyrinogen III synthase (which is concomitant isomerase and deaminase), results in the formation of uroporphyrinogen III due to the reversal of one porphobilinogen residues (major series under normal conditions).
- N.B.** Pyrrole No IV acetic acid (A) and propionic acid (P) side chains are reversed.

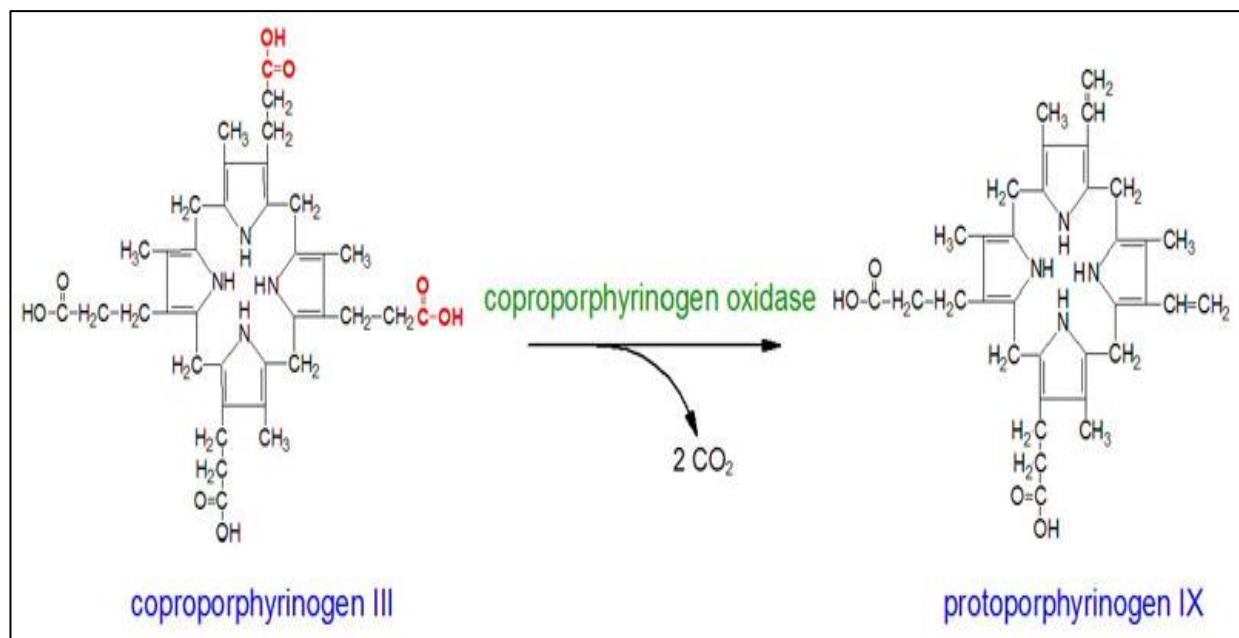
Step 4:

- Coproporphyrinogen III are formed by decarboxylation of uroporphyrinogen III. The 4 acetic acid side chains (-CH₂ COOH) are changed into methyl groups (CH₃).



Step 5:

- Coproporphyrinogen III enters the mitochondria, and becomes converted into protoporphyrinogen III by Coproporphyrinogen oxidase which leads to oxidation and decarboxylation of two propionic acid side chains of rings I, II.
- Two propionates (CH₂CH₂COOH) are converted into vinyl groups (CH=CH₂).



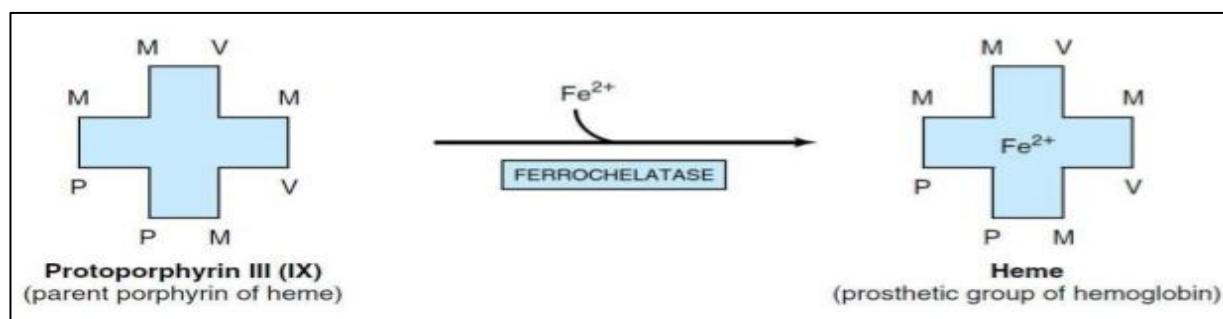
Stage (3): Formation of Heme:

Step 6:

- Protoporphyrinogen III is oxidized by protoporphyrinogen oxidase enzyme , into protoporphyrin III.

Step 7:

- The heme formation is completed by incorporation of iron (Fe^{++}) into protoporphyrin III by **heme synthetase** or **ferrochelatase**.
➤ All these reactions occurs in the mitochondria.



Regulation of heme Synthesis

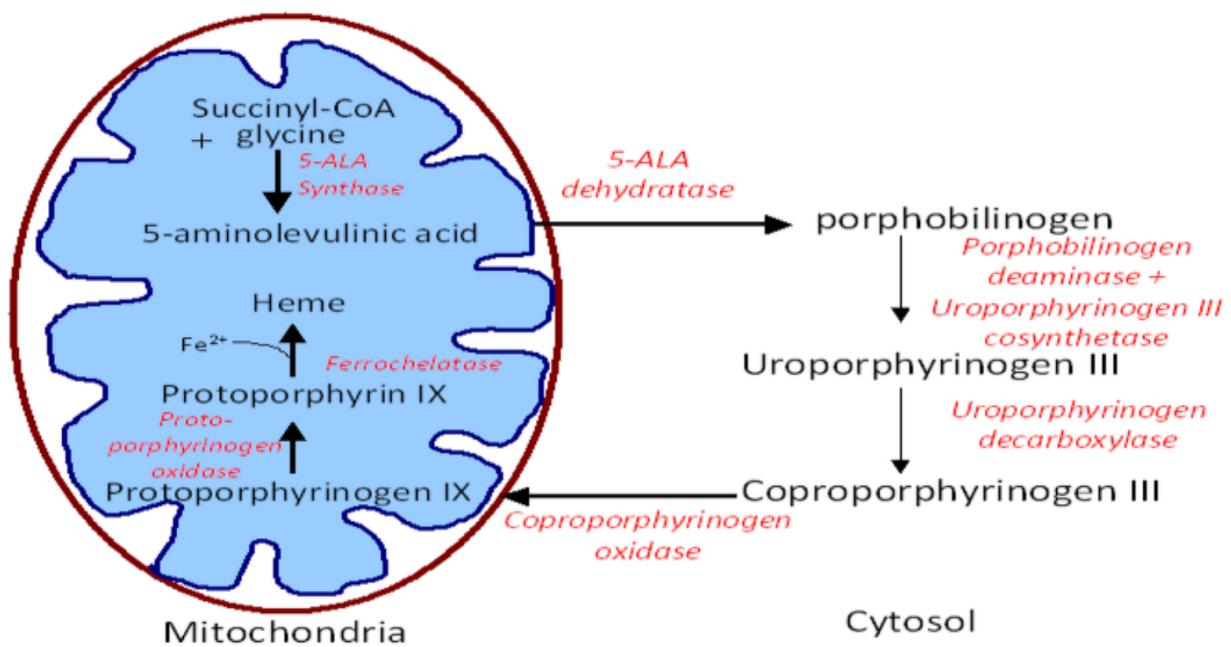
- Delta (δ) amino levulinic synthase (δ -ALA synthase) is the key enzyme of heme synthesis.

It is stimulated by:

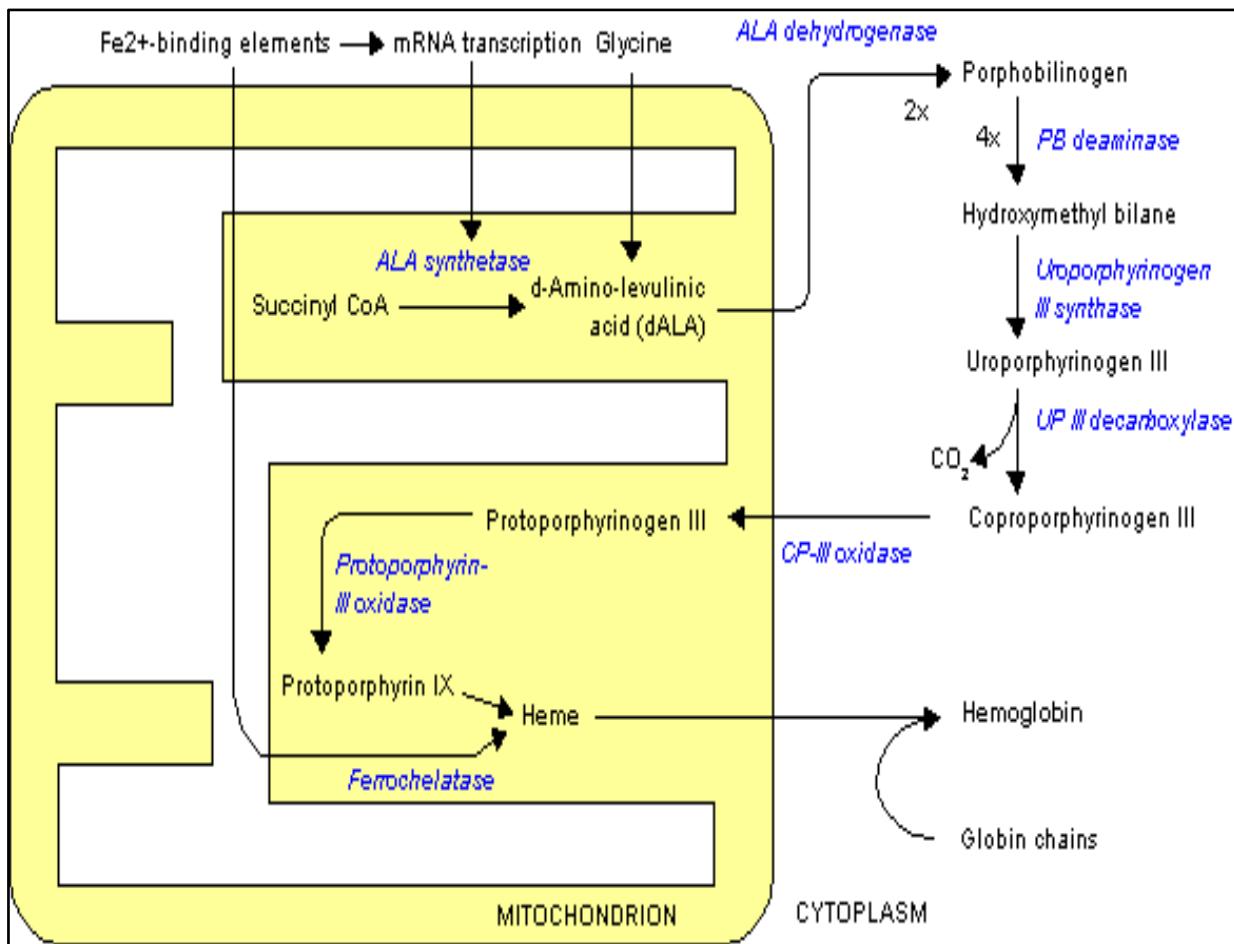
- Drugs e.g. phenobarbital, griseofulvin (an antifungal agent) and iron. Almost 100 drug and metabolites can cause induction of hepatic δ -ALA synthase.
- Some patients with certain kinds of porphyria might suffer exacerbations of the disease, due to faulty intake of drugs that stimulate the enzyme with consequent excess production of porphyrins.

It is inhibited by:

- Heme “feed back inhibition”: When porphyrin production exceeds the availability of globin, heme accumulates and is converted to **hemin** by the oxidation of Fe^{2+} to Fe^{3+} . Hemin decreases the activity of hepatic ALA synthase enzyme by decreasing synthesis of the enzyme.
- Glucose and steroids.
- **N.B:** Lead interacting with zinc cofactors for ALA dehydratase and ferrochelatase, leading to inhibition of heme synthesis pathway.



Summary of heme biosynthesis



Importance of Heme:

Many important proteins contain heme as a prosthetic group.

Heme proteins

- Hemoglobin (oxygen transport).
- Myoglobin (oxygen carrying in muscle).
- Cytochromes (of electron transport and cytochrome P450).
- Catalase and peroxidase (H₂O₂ utilization).

Disorders of heme synthesis (Porphyria)

Definition: A group of diseases characterized by defects in heme synthesis, resulting from deficiency of one of enzymes involved in heme synthesis.

- Two types: hereditary or acquired.
- All hereditary types are autosomal dominant except congenital erythropoietic porphyria: autosomal recessive.



- Porphyria refers to purple color caused by pigment like porphyrin in the urine.

Symptoms:

1. Anaemia
2. Abdominal pain and neuropsychiatric disorders.
3. Photosensitivity: porphyrin derivatives when exposed to light become excited and react with molecular O₂.



Types of Porphyria

Types	Enzyme involved	Symptoms
Hepatic porphyria	Uroporphyrinogen I synthase	Abdominal pain. Neuropsychiatric disorders.
	Uroporphyrinogen decarboxylase	Photosensitivity.
	Coproporphyrinogen oxidase	Abdominal pain. Neuropsychiatric disorders. Photosensitivity.
	Protoporphyrinogen oxidase	Abdominal pain. Photosensitivity.
Erythropoietic porphyria	Uroporphyrinogen III synthase	Photosensitivity.
Erythrohepatic porphyria	Ferrochelatase	Photosensitivity.

Treatment of porphyria:

- Avoid drugs that decrease heme synthesis.
- High carbohydrate diet.
- Antioxidant: b-carotene.
- Avoidance of sunlight.
- Blood transfusion to correct anemia.
- Bone marrow transplantation.
- Hematin.
- Gene therapy.

Catabolism of Hemoglobin

In the Reticuloendothelial Cells:

1. The life span of RBCs is about 120 days. After which, they are removed from the circulation by the reticuloendothelial system, present in the liver, spleen and bone marrow. RBCs are hemolyzed and hemoglobin comes out.
2. Globin part is detached, and hydrolyzed into amino acids that join amino acids pool (recycled).
3. The microsomal heme oxygenase of the reticuloendothelial cells catalyzes the conversion of heme into biliverdin.
 - This reaction needs O_2 and $NADPH + H^+$.
 - Iron is removed, in the Fe^{+++} form to be recycled.
 - Methenyl bridge between rings I and II (vinyl containing) is cleaved.
 - CO is produced. It appears that the only source of endogenous carbon monoxide production, is this α methenyl carbon.
4. Biliverdin (green pigment) is reduced into bilirubin (golden yellow), in a reaction that needs Reductase enzyme and $NADPH + H^+$.

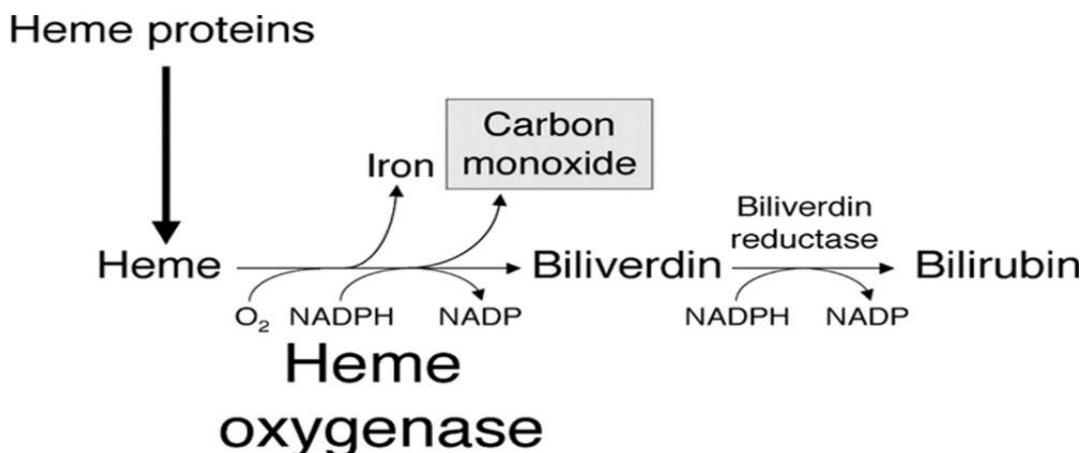


Fig. shows conversion of heme into bilirubin

In the plasma: Bilirubin – a non polar compound – is carried on albumin by a non-covalent bond forming “unconjugated” or “indirect Bilirubin”.

In the liver:

- Bilirubin dissociates from the carrier albumin and enters hepatocytes. It becomes conjugated with one or two glucuronic acid molecules forming bilirubin diglucuronide.
- This form is called “**conjugated bilirubin** or “**direct bilirubin**”. UDP-glucuronyl transferase enzyme is needed.
- Bilirubin is transported against concentration gradient into bile canaliculi and hence the intestine.

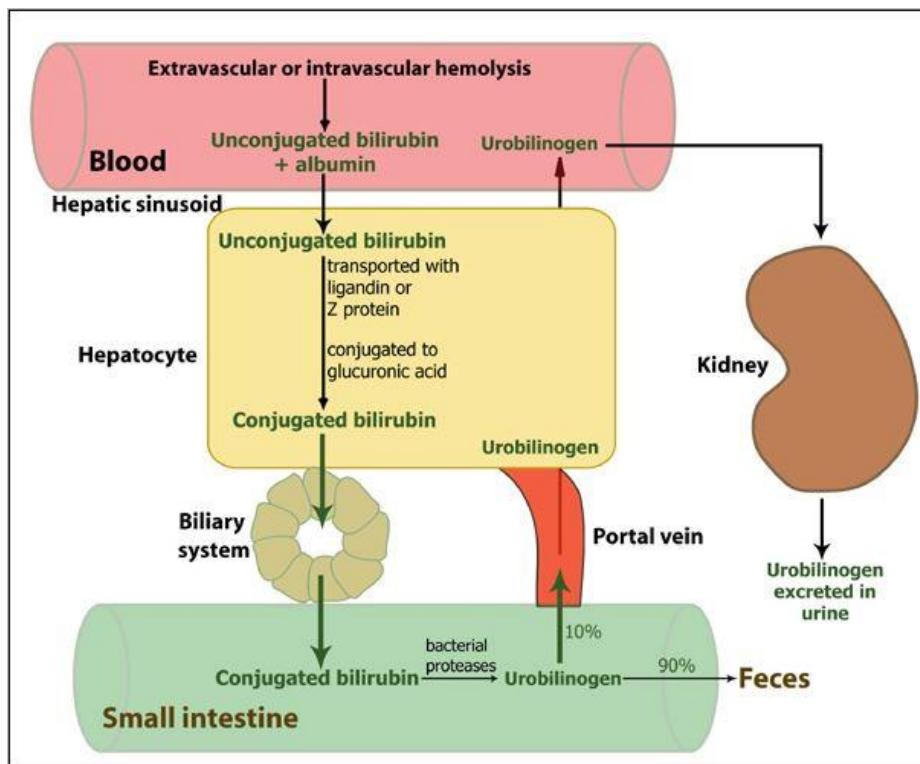
In the intestine:

Bilirubin diglucuronide is acted upon by intestinal bacteria where:

- 1- Glucuronides are removed by β -glucuronidase enzyme.
 - 2- Reduction of bilirubin to colourless urobilinogen occurs.
- ❖ Most of urobilinogen (stercobilinogen) is excreted in the stool as an oxidized form (urobilin or stercobilin).
 - ❖ Part of urobilinogen is absorbed to be re-excreted again “enterohepatic circulation”.
 - ❖ Part of urobilinogen is absorbed to the blood \rightarrow kidney and is excreted in urine as “urobilin”.

Serum bilirubin levels:

- Total bilirubin: 0.2-1.1 mg/dl
 - Direct bilirubin: 0- 0.2 mg/dl
 - Indirect bilirubin: 0.2- 0.9 mg/dl
-
- The clinical determination of serum bilirubin distinguishes between conjugated (direct) and unconjugated (indirect) bilirubin.
 - The reaction, called the **van den Bergh reaction**, is a coupling of bilirubin with a diazo reagent to form a red colored complex.
 - **Conjugated** bilirubin is water soluble and reacts with diazo directly, so, it is called **DIRECT bilirubin**.
 - **Unconjugated** bilirubin bound to albumin, so, alcohol is added to release it from albumin, now, it can react with diazo. So, it is called **INDIRECT bilirubin**.



Hyperbilirubinemia and Jaundice

- ❖ Normal serum total bilirubin amounts up to 1mg / dl (17.1 $\mu\text{mol/l}$).
- ❖ Hyperbilirubinemia: serum total bilirubin exceeds 1 mg / dl.
- ❖ Jaundice or icterus: Yellowish discoloration of eye, skin. It occurs when bilirubin level reaches 3mg / dl.

Types of jaundice:

(1) Hemolytic (Pre-Hepatic):

Occurs in states of increased hemolysis of RBCs e.g. severe malaria, genetic diseases, as sickle cell anemia, thalassemia and G6PD deficiency.

Biochemically there is:

- Increased bilirubin production above the capacity of the liver to deal with.
- Increased excretion of urobilin in urine and stools.
- No bilirubin appears in urine.
- Plasma indirect bilirubin is the fraction elevated.

(2) Obstructive (Post-Hepatic Or Cholestatic):

This is due to mechanical obstruction of biliary tree by e.g. stones or cancer head of pancreas.

Biochemically there is:

- Urobilin is absent from urine or stools, with characteristic clay colored stools.
- Bilirubin appears in urine leading to dark urine.
- Plasma direct bilirubin is the fraction elevated.
- Patients also can present with elevated serum cholesterol, and often complain of severe itching or "pruritus" because of the deposition of bile salts.

(3) Hepatocellular (Toxic-infective ,hepatic):

- This type is due to liver diseases mostly viral e.g. HAV, HBV, HCV infections.
- In this type there is, in addition to liver cell damage, element of obstruction in the biliary canaliculi.
- Hyperbilirubinemia is a mixture of conjugated and unconjugated types (direct and indirect).
- Urobilin decreases in urine and stool.
- Bilirubin appear in urine.
- Plasma levels of AST (SGOT) and ALT (SGPT) are elevated, plasma albumin level is low and the patient experiences nausea and anorexia.

Physiological jaundice

- Is a yellow discolouration of the skin, sclera and mucous membrane due to an increase in the serum bilirubin level in a newborn infant. A bilirubin level of more than 85 µmol/l (5 mg/dL) manifests clinical jaundice in neonates.
- It is usually harmless: often seen in infants around 2nd day after birth, lasting until 8th day in normal births, or to around day 14 in premature births.
- Serum bilirubin normally drops to a low level without any intervention required. In cases where bilirubin in excess of the binding capacity of albumin (> 20 mg/dL), it can diffuse into the basal ganglia and cause toxic encephalopathy (kernicterus).

Causes of Physiological Jaundice

- ❖ Short life span of fetal red blood cells (being approximately 80 to 90 days in a full term infant, compared to 100 to 120 days in adults).
- ❖ Insufficient albumin to bind to the excess unconjugated bilirubin, leads to free unconjugated fat soluble bilirubin.

- ❖ Sterile gut (low conversion of bilirubin to urobilinogen by the intestinal flora).
- ❖ Poor peristalsis allows the β glucuronidase to hydrolyse the conjugated bilirubin back to un-conjugated bilirubin which then goes back to the liver for further metabolism.
- ❖ Immature liver that reduces the hepatic metabolism
- ❖ Low enzymatic activity in intestine (UDP glucuronyl transferase)
- ❖ Higher levels of red blood cells, which is more common in small-for-gestational age (SGA) babies and some twins.

Asking for :

- History of bruising / cephalohematoma / birth trauma.
- Blood grouping and rhesus factor.
- Feeding pattern.
- Infection.
- Drugs.

Laboratory investigations:

- Total serum bilirubin: for baseline level and to assess response to treatment.
- Direct Coombs test.
- Direct serum bilirubin.
- Glucose-6-phosphate dehydrogenase screening.
- Osmotic fragility test.
- Blood culture.
- Liver function tests.

N.B: Tests other than serum bilirubin to exclude other causes of neonatal jaundice.

Management

- No action for the vast majority of babies with physiological jaundice.
- Any newborn with a total serum bilirubin greater than 21 mg/dL should receive phototherapy.
- **Mode of action:** Isomerization that changes trans-bilirubin into the water-soluble cis-bilirubin isomer that is non-toxic and easily excreted by kidney. Bilirubin can absorb blue light (420nm-470nm). In phototherapy, blue light is typically used because it is more effective at breaking down bilirubin.



Phototherapy

Other types of jaundice:

1- Gilbert's syndrome

- Due to mutation in promoter region of bilirubin glucuronyl transferase (BRGT) gene.
- Total bilirubin around 3mg/dl, usually asymptomatic.

2- Crigler-Najjar syndrome

- Mutations in coding region of bilirubin glucuronyl transferase (BRGT) gene leading to nonfunctional protein.
- Type I – homozygous → complete lack of protein → jaundice appears within 24 hours. Total bilirubin reaches 20 mg/dl, fatal.
- Type II – heterozygous → less severe than type I, ↓levels of protein.

3- Dubin-Johnson syndrome

- ❖ Inability of the hepatocytes to secrete conjugated bilirubin after it has been formed.
- ❖ Conjugated bilirubin returns to the blood and deposited in the liver become black Type II – heterozygous → less severe than type I, ↓levels of protein.
- ❖ It is usually asymptomatic.

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