Basic Biomedical Sciences I

Case 2: Eat-All-You-Can

Block 5 Module 1

EMBRYONIC DERIVATIVES OF THE MIDGUT

- The **Midgut**
  - Part of the gut tube that will eventually form the small intestine (distal to the opening of the bile duct), and the proximal colon (including the cecum, vermiform appendix, ascending colon, and the proximal 2/3rds of the transverse colon).
- The **Superior Mesenteric Artery (SMA)** and its branches
  - Supply the midgut and all its derivatives.
  - Useful to note that the anastomosis between the circulation of the foregut (via the celiac trunk) and the midgut is well-developed.
  - However, the anastomosis between the circulation of the midgut and the hindgut (via the Inferior Mesenteric Artery) is poorly developed, and results in a watershed area involving the transverse colon at the splenic flexure.
    - This part of the colon is therefore prone to ischemia if the IMA is occluded.

DEVELOPMENT OF THE MIDGUT

- Undergoes three major processes:
  - Elongation
  - Rotation
  - Retraction into the abdominal cavity
    - Elongation and rotation of the midgut usually occur at the same time.

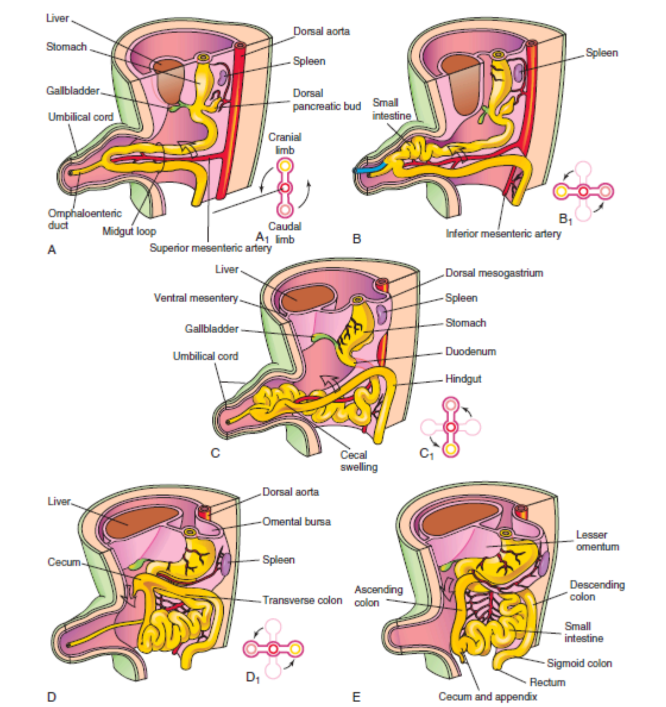


FIGURE 11–13 Drawings illustrating herniation and rotation of the midgut loop. A, At the beginning of the sixth week. A₁, Transverse section through the midgut loop, illustrating the initial relationship of the limbs of the loop to the superior mesenteric artery. Note that the midgut loop is in the proximal part of the umbilical cord. B, Later stage showing the beginning of midgut rotation. B₁, Illustration of the 90-degree counterclockwise rotation that carries the cranial limb of the midgut to the right. C, At approximately 10 weeks, showing the intestine returning to the abdomen. C₁, Illustration of a further rotation of 90 degrees. D, At approximately 11 weeks, showing the location of the viscera after retraction of the intestine. D₁, Illustration of a further 90-degree rotation of the viscera, for a total of 270 degrees. E, Later in the fetal period, showing the cecum rotating to its normal position in the lower right quadrant of the abdomen.

- During development, around **6 weeks**, the midgut grows in length rapidly.
- The rapid rate of growth exceeds the capacity of the abdominal cavity to hold all the contents of the midgut.
  - As a result, the midgut herniates into the umbilical cord, taking its blood supply (SMA) with it, forming a midgut loop with a cranial and caudal limb.
- The **yolk sac** is connected to the midgut at the tip of this loop.
  - This movement of the midgut into the umbilical cord is called physiological **umbilical herniation**.
- The cranial (superior) limb of the midgut loop will eventually form the **jejunum**, while the caudal limb of the loop will eventually form the **ileum** and **cecum**.
- The part of the midgut immediately distal to the caudal end of the loop will eventually form the **ascending** and the **transverse colon.**
- After herniating into the umbilical cord, the midgut loop will undergo 270° of counterclockwise rotation around the axis of the SMA (anterior-posterior axis) before returning back into the abdominal cavity by week 16.
  - This rotation will determine the final position of the midgut derivatives in the abdominal cavity.

THE ROTATION AND HOW IT AFFECTS THE SUPERIOR LIMB OF THE MIDGUT LOOP

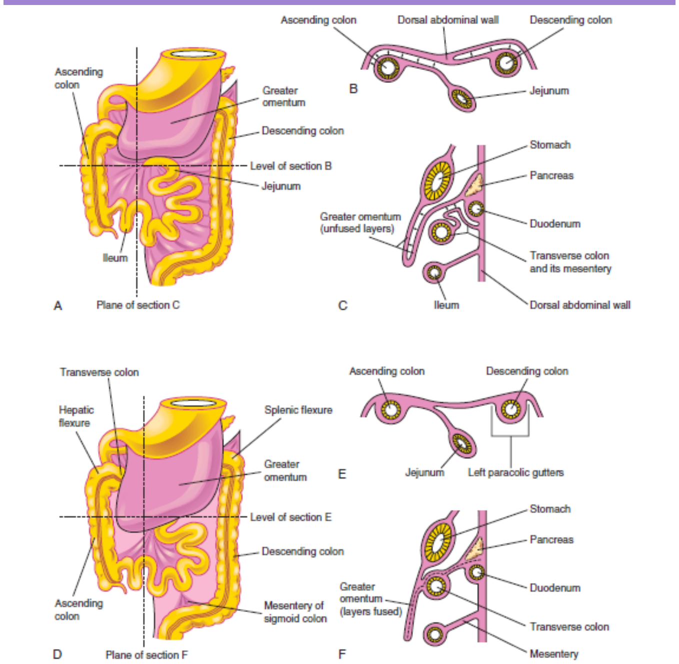


FIGURE 11–15 Illustrations showing the mesenteries and fixation of the intestine. A, Ventral view of the intestines before fixation. B, Transverse section at the level shown in A. The arrows indicate areas of subsequent fusion. C, Sagittal section at the plane shown in A, illustrating the greater omentum overhanging the transverse colon. The arrows indicate areas of subsequent fusion. D, Ventral view of the intestine after fixation. E, Transverse section at the level shown in D after disappearance of the mesentery of the ascending colon and descending colon. F, Sagittal section at the plane shown in D, illustrating fusion of the greater omentum with the mesentery of the transverse colon and fusion of the layers of the greater omentum.

Superior Limb of the Midgut Loop

- Viewing the **embryo** ventrally (from the front), applying the **first 90° rotation** (counterclockwise) will bring the superior limb down to the right.
- Next, applying the **second 90° rotation** will bring the limb to the right side.
- As the midgut loop is retracted back into the abdomen, the derivatives of the superior limb, the jejunum, will therefore occupy the left side of the abdomen.

Inferior Limb of the Midgut Loop

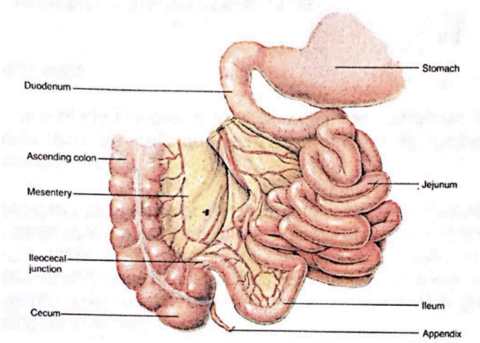
- Using the same principles to the **inferior limb of the midgut loop** (the future ileum and cecum), when we apply the **first 90° rotation (counterclockwise)**, this will bring the limb cranially.
- When the **final 90° rotation** is done, it will bring the limb to the right.
- As the midgut loop is retracted back into the abdomen, the derivatives of the inferior limb, the ileum, and the cecum, will occupy the left side of the abdomen.
- In rare cases, the reduction of the physiologic midgut hernia doesn't occur and the midgut loop remains in the umbilical cord. This would result in an **omphalocele**.
- As the midgut loop returns into the abdominal cavity, fixation of the intestines will occur. The mesentery of the ascending colon will come into contact with the parietal peritoneum of the posterior

abdominal wall and will fuse. As a result, the ascending colon becomes retroperitoneal.

- Also, the peritoneum of the duodenum, pancreas and descending colon fuses with the posterior abdominal wall. This fusion is important in limiting the mobility of the gut tube in adulthood.
  - If fusion failed to occur, the gut tube would be highly mobile, increasing the risk for volvulus.
- Also, in other parts of the gut tube, the endodermal cells lining the midgut undergo a **period of rapid proliferation** that temporarily obliterates the lumen.
  - However, these cells will un midgut in a process called **recanalization**.
- If apoptosis fails to occur, the lumen will remain obliterated.
  - This would result in **duodenal atresia** (failure of recanalization in the duodenum).

SMALL INTESTINES

- The small intestine is about 6 meters long and consists of three parts:
  - Duodenum
  - Jejunum
  - Ileum
- Occupies the central and lower parts of the abdominal cavity, usually within the colonic loop;
- It is related in front to the greater omentum and abdominal wall; a portion may reach the pelvis in front of the rectum.



ANATOMIC STRUCTURES AND ITS RELATIONS

Duodenum

- Is about 25 cm in length, firmly fixed to the dorsal wall of the abdomen, and largely retroperitoneal.
- It has a C-shaped course around the head of the pancreas and is continuous at its distal end with the jejunum, which is suspended from the dorsal wall of the cavity on a mesentery.
- It is situated entirely above the level of the umbilicus.

Jejunum

- Is freely moveable on its mesentery and occupies the proximal **two-fifths** of the length of the small intestine, whereas the ileum occupies about **three-fifths**.
- The convolutions of the jejunum occupy the central region of the abdomen, whereas the ileum is situated in the lower portion of the cavity.

HISTOLOGIC STRUCTURES

- There are minor differences in the histology of the mucosa in the three segments of the small intestine but there are no distinct boundaries between them.
- Throughout its length of 5 – 6 meters, the wall of the intestine consists of **four concentric layers**:
  - Mucosa
  - Submucosa
  - Muscularis
  - Serosa

Intestinal Mucosa

- The efficiency of the absorptive function of the small intestine is augmented by a number of structural devices that increase the total area of the mucosa.
  - The most obvious of these are the **plicae circulares (Valves of Kerckring)**
    - Visible to the naked eye as crescentic folds that extend for one-half to two-thirds of the distance around the lumen.
    - These are permanent structures including both mucosa and submucosa.
    - The larger the plicae are 8–10 mm in height, 3–4 mm in thickness, and up to 5 cm in length.
    - They are absent from the first portion of the duodenum but begin about 5 cm distal to the pylorus and reach their greatest abundance in the terminal portion of this segment and the first portion of the jejunum.
    - From there onward they gradually diminish in size and number and are seldom found beyond the middle of the ileum.
  - A second and more effective means of augmenting the surface area of the mucosa is the presence of enormous numbers of intestinal villi.
    - These finger-like projections of the mucosa have a length of 0.5 to 1.5 mm, depending on the degree of contraction of smooth muscle fibers in their interior.
    - Villi covers the entire inner surface of the intestine and gives it a characteristic velvety appearance in the freshly opened organ.
    - They are most numerous in the duodenum and proximal jejunum.
  - A further amplification in surface area is achieved by invaginations of the mucosa between the bases of the villi, called the **crypts of Lieberkuhn** or **intestinal glands**.
    - These tubular glands extend downward nearly to the muscularis mucosa.
    - Between the intestinal glands is loose connective tissue forming the lamina propria of the intestinal mucosa.

CELLS OF THE INTESTINAL MUCOSA

ABSORPTIVE CELLS

- The surface of the mucosa is a simple columnar epithelium in which three cell types can be distinguished:
  - absorptive cells
  - goblet cells
  - enteroendocrine cells
- The absorptive cells (enterocytes) are columnar, and 20 to 26 µm in height with a centrally situated, vertically elongated nucleus.
- The **luminal surface** has a prominent **brush border** (striated border), beneath which is a clear zone devoid of organelles but containing a distinct terminal web, a layer of transversely oriented fine filaments that exhibit birefringence under a polarizing microscope.
- In electron micrographs, the striated border consists of **closely packed microvilli**.
- Thin filaments radiating from the tips of the microvilli intermingle to form a continuous surface coat or **glycocalyx**.
- The filaments comprising the surface coat are of molecular dimensions, each consisting of the core polypeptide and the oligosaccharide side-chains of a glycoprotein that is an integral part of the plasmalemma.
- The layer they form is resistant to mucolytic and proteolytic agents and may, thus, protect the striated border.
- In the core of each microvillus, there is a bundle of about 20 parallel actin filaments.
- These are anchored in a cap-like subplasmalemmal density at the tip of the villus and they extend downward into the apical cytoplasm, where they intermingle with the transversely oriented cytoskeletal filaments of the terminal web.
- The actin filaments of the villus core are cross-linked by two proteins, fimbrin and villin, and the bundle as a whole attached to the membrane by a helical array of lateral arms or bridges that are visible in electron micrographs.

- The epithelium lining the intestinal tract is covered by a lubricating and protective layer of mucus.
- The surface membrane of the cells is occasionally disrupted by abrasive contents of the lumen, and the cells need considerable potential for repair.

GOBLET CELLS

- Mucus-secreting unicellular glands scattered among the absorptive cells of the intestinal epithelium.
- The apex has an expanded cup-shaped rim of cytoplasm, called the **theca**, filled with secretion, and a narrow base extending downward to the basal lamina.
- The secretory material is in the form of large pale granules that may be more or less confluent.
- The shape that gives the cell its name is now known to be an artifact.
- The common fixatives alter the permeability of the cell membrane and the hydrophilic mucin takes up water, resulting in swelling of the apical portion of the cell.
- The **luminal surface** of the cell bears a **few microvilli** around the periphery, but it is usually smooth and convex over the secretory granules.
- Goblet cells are firmly attached to neighboring absorptive cells by junctional complexes and there may be shallow interdigitations on their otherwise smooth lateral surfaces.
- The goblet cells has a well-developed cytoskeleton.
- **Intermediate filaments** are abundant in the theca.
- An **inner basket-like layer** is surrounded by circumferential bundles of filaments arranged like barrel hoops around the mass of secretory granules.
- Between the inner layer of filaments and the mucin granules, there are numerous vertically oriented **microtubules**.
  - These may play a role in the upward movement of newly formed mucin granules from the Golgi complex to the cell apex.
- The **basket-like filaments** in the theca contains little or no actin and there is no evidence that its contractions are involved in release of the cells secretory product.
- **Mucin** is synthesized and secreted at a relatively constant basal rate throughout the limited life span of the goblet cells.
  - It is normally released by exocytosis of one granule at a time, but in accelerated secretion there may be fusion of granule membranes resulting in chains of intercommunicating granules opening at the cell surface, a process called **compound exocytosis**.
- Within a few seconds of release, the content of the granules undergoes several-hundredfold expansion in volume due to its rapid hydration.
- The resultant gel forms a layer over the surface that protects the epithelium from abrasion and prevents adherence and invasion by pathogenic bacteria.

ENTEROENDOCRINE CELLS

- The **microvilli** of the enteroendocrine cells may be longer and thicker than those of the adjacent absorptive cells.
- The **cytoplasm** is relatively electron lucent and the organelles do not differ significantly from those of other epithelial cells.
- The **rough endoplasmic reticulum** varies in amount from one cell type to another, but in no case is it highly developed.
- **The substances that have been identified in enteroendocrine cells include**:
  - 5-hydroxytryptamine (serotonin)
  - Somatostatin
  - Glucagons/glicentin
  - Cholecystokinin
  - Gastrin
  - Motilin
  - Secretin
  - Neurotensin
  - Substance-P
  - Gastric-inhibitory polypeptide
  - B-endorphin
- Enteroendocrine cells are found in the greatest number and variety in the **duodenum** and **jejunum**.

PANETH CELLS

- Paneth cells do not participate in the upward migration of cells.
- Groups of them remain at the **bottom of the crypts.**
- They are **pyramidal** in form with a round or ovoid nucleus near their base.
- Paneth cells have an ultrastructure typical of cells active in protein synthesis.

CRYPTS OF LIEBERKUHN AND CELL TURNOVER

- The epithelium covering the villi continues into the intestinal glands or crypts of Lieberkuhn.
- Approximately, the upper half of the wall of the crypts is lined with columnar epithelium containing absorptive cells and goblet cells.
- In the lower half of the crypts, the cells are less differentiated except for groups of secretory cells called **Paneth cells**.
- Numerous cells in the crypts are found in mitosis. It is here that new cells are formed to replace those that are continually lost at the tips of the villi.
- This process of renewal is referred to as the cell turnover of the epithelium and its duration is the cell turnover time.
- The mucosa of the jejunum has the fastest rate of turnover of any tissue in the body.

LAMINA PROPRIA

- Is a loose connective tissue that occupies the interstices between the crypts of Lieberkuhn and the cores of the intestinal villi.
- It consists of **fixed** and **wandering cells** in a delicate network of reticular and elastic fibers and contains a rich network of capillaries subjacent to the epithelium.
- **Fibroblasts-like cells** are found immediately beneath the epithelium.
- These appear fusiform in sections and are commonly referred to as **subepithelial fibroblasts**.
  - But in preparations examined by scanning electron microscopy, after removal of epithelium, these cells are found to be stellate in form and they are attached to one another via gap junctions on their multiple radiating processes.
- The cytoplasm of these cells contains bundles of filaments that are not commonly seen in typical fibroblasts.
- Actin and myosin have been demonstrated in them histochemically.
- It is speculated that this network of cells, interposed between the epithelium and the subepithelial capillaries, are contractile and may contribute to the intermittent shortening and lengthening of the villi observed in vivo.
  - However, the principal agents of villus motility are very thin strands of smooth muscle that extend vertically from the muscularis mucosae into the core of the villus where they run parallel to the central lacteal, a slender lymphatic vessel that ends blindly near the tip of each villus
- The **lacteals** are terminal branches of a submucous lymphatic plexus.
  - They are important pathways for the transport of absorbed lipid and other nutrients.
- The periodic contractions of the smooth muscle in the lamina propria of the villi empty their lacteals and propel lymph toward the plexus, from where it flows onward to the mesenteric lymph nodes and ultimately to the thoracic duct.
- The intestinal mucosa is exposed to a lumen containing potentially harmful ingested substances and an immense and varied bacterial flora.
- The constant threat of penetration of the epithelial barrier by toxins and pathogenic bacteria has been countered by the development of special immunological defenses, in which the major participants are the lymphocytes, plasma cells, macrophages, and mast cells that infiltrate the lamina propria.
- **Macrophages** vary in number and location in the different segments of the intestine.

  - In the small intestine, they are located mainly in the lamina propria of the upper half of the villi.
  - They are avidly phagocytic and are the first line of defense against any microorganisms that may invade the mucosa from the lumen.

TWO KINDS OF MAST CELLS

- **Typical Mast Cells**
  - Are found in connective tissues throughout the body
- **Atypical Mast Cells (Mucosal Mast Cells)**
  - More restricted distribution.
- **Typical mast cells** predominate in the submucosa, whereas those in the lamina propria are the atypical mast cells.
- **Intestinal mast cells** are thought to be involved in local defenses against enteric parasites.
- The most abundant of the free cells of the lamina propria are the **lymphocytes**, which constitute a ready reserve of immunocompetent cells.

IMMUNOLOGICAL SURVEILLANCE OF LUMINAL ANTIGENS

- The **intestinal epithelium** with its intercellular tight junctions normally provides an effective barrier to entry of bacteria deeper into the tissues but in addition to this barrier function, certain cells take up samples of intraluminal foreign matter, including bacterial antigens, and pass these on to the mucosal immune system.
- This system consists of great numbers of individual **lymphocytes** found in the epithelium and its lamina propria and smaller lymphoid nodules are confined to the portion of the mucosa superficial to the muscularis mucosae, but the larger ones may occupy its entire thickness, extending down into the submucosa.
- In some areas, groups of lymphoid nodules coalesce to form aggregated lymphoid nodules, also called **Peyer's patches.**
  - They are usually located in the mucosa opposite the line of attachment of the mesentery.

SECRETORY IMMUNE SYSTEM OF THE INTESTINE

- The general immunological defenses of the body depend on the **IgG class** of immunoglobulins present in the blood and tissue fluids.
- The very large mucosal surface of the gastrointestinal tract exposed to a lumen inhabited by a host of potentially invasive microorganisms requires special protective mechanisms.
- A major component of these defenses is the secretory immune system which produces immunoglobulins of the **IgA class**.

MUSCULARIS MUCOSA

- Averages 38 μm in thickness and consists of thin inner and outer layers of smooth muscle together with networks of elastic fibers.
- Its contraction increases the height of folds of the mucosa.

SUBMUCOSA

- The submucosa consists of moderately dense connective tissue rich in elastic fibers.
- It may also contain small clusters of adipose cells.
- In the duodenum, it is largely occupied by the **glands of Brunner**.

SUBMUCOSAL GLANDS (BRUNNER'S GLAND)

- Are found in the submucosa of the plicae circulares.
  - A few of these Brunner's glands may also be found in the **pyloric antrum**.
- The secretory portions of the glands are coiled tubules forming small lobules.
- The ducts ascend through the muscularis mucosae to open into crypts of Lieberkuhn or occasionally onto the surface between villi.
- Under the light microscope, the gland cells have the pale appearance of mucus cells but in electron micrographs, they bear a superficial resemblance to pancreatic acinar cells in having dense secretory granules, a large Golgi complex, and abundant rough endoplasmic reticulum.
- The secretion of the duodenal glands is a clear, viscous, and distinctly alkaline fluid.
- Its principal function is to protect the duodenal mucosa against potentially damaging effects of the strongly acidic gastric juice periodically discharged through the pyloric sphincter.
- The mucoid nature of the secretion, its alkaline pH, and the buffering capacity of its bicarbonate content make it well suited to this role.
- Brunner's glands synthesize and secrete a low-molecular weight polypeptide that was originally called **urogastrone**.

MUSCULARIS

- The muscular coat of the small intestine consists of outer longitudinal and inner circular layers of smooth muscle, but some strands of smooth muscle fibers pass from one layer into the other.
- Between these layers is the **sympathetic myenteric nerve plexus.**
- The smooth muscle of the muscularis was formerly regarded as a static population, but autoradiographic studies have now shown that there is a slow rate of cell replication throughout the external layer and the rate differs in different portions of the alimentary tract.
- The **muscularis** is responsible for peristalsis, wave-like contraction that travels along the intestine at a rate of a few centimeters per second and propels the luminal contents onward.
- The **peristaltic waves** are propagated for short distances along the intestine and then die out, to be followed a few minutes.
- In the terminal portion of the ileum, the muscularis is somewhat thickened, forming the **ileocaecal sphincter**.
- This normally remains partially contracted, delaying emptying of the contents of the small intestine into the cecum.

SEROSA

- The outermost layer of the gut wall, the serosa, consists of a continuous sheet of squamous cells, the mesothelium, separated from the underlying muscularis by a very thin layer of loose connective tissue.
- For most of its length, the gastrointestinal tract is suspended from the dorsal wall of the abdomen by a mesentery, a thin bilaminar sheet of mesothelium through which the blood vessels reach the gut.
- Along the line of attachment of the mesentery, the serosa of the intestine is continuous with the two apposed leaves of the mesentery, and at the base of the mesentery these are, in turn, continuous with the serous lining of the abdominal cavity.
- The inner aspect of the abdominal wall and the surface of all of the organs suspended from it are covered by a continuous layer of mesothelium, usually referred to as the **peritoneum**.
  - That portion lining the cavity is called **parietal peritoneum** and that covers the organs is the visceral peritoneum.

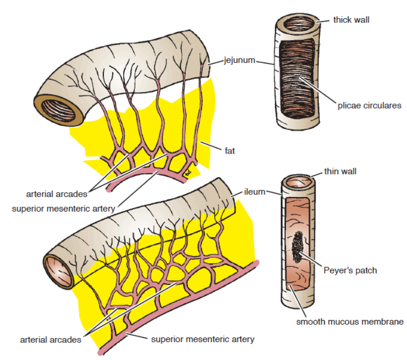


FIGURE 5.31 Some external and internal differences between the jejunum and the ileum.

BLOOD VESSEL OF THE INTESTINAL TRACT

- Arteries supplying the duodenum arise from the right gastric, supraduodenal, right gastro-epiploic and superior and inferior pancreaticoduodenal arteries, the first part receives leashes of small rami, one from hepatic artery proper and one from the gastroduodenal artery.
- These branches also supply the adjacent pyloric canal, with some anastomosis in the muscular layer across the pyloroduodenal junction.

- Blood vessels supplying the duodenum and ileum stem from the **superior mesenteric artery**, branches of which, reaching the mesenteric border, extend between the serosal and muscular layers.
- In the **intestine**, the vessels reach the organ from the mesentery and break up into large branches that penetrate the muscularis externa to enter the submucosa, where they form a large plexus.
- In the **small intestine**, the submucous arterial plexus gives off two kinds of branches.
    - Some of these ramify on the inner surface of the muscularis mucosae and break up into capillary networks that surround the crypts of Lieberkuhn.
    - Other branches are destined for the villi, each villus receiving one, and sometimes two or three such small arteries.
- In the villi, they form a dense capillary network immediately beneath the epithelium.
- **Venous drainage** is by the **superior mesenteric vein** which joins other veins to form the portal vein.
- Near the tip of the villus **one or two small veins** arise from the capillary network and run downward to anastomose with the venous plexus. These small veins of the intestine have no valves.

LYMPH VESSELS OF THE INTESTINAL TRACT

- The lymphatics begin as an extensive system of large lymphatic capillaries in the superficial portion of the mucosa between the glands. They are always situated below the blood capillaries.
- They anastomose extensively around the glands and take a downward course to the inner surface of the mucosa where they form a plexus of lymphatics that are provided with valves.
- From the submucous plexus, larger lymphatics run through the muscularis externa. Here, they receive numerous lymphatics from the lymphatic plexus in the muscular coat and then follow the blood vessels into retroperitoneal tissues.
- **Lymphatics** are very important for the absorption of fat in the small intestine.
- During digestion, they become filled with **milky white lymph**, a fine emulsion of neutral fats.
    - This white lymph draining from the epithelium is called **lacteals**.
- The most interesting of the lymphatics of the small intestine is the **central lacteals** in the core of the villi. Each conical villus has an axial lacteal that ends blindly near its tip.
- The broader the villi of the duodenum may contain two or more lacteals that intercommunicate.
- When distended, their lumen is considerably larger than that of a blood capillary.
- The wall consists of **very thin endothelial cells** supported by an **argyrophilic reticulum** and surrounded by thin longitudinal strands of smooth muscle.
- At the **base of the villi**, the central lacteals join the lymphatic capillaries around the glands and continue downward to form a plexus on the inner surface of the muscularis mucosae.
- From this plexus, branches provided with valves penetrate the muscularis mucosae and form a second loose plexus of larger lymphatics in the submucosa.
- These vessels receive tributaries from the dense networks of thin-walled lymphatics that surround the solitary and the aggregated lymphoid follicles.

NERVES OF THE INTESTINAL TRACT

- The small intestines are supplied from the **vagi and thoracic splanchnic nerves** through the coeliac ganglia and superior mesenteric plexuses.
- Fibers pass to the myenteric plexus of nerves and ganglia between the circular and longitudinal layers of the muscularis externa, which they supply.
- From this secondary, **submucous plexus** is derived, formed by branches perforating the circular muscular layer;
    - It also contains ganglionic neurons from which fibers pass to the muscularis mucosae and the rest of the mucosa.
    - Nerve bundles in the submucous plexus are finer. Ganglionic cells in both plexuses are essentially parasympathetic (vagal).
- The **sympathetic system** inhibits peristalsis but stimulates the sphincters and muscularis mucosae.
- The **parasympathetic** augments peristalsis and inhibits the sphincters, the result of parasympathetic stimulation depending on the state of contraction or relaxation of the organ at the time of stimulation. This also augments intestinal secretion.
- The most superficial neural elements in the gut wall form a **subserous plexus** which generally lacks ganglia and is made up of loose network of finer nerve fibers that connect the extrinsic nerves with the more deeply situated intrinsic nerve plexuses.
- The majority of the nerve coursing from the mesentery to the deeper enteric plexuses traverse the longitudinal muscle layer near the attachment of the mesentery.
- The most conspicuous enteric plexus is found between the longitudinal and circular layers of the muscularis. This **myenteric plexus (Auerbach's plexus, plexus entericus-externa)** consists of ganglia containing from 3 to 50 or more nerve cell bodies and bundles of unmyelinated axons that connect the ganglia to form a continuous network.
- Most of the unmyelinated fibers in the ganglia and in the internodal strands of the plexus are processes of enteric neurons.
- The remainder is axons of extrinsic vagal or sympathetic origin.
    - The vagal fibers terminate as perikaryal arborization on ganglion cells of the second type.
    - The sympathetic fibers do not seem to have synaptic relationships with the nerve cells of the ganglia but are thought to terminate in the muscularis and on blood vessels.

CELLS OF THE GANGLIA

- The cells of the ganglia are **two morphological types**.
    - One is a multipolar cell with short dendrites in contact with the bodies of similar cells within the same ganglion, whereas the axon can be traced for a considerable distance to sites of synaptic contact with cells of the second type in neighboring ganglia.
    - Cells of the second type are far more numerous and more variable in form.
        - The dendrites are diffuse receptor endings related to cells of the first type or to the same type, in the same or in other ganglia.
        - The axon enters one of the fiber bundles associated with the ganglion and its fibers terminate in the circular or longitudinal muscle layers.
- Cells of the **first type** appear to be associative while those of the **second type** are motor.
    - A **third cell type**, called the **interstitial cell**, has short branching processes that intermingle with those of the other cell type.
        - It does not contain demonstrable neurofibrils and may be a form of glial cells.

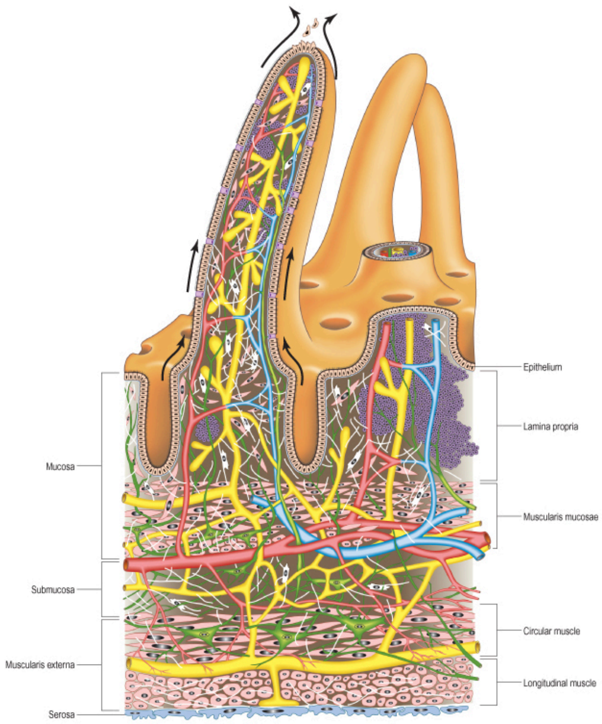
DEEP MUSCULAR PLEXUS

- Otherwise known as plexus muscularis profundus
- Is situated on the mucosal aspect of the circular muscle layer.
- It is devoid of ganglia & consists of thin anastomosing nerve bundles with their prevailing orientation parallel to the muscle fibers.
- Branches from this plexus penetrate into the muscle layer and some are connected with the myenteric plexus.

DEEP MUSCULAR PLEXUS

- AKA **Meissner's plexus** or **plexus entericus interna**
- Is a network of ganglia and interconnecting nerve bundles within the connective tissue of the submucosa.
- Its fibers innervate the muscularis mucosae and smooth muscle fibers in the cores of the intestinal villi.
- Fibers from the submucous plexus also form a mucosal plexus situated in the lamina propria and sending components between the intestinal glands and into the villi.

- Although these several plexuses are distinguished on the basis of their architecture and location in the intestinal wall, they do not function independently.
- Connections can be traced from the subserous to the myenteric plexus; from the myenteric plexus to the submucous plexus; and from the latter to the mucosal plexus and to paravascular nerves along the submucosal arteries.
- **Cholinergic neurons** in the intestine are the only intrinsic nerves for which both the transmitter and the functions are known.
    - The cholinergic neurons of the enteric plexuses supply both longitudinal and circular muscle and are of prime importance in the peristaltic reflex.
- **Non-cholinergic and non-adrenergic inhibitory neurons** are another class of neurons responsible for relaxation of intestinal smooth muscle.

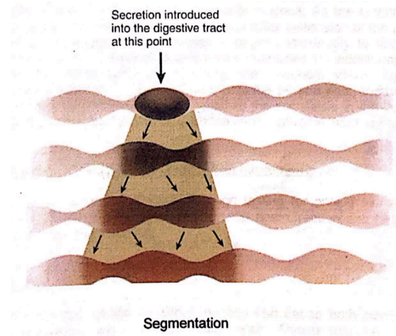


MOVEMENTS OF THE SMALL INTESTINE

- Can be divided into mixing contractions and propulsive contractions

MIXING CONTRACTIONS (SEGMENTATION CONTRACTIONS)

- When a portion of the small intestine becomes distended with chyme, the stretching of the intestinal wall elicits localized concentric contractions spaced at intervals along the intestine and lasting a fraction of a minute.
- The contractions cause **"segmentation"** of the small intestine.
    - They divide the intestine into spaced segments that have the appearance of a chain of sausages.
- As one set of segmentation contraction relaxes, a new set often begins, but the contractions this time occur mainly at new points between the previous contractions.
- Therefore, the segmentation contractions can **"chop"** the chyme about two or three times per minute, in this way promoting the progressive mixing of the food particles with the secretions of the small intestine.
- The maximum frequency of the segmentation contraction in the small intestine is determined by the frequency of the slow waves in the intestinal wall.
- Because this frequency is normally about **12 per minute** in the **duodenum** and **proximal jejunum**, the maximum frequency of the segmentation contractions in these areas is also about 12 per minute, but this occurs only under extreme conditions of stimulation.
- In the terminal **ileum**, the maximum frequency is usually **eight to nine contractions per minute.**
- The segmentation contractions become <u>exceedingly weak</u> when the excitatory activity of the enteric nervous system is blocked by **atropine**.
- Therefore, even though it is the slow waves in the smooth muscle itself that controls the segmentation contractions, these contractions are not effective without background excitation from the enteric nervous system, especially from the myenteric plexus.



PROPULSIVE MOVEMENTS

PERISTALSIS IN THE SMALL INTESTINE

- **Chyme** is propelled through the small intestine by peristaltic waves.
- These can occur in any part of the small intestine, and they move analward at a velocity of 0.5 to 2.0 cm/sec, much faster in the proximal intestine and much slower in the terminal intestine.
- They are normally <u>very weak</u> and usually die out after traveling only 3 to 5 centimeters, very rarely farther than 10 centimeters, so that forward movement of the chyme is very slow, so slow in fact than net movement along the small intestine normally averages only 1 cm/min.
- This means that <u>3 to 5 hours</u> are required for the passage of chyme from the pylorus to the ileocecal valve.

CONTROL OF PERISTALSIS

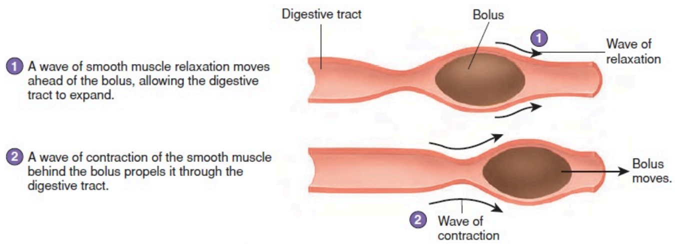
- Peristaltic activity of the small intestine is greatly increased after a meal.
- This is caused partly by the beginning entry of chyme into the duodenum but also by a so-called **gastroenteric reflex** that is initiated by distension of the stomach and conducted principally through the myenteric plexus from the stomach down along the wall of the small intestine.
- In addition to the nervous signals that affect small intestinal peristalsis, **several hormonal factors affect peristalsis.**
    - They include <u>gastrin, CCK, insulin, and serotonin,</u> all of which enhance intestinal motility and are secreted during the various phases of food processing.
    - Conversely, **secretin** and **glucagon** <u>inhibit small intestinal motility.</u>
- The function of the peristaltic waves in the small intestine is not only to cause progression of the chyme towards the ileocecal valve but also to spread out the chyme along the intestinal mucosa.
- As the chyme enters the intestine from the stomach and causes initial distension of the proximal intestine, the elicited peristaltic waves begin immediately to spread the chyme along the intestine; this process intensifies as additional chyme enters the duodenum.
- On reaching the ileocecal valve, chyme is sometimes blocked for several hours until the person eats another meal; at that time, a **gastroileal reflex** intensifies the peristalsis in the ileum and forces the remaining chyme through the ileocecal valve into the cecum.

PROPULSIVE EFFECT OF THE SEGMENTATION MOVEMENTS

- The segmentation movements although lasting for only a few seconds, often also travel 1 centimeter or so in the anal direction and help propel the food down the intestine.

PERISTALTIC RUSH

- Intense irritation of the intestinal mucosa can cause both powerful and rapid peristalsis called the **peristaltic rush.**
- This is initiated partly by nervous reflex that involve the autonomic nervous system and the brain stem and partly by intrinsic enhancement of the myenteric plexus reflexes within the gut wall itself.
- The powerful peristaltic contractions travel long distances in the small intestine within minutes, sweeping the contents of the intestine into the colon and thereby relieving the small intestine of irritative chyme and excessive distension



PROCESS Figure 16.9 Peristalsis

ACCESSORY ORGANS OF DIGESTION

- Liver
- Gallbladder
- Pancreas

EMBRYONIC DERIVATIVES OF THE LIVER, BILIARY TREE AND THE PANCREAS

LIVER AND BILIARY APPARATUS

- The liver, gallbladder, and biliary duct system arise as ventral outgrowth from the caudal part of the foregut early in the *fourth week.*
- The hepatic diverticulum (liver bud) extends into the **septum** transversum, a mass of splanchnic mesoderm between the developing heart and midgut.
- The septum transversum forms the central tendon of the diaphragm and the ventral mesentery in this region.
- The hepatic diverticulum enlarges rapidly and divides into two parts as it grows between the layers of the ventral mesentery.
- The larger cranial part of the hepatic diverticulum is the **primordium of the liver.**
- The proliferating endodermal cells give rise to interlacing cords of hepatic cells and to the epithelial lining of the intrahepatic portion of the biliary apparatus.
- The **hepatic cords** anastomose around endothelium-lined spaces, the primordia of the hepatic sinusoids.
- The **fibrous and hematopoietic tissue** and **Kupffer cells** of the liver are derived from mesenchyme in the septum transversum.

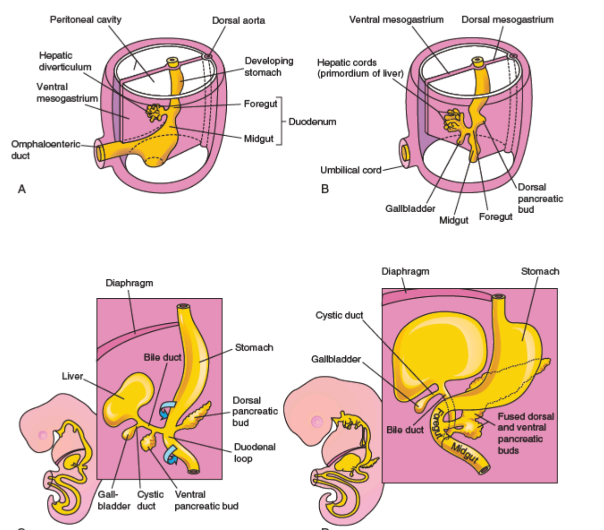


FIGURE 11–5 Progressive stages in the development of the duodenum, liver, pancreas, and extrahepatic biliary apparatus. A, Embryo of 4 weeks. B and C, Embryo of 5 weeks. D, Embryo of 6 weeks. During embryologic development, the dorsal and ventral pancreatic buds eventually fuse, forming the pancreas. Note that the entrance of the bile duct into the duodenum gradually shifts from its initial position to a posterior one. This explains why the bile duct in adults passes posterior to the duodenum and the head of the pancreas.

- The liver grows rapidly and, from the fifth to tenth weeks fills a large part of the abdominal cavity.
- The quantity of oxygenated blood flowing from the umbilical vein into the liver determines the development and functional segmentation of the liver.
- Initially, the right and left lobes are about the same size, but the right lobe soon becomes larger.
- **Hematopoiesis** begins during the sixth week, giving the liver a bright reddish appearance.
  - This hematopoietic activity (formation of various types of blood cells and other formed elements) is mainly responsible for the relatively large size of the liver between the seventh and ninth weeks of development.
  - By ninth week, the liver accounts for about 10% of the total weight of the fetus.
- **Bile formation** by the hepatic cells begins during the twelfth week.
- The small caudal part of the hepatic diverticulum becomes the gallbladder, and the stalk of the diverticulum forms the cystic duct.
- Initially, the extrahepatic biliary apparatus is occluded with epithelial cells, but it is later canalized because of vacuolation resulting from the degeneration of these cells.
- The stalk connecting the hepatic and cystic ducts to the duodenum becomes the **bile duct (common bile duct).**
- Initially, this duct is attached to the ventral aspect of the duodenal loop; however, as the duodenum grows and rotates, the entrance of the bile duct is carried to the dorsal aspect of the duodenum.
- The bile entering the duodenum through the bile duct after the thirteenth week gives the **meconium** (intestinal contents) a dark green color.

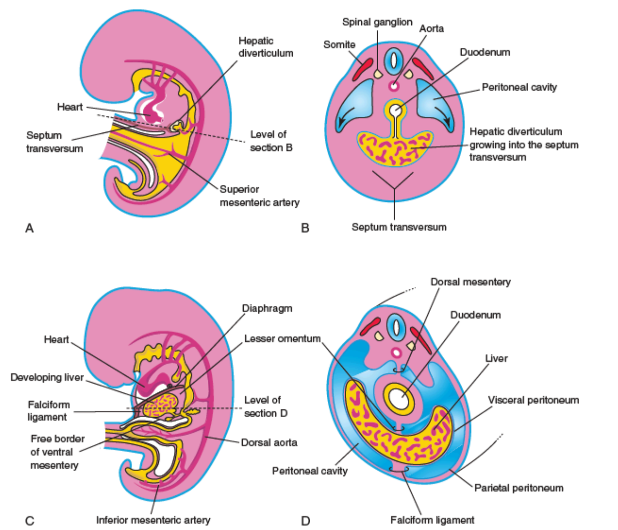


FIGURE 11–8 A, Median section of a 4-week embryo. B, Transverse section of the embryo showing expansion of the peritoneal cavity (*arrows*). C, Sagittal section of a 5-week embryo. D, Transverse section of the embryo after formation of the dorsal and ventral mesenteries.

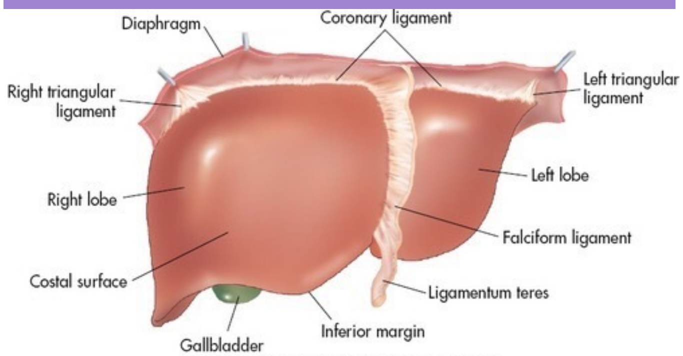
LIVER

EXTERNAL FEATURES

- The **liver** lies in the upper right part of the abdominal cavity, occupying most of the right hypochondrium and epigastrium and extending into the left hypochondrium.
- In males it generally weights 1.4–1.8 kg and in females 1.2–1.4 kg with a range of 1.0–2.5 kg.
- It is somewhat cuneiform, is reddish brown in color in the fresh state, and though firm and pliant, is easily lacerated.
- The liver is a wedge-shaped organ, its narrow end pointing left and its anterior edge directed downwards.
- It is convex in the front, to the right, above, and behind and it is somewhat concave inferiorly.
- The liver is attached to the body wall by the **falciform ligament**, and above and behind to the diaphragm by the coronary ligament, with its lateral limits, the **right and left triangular ligament** (forming reflections of the peritoneum from the liver surface to the diaphragm).

- Below, it is attached to the stomach and first part of the duodenum by the lesser omentum, along the right (free border) or which the hepatic arteries, hepatic portal vein, lymphatics, nerves and hepatic ducts enter or leave the liver at the **porta hepatis** (the door to the liver), an area also termed the **hilus**.
- The gallbladder adheres to the anterior part of the liver's inferior surface.
- The anterior surface is marked near the midline by a sharp fissure, which anteriorly receives the **ligamentum teres** (the obliterated fetal left umbilical vein) from the free edge of the falciform ligament, and posteriorly contains the **ligamentum venosum**, another obliterated relic of the fetal circulation.
- Posteriorly, the liver is deeply grooved where it partially surrounds the inferior vena cava (the caval groove), which receives the large hepatic veins in this region.

LOBES



- Although much of the surface is smoothly continuous, the liver is apportioned into a larger right and a much smaller left lobe according to some markings and peritoneal attachments, namely the line of attachment of the falciform ligament anteriorly, and the fissure of the ligamentum teres and ligamentum venosum on the liver's inferior surface.
- To the right of this groove are **two prominences**, the quadrate lobe in front, and the caudate lobe behind, separated from each other by the **porta hepatis**.
- The gallbladder lies in a shallow fossa to the right of the quadrate lobe.

Right Lobe

- Much greater in volume, it contributes to all surfaces including the entire costal aspect.
- Its surfaces (anterior, superior, inferior, and posterior) all pass uninterruptedly on to the **left lobe**, except where shallow grooves partially demarcate the quadrate and caudate 'lobes', really parts of the left lobe.

Quadrate Lobe

- Visible on the inferior surface
- It appears somewhat rectangular and is bounded in front by the inferior border, on the left by the fissure for ligamentum teres, behind by the porta hepatis and on the right by the fossa for the gallbladder.

Caudate Lobe

- This is visible on the posterior surface, bounded on the left by the fissure for the ligamentum venosum, below by the porta hepatis and on the right by the groove for the inferior vena cava.
- Above, it continues into the superior surface of the right of the upper end of the fissure for the ligamentum venosum.
- Below and to the right, it is connected to the right lobe by a narrow caudate process, which is immediately behind the porta hepatis and above the epiploic foramen.
- Below and to the left, the caudate lobe has a small rounded papillary process.
- Due to the depth of the fissure for the ligamentum venosum, the caudate lobe has an anterior surface, which forms the posterior wall of the fissure and is in contact with the lesser omentum (hepatic part).

PERITONEAL LIGAMENTS

- Except for a triangular area on its posterior surface (the "**bare area**"), and the liver is almost completely covered by **peritoneum**, which connects it to the stomach, duodenum, diaphragm and anterior abdominal wall by several folds, their lines of attachment, being devoid of peritoneum.
- These folds include the falciform ligament, right and left triangular and coronary ligaments and the lesser omentum.

Falciform Ligament

- The falciform ligament is a crescentic or "sickle shaped" sagittal fold of 2 layers of peritoneum and it connects the liver to the diaphragm and the supra-umbilical part of the anterior abdominal wall.
- At its diaphragmatic end, its layers separate to expose a triangular area on the superior hepatic surface devoid of peritoneum.
- The left layer continues into the anterior layer of the left triangular ligament and the right layer into the upper layer of the coronary ligament.

Coronary Ligament

- This name is given to the reflexion of the peritoneum from the diaphragm to the superior and posterior surfaces of the right lobe of the liver, forming the perimeter of the approximately triangular but variable '**bare area**' of the liver, i.e., that part of its surface, which is apposed to the diaphragm without intervening peritoneum.
- The **coronary ligament** has upper and lower margins or layers, united laterally at angular extensions, the right and left and triangular ligaments.

Left Triangular Ligament

- It ascends back from the superior surface of the left lobe to the diaphragm.
- Its closely applied layers become fused at the left edge of the ligament.
- To the right, the anterior layer merges with the left layer of the falciform ligament, the posterior with the anterior layer of the lesser omentum at the upper end of the fissure for the ligamentum venosum.
- The left triangular ligament lies in front of the abdominal part of the esophagus, the upper end of the lesser omentum and part of the fundus of the stomach.

Right Triangular Ligament

- This is a short V-shaped fold connecting the lateral and posterior aspects of the right lobe to the diaphragm.
- It is situated in the right extremity of the 'bare area'.
- At its margin, its two layers are continuous.
- The ligament is really the right extremity of the coronary ligament.

Lesser Omentum

- The lesser omentum is attached along the line of the fissure for the ligamentum venosum, at the upper end of which its anterior layer merges with the posterior layer of the left triangular ligament and its posterior layer with the line of reflexion of the peritoneum from the upper end of the right caudate lobe and so indirectly with the lower coronary layer.

SURFACES

- The liver is described as having **superior**, **anterior**, **right**, **posterior**, and **inferior surfaces**, and a distinct **inferior border**.
- The superior, anterior, and right surfaces are continuous at rounded 'borders', but the sharp inferior border separates the right and anterior surfaces from the inferior surface.
    - This border is rounded between the right lateral and inferior surfaces, but becomes thin and angular at the lower limit of the anterior surface and it is notched along this edge by the ligamentum teres, just to the right of the midline.
- Lateral to the fundus of the gallbladder, which often corresponds to a second notch 4 - 5 cm to the right of the midline, the inferior border largely follows the costal margin.

- Left of the fundus, it ascends less obliquely than the right costal margin near the tip of the eighth costal cartilage.
    - It ascends sharply to merge with the thin margin of the left lobe.
- At the infrasternal angle, the inferior border adjoins the anterior abdominal wall and is accessible to examination by percussion, but is not usually palpable;
- In the midline the inferior border of the liver is near the **transpyloric plane**, about a hand's breadth below the xiphisternal joint.
    - In women and children the border often projects a little below the right costal margin.

Superior Surface

- The **superior surface** includes parts of the right and left lobes.
- It fits closely under the diaphragm, separated from it by peritoneum except for a small triangular area where the two layers of the falciform ligament diverge.
- **Right and left** it is convex but **centrally** it presents a shallow cardiac impression corresponding with the position of the heart above the diaphragm.
- It is related to the right diaphragmatic pleura and base of the right lung, to the pericardium and ventricular part of the heart and to part of the left diaphragmatic pleura and base of the left lung.

Anterior Surface

- The **anterior surface,** which is **triangular and convex,** is covered by peritoneum except at the attachment of the falciform ligament.
- Much of it is in contact with the diaphragm, which separates it on the right from the pleura and sixth to tenth ribs and cartilages, and on the left from the seventh and eight costal cartilages.
- The thin margins of the base of the lungs are thus quite close to the upper part of this surface, more extensively on the right.
- The **median area** of the anterior hepatic surface lies behind the xiphoid process and the anterior abdominal wall in the infra-costal angle.

Right Surface

- The **right surface**, covered by peritoneum, adjoins the right dome of the diaphragm, which separates it from the right lung and pleura and the seventh to eleventh ribs.
- **Above its upper third**, both right lung and pleura are inserted between the diaphragm and ribs
- Over its **middle third**, only the costodiaphragmatic pleura is interposed
- Over its **lower third**, the diaphragm and thoracic wall are in contact.

Posterior Surface

- The posterior surface is convex and wide on the **right** but narrow on the **left**, with a deep median concavity corresponding to the forward convexity of the vertebral column.
- Much of its surface is devoid of peritoneum, being attached to the diaphragm but loose connective tissue, forming the so-called **'bare area'**, triangular in shape and limited above and below by layers of the coronary ligament.
- The base of the posterior hepatic surface to the left is the **caval groove**; its apex, directed down and right, corresponds to the right triangular ligament.
- The groove for the inferior vena cava **(caval groove)**, which is deep and occasionally a tunnel, lies at the posterior surface and is bare of peritoneum and adapted to the upper part of the vessel it contains; its floor is pierced by the **hepatic veins**.
- Lateral to its lower end the 'bare area' adjoins the upper pole of the right suprarenal gland.
- Left to the the groove the caudate lobe forms the posterior surface in the superior omental recess; the peritoneum on its posterior aspect curves round its left border to its anterior aspect, which is the posterior wall of the fissure for the ligamentum venosum.
- The caudate lobe projects into the superior omental recess from the right; its posterior surface is related to the diaphragmatic crura (above the aortic opening) and the right inferior phrenic artery, separated by them from the **descending thoracic aorta.**
- The **papillary process** often descends in front of the origin of the coeliac artery.
- The fissure for the ligamentum venosum separates the posterior aspect of the caudate from the main part of the left lobe.
- The fissure cuts deeply in front of the caudate lobe and contains two layers of the lesser omentum.
- Below it curves laterally in front of the papillary process to the left end of the porta hepatis.
- The **ligamentum venosum**, the fibrous remnant of the ductus venosus, is attached below to the left branch of the portal vein's posterior aspect; ascending in the floor of the fissure and passing laterally at the upper end of the caudate lobe it joins the left hepatic vein near its entry into the inferior vena cana, or sometimes the vena cava itself.
- The left lobe's posterior aspect has a shallow esophageal impression near the upper end of the fissure for the ligamentum venosum, occupied by the abdominal part of the esophagus.
- Left of this the left lobe is related to part of the fundus of the stomach

Inferior Surface

- The inferior surface bears the imprint of the adjacent viscera.
- It is covered by visceral peritoneum except at the porta hepatis, fissure for the ligamentum venosum and fossa for the gallbladder.
- On the **left lobe**, continuous with the esophageal groove, is a gastric impression.
- On the right of this the rounded **omental tuberosity**, in the concavity of the lesser curvature, is in contact with the lesser omentum.
- The fissure for the ligamentum teres ascends backwards from its notch on the inferior hepatic border to the left end of the fissure for ligamentum venosum.
- It is the left boundary of the quadrate lobe and may be, partially or wholly, bridged by a band of liver.
- **On its floor** is the ligamentum teres.
- From the umbilicus this ligament ascends in the edge of the falciform ligament to the inferior hepatic border, where it traverse the fissure to join the left branch of the portal vein at the left end of the porta hepatis, opposite the attachment of the ligamentum venosum

HEPATIC VESSELS

- The vessels connected with the liver are the **portal vein, hepatic artery proper,** and **hepatic veins**.
- The portal vein and hepatic artery proper ascend in the lesser omentum to the porta hepatis, where each bifurcates.
- The bile duct and lymphatic vessels descend from the porta in the same omentum (the hepatic artery lying anteriorly and to the left, the bile duct anteriorly and right, and the hepatic portal vein posteriorly).
- All these structures are enveloped in the **perivascular capsule (hepatobiliary capsule of Glisson)**, a sheath of loose connective tissue, which also surrounds the vessels as they course through the portal canals in the liver.
- It is also continuous with the fibrous capsule.

Hepatic Artery

- The hepatic artery arises from the **coeliac trunk** and bifurcates unto the right and left branches.
- The hepatic artery and its branches pursue a variable course in the porta hepatis.
- The smaller branches finally become associated with a specific branch of the portal vein and are distributed in the same territory.
- There are no anastomoses between their territories; each is an end artery.

Hepatic Veins

- The hepatic veins convey blood from the liver to the inferior vena cava.
- It commences in the **interlobular veins**, which collect blood from the sinusoids of the liver lobules.

- The **interlobular veins** open into sublobar veins and these in turn unite to form the hepatic veins, which emerge from the posterior surfaces of the liver and open immediately into the inferior vena cava as it lies in a groove on the posterior surface of the liver.
- The hepatic veins are arranged in upper and lower groups.
  - The **upper** are usually large veins, right, left, and middle, the last from the caudate lobe;
  - the **lower** varying in number, are small and from the right and caudate lobes.
- The **hepatic veins** are contiguous with hepatic tissue and have no valves.

Portal Vein

- The portal vein is an afferent vessel that carries blood from the digestive tract and the spleen.
- The portal vein is about 8 cm long and begins at the second lumbar vertebral level from the convergence of superior mesenteric and splenic veins, anterior to the inferior vena cava, posterior to the neck of the pancreas.
- It inclines slightly to the right as it ascends behind the superior part of the duodenum, bile duct and gastroduodenal artery and directly anterior to the inferior vena cava and reaches the right end of the porta hepatis, where it divides into right and left stems, which accompany the corresponding branches of the hepatic artery into the liver.
  - The **right branch** enters the right hepatic lobes but usually receives the cystic vein.
  - The **left branch**, longer but smaller caliber, branches into caudate, quadrate and left lobes.
- As it enters the left lobe, it is joined the paraumbilical veins and the ligamentum teres.
- It is connected to the inferior vena cava by the ligamentum venosum.

Deep Hepatic Lymphatics

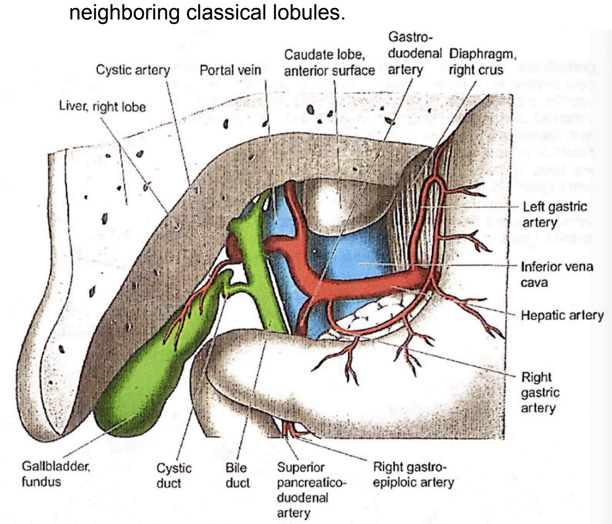
- They form the ascending and descending trunks
- The ascending trunks accompany the hepatic veins and pass through the vena caval opening to end in the nodes found the end of the inferior vena cava;
- The descending trunks emerge from the porta hepatis to end in the hepatic nodes.

INNERVATION OF THE LIVER

- The hepatic nerves arise from the **hepatic plexus** containing sympathetic and parasympathetic (vagal) fibers.
- They enter at the **porta hepatis** and largely accompany blood vessels and bile ducts; very few runs among the liver cells and their terminations are uncertain.
- Both myelinated and non-myelinated fibers reach the liver from nerves in its various peritoneal folds.

HISTOLOGY OF THE LIVER

- The majority of exocrine glands are partitioned by connective tissue into distinct globes and smaller lobules, and parenchyma is made up of epithelial cells forming bulbous acini at the ends of a branching system of ducts.
- The liver is quite different, in that there is little connective tissue in its interior.
- Its epithelium presents a remarkably uniform appearance throughout the organ and structurally subunits are not easily identifiable.
- It is possible, however, to detect a repeating pattern of roughly hexagonal areas, in which fenestrated plates of parenchymal cells are radially arranged around a central vein.
- At three corners of these polygonal areas there is a small triangular area of connective tissue enclosing a small bile duct, a branch of hepatic artery, and a branch of the portal vein. This complex is referred to as the **portal triad or portal area**.
- Lateral branches of these vessels, occurring at short intervals along their length are confluent with thin-walled hepatic sinusoids that occupy the spaces between radially arranged trabeculae and drain into the central vein.
- The fenestrated rates of hepatic cells are, thus, exposed to a large volume of blood flowing centripetally in the labyrinthine system of sinusoids.
- **Bile** is continuously secreted into a network of intercellular bile canaliculi within the cell plates and flows outward to bile ductules in the portal areas at the periphery.
  - This polygonal unit, about 0.7 mm in diameter and 2 mm long, was called the hepatic lobule and for a century or more was considered to be the structural and functional unit of the liver.
  - It is now commonly referred to as the **classical lobule** to distinguish it from other subunits described in more recent interpretations of liver architecture.
- Around the turn of the century, an interpretation of liver organization was proposed.
  - In this, the liver lobule was considered to consist of the mass of parenchyma around each portal area, including all of those cells secreting into its bile ductule.
  - This structural subunit was called **portal lobule**.
    - In section, it is roughly triangular in shape and includes sectors of three neighboring classical lobules.
  - Its proponents argued that it is more consistent with the organization of other glands, in having a blood supply radiating from axial vessels and its secretory product training to a central duct, but it has not been widely accepted.
- Since the 1950s, the majority of investigators have preferred the **hepatic acinus** as the structural and functional unit of the liver.
  - This is a roughly ovoid mass of parenchymal cells around each terminal arteriole, venule, and bile duct that branch laterally from the portal area.
  - At either end of the acinus is a vessel that was called the **central vein** in the classical lobule but is now referred to as the **terminal hepatic venule** in reference to the acinus.
  - The **acinus** is a smaller unit including a sector of two neighboring classical lobules.



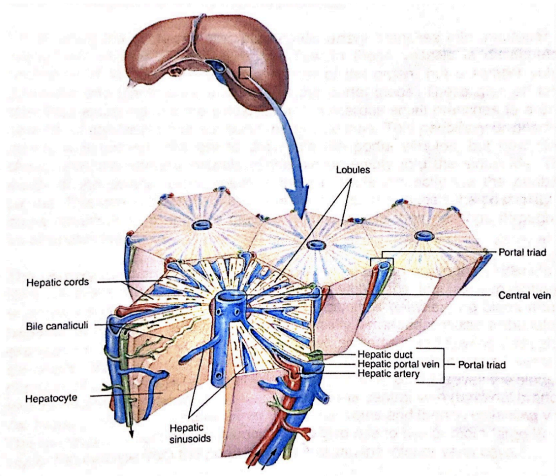
HEPATIC LYMPHATIC VESSELS

- Hepatic collecting vessels are subdivided into superficial and deep systems.

SUPERFICIAL HEPATIC VESSELS

- These run in subserosal areolar tissue over the whole surface of the liver, draining in 4 directions:
  - From the middle part of its posterior surface, the caudate lobe, the posterior part of the convex surfaces of both lobes near the hepatic attachment of the falciform ligament, the posterior part of the inferior surface of the right lobe, vessels accompany the inferior cava to nodes around its terminal part.
    - Vessels in the coronary and right triangular ligaments may directly enter into the thoracic duct without any intervening node.

- Vessels from the rest of the inferior surface and anterior part of the convex surfaces of both lobes near the attachment of the falciform ligament all converge to the porta hepatis to end in the hepatic nodes.
- From the posterior region of the left lobe a few vessels path towards the esophageal opening to end in the pericardial nodes.
- From the remaining convex surface of the right lobe one or two trunks accompanied the inferior phrenic artery across the right cross to the coeliac nodes.



- The **classical lobule, portal lobule, and acinus** are not conflicting interpretations but alternative ways of visualizing its organization.
- The acinus was adopted, in part, because it facilitated the explanation of the pattern of cell degeneration seen in hypoxic and toxic damage to the liver, and it has become the basis for most contemporary considerations of liver function.
- However, the interpretation of the classical polygonal lobule as the true anatomical subunit derives support from the observation that this unit is clearly demarcated by connective tissue septa in the liver of pig, camel, bear and raccoon.
- Although the basic architecture of the liver, in these species, conforms to the classical concept of polygonal lobules with a hexagonal cross section, pentagonal cross sections are common, and reconstruction from serial sections has shown that neighboring units are often continuous at their base to form compound lobules.

BLOOD SUPPLY

- To understand the physiology of the liver, it is essential to understand some unusual features of its blood supply.
- The processing and metabolism of absorbed nutrients depends on the unique position of the liver between the portal vascular system and the general circulation.
- Its principal afferent blood supply is via the **portal vein** which carries poorly oxygenated blood that has already circulated through the intestine, pancreas and the spleen.
- Entering the porta hepatis, it divides into **interlobal veins**, and these, in turn divide into **conducting veins** and are about 400 μm in diameter and have thinner walls than vessels of comparable size elsewhere in the body.
- Their branching gives rise to **interlobular veins**. Smaller veins arising from these are 280 μm in diameter and very thin walled.
- These, accompanied by a branch of the hepatic artery and a bile ductule, are components of the **portal triads** or portal areas that course parallel to the central vein at the corners of the classical lobules.
- Small lateral branches of these, called **terminal portal venules** or **perilobular venules**, given off at short intervals along their length, course along the boundaries between classical lobules and give off short **inlet venules** that empty into the sinusoids.
- On entering the portal hepatis, the hepatic artery branches into interlobar and interlobular arteries.
- The bulk of the flow in these vessels is distributed to capillaries of the connective tissue stroma of the organ, but a smaller volume continues into the hepatic arterioles of the portal triads.
- These give off lateral branches emptying into the sinusoids and numerous small branches to a dense network of capillaries that surround the bile ductule.
- This **peribiliary or periductal plexus** was formerly thought to drain into the portal venules, but now clearly shown that efferent vessels of the plexus empty into the sinusoids.
  - Thus, much of the arterial blood reaches the sinusoids indirectly via the peribiliary plexus.
- This rich vascularity of the smallest bile ducts suggests the possibility that some constituents of the bile may be reabsorbed in their passage through the **intrahepatic bile ducts**.
- The primary function of the hepatic circulation is carried out and the sinusoids that form an elaborate three-dimensional plexus within the lobules presenting an enormous surface area for exchange of metabolites between the blood and hepatic parenchyma.
- Every cell and the radially arranged cellular trabeculae is exposed on at least one, and usually on two sides to blood flowing through the sinusoids.
- **Vascular casts**, viewed with a scanning microscope reveal the richness of the vascularity of the hepatic parenchyma.
- Blood leaves the sinusoids through numerous openings in the thin wall of the central vein (terminal branch of the hepatic vein) and continues into sublobular veins and then to collecting veins.
- The numerous collecting veins converge to give rise into two or more large hepatic veins that emerge from the porta hepatis and join the inferior vena cava.

HEPATIC SINUSOIDS

- The **hepatic sinusoids** are wider than capillaries and their walls conform to the surface of the plates of hepatocytes on either side but are separated from them by a narrow space.
- The **endothelial wall** is made up of individual endothelial cells.
- Physiological studies on the rate of clearance of solutes from the blood during its passage through the liver and observations on the size of colloidal particles that pass through the wall of the sinusoids suggested that there are discontinuities in the wall that are permitted direct access of blood plasma to the hepatic cells.
  - This has been confirmed in electron micrographs which show that the endothelial cells have typical overlapping junctions in some areas but in other areas, the thin margins of cells may have separated by 0.1 to 0.5 μm.
- In addition, the thin peripheral portions of the cells have **fenestrations** that are more variable in size and shape than the pores and endothelium of fenestrated capillaries elsewhere in the body.
- These fenestrae often occur in groups that have been called **"sieve-plates".**
- Thus, the walls of the sinusoids have both discontinuities between cells and transcellular fenestrations.

KUPFFER CELLS

- In 1898, von Kupffer observed **stellate cells** in the hepatic sinusoids that could be selectively stained with **gold chloride**.
- They were depicted with processes crossing the lumen and were thought to lie within the sinusoid but fixed to its endothelium.
- These **Kupffer cells** frequently contained gulfed erythrocytes and deposits of iron containing pigment.
- Kupffer cells are derived from circulating **monocytes** and are members of the body's **mononuclear phagocyte system.**
- Kupffer cells are situated on the surface of the endothelial cells with processes extending into the lumen and between the underlying endothelial cells.
- Electron micrographs show that they have slender villi and **undulant lamellipodia** projecting from the surface exposed to the blood.
- Narrow invaginations of the plasmalemma extend into the cytoplasm.

- These form **sinuous vermiform bodies** consisting of two parallel membranes with a dense line between them and faint transverse striations.
- This structure is occasionally seen in **macrophages** in other organs.
- The Kupffer cell has a small juxtanuclear Golgi Complex and numerous mitochondria.
- There are short profiles of endoplasmic reticulum that can be stained with the histochemical method for peroxidase.
    - This reaction serves to distinguish Kupffer cells from endothelial cells which lack this enzyme.
- The cytoplasm is crowded with clear vacuoles, phagosomes, lysosomes and lipochrome pigment deposits.
- The Kupffer cells are able to recognize and phagocytize effete and damaged erythrocytes and they clear the blood of colon bacilli that manage to get into the portal blood during its circulation through the intestines.

PERISINUSOIDAL SPACE

- The **perisinusoidal space (space of Disse)** is the narrow space between the sinusoids and the parenchymal cells.
- The **endothelium** rests lightly on the tips of the numerous irregularly oriented **hepatocyte** microvilli that project into the narrow perisinusoidal space.
- Slender bundles of collagen fibers in this space form a loose network that corresponds to the argyrophilic reticulum demonstrable around the sinusoids by silver impregnation methods.
- The networks of reticular fibers around neighboring sinusoids are connected by coarser bundles of collagen that pass between the cells of the intervening liver cell plate.
- Occasional **unmyelinated nerve axons** are found in the perisinusoidal space.
- The gel-like matrix commonly associated with connective tissue appears to be lacking in the perisinusoidal space, and plasma escaping through fenestrations in the endothelium of the sinusoids has direct access to the surface of hepatocytes.
    - This facilitates exchange of metabolites between the blood and the liver cells.
    - The efficiency of this interchange is also enhanced by a six-fold amplification of surface area achieved by the microvilli on the liver cells.
- **Typical fibroblasts** are rarely found in the perisinusoidal space, but there are sparse populations of two other cell types: fat storing cells and pit cells.
    - The fat storing cells occupy shallow recesses between hepatic cells and usually have processes that contact endothelial cells.
    - They can be selectively stained with gold chloride, but their distinguishing feature in routine histological preparations have been given to these cells: stellate cells, interstitial cells, and lipocytes.
    - They are more common near the center of the classical lobule than they are at its periphery.
    - Their origin and functional significance remain obscure.
    - When exogenous vitamin A is administered, it is stored in these cells owing to its lipid solubility

ZONATION WITHIN THE LOBULE

- Some 70 years ago, histologists using the light microscope noted minor differences and the appearance of hepatic cells in three concentric zones within the classical lobule.
- These variations were believed to reflect differences in the degree of metabolic activity of the cells in the three zones.
- A region at the periphery of the lobules was designated as **"zone of permanent function"**; an intermediate region, a **"zone of variable function"**; and the area around the central vein, a **"zone of permanent repose"**.
- The afferent blood enters the periphery of the classical lobule and exits via the central vein.
- The activity of the hepatocytes depended on their location with respect to a gradient in concentration of oxygen along the length of sinusoids.
- The cytological heterogeneity of hepatocytes and different regions of the lobules are no longer believed to depend on their position with respect to a gradient of available oxygen but the concept of zonation within the microvascular unit is still a basic tenet of hepatology.
- The three concentric zones of the lobule have been replaced in our thinking by three comparable zones in hepatic acinus:
    - **Zone-1**, an ellipsoidal area immediately surrounding the hepatic arteriole and terminal portal venule
    - **Zone-2**, intermediate
    - **Zone-3**, cells near ends of the acinus.
        - Blood flows sequentially through these zones and exits via terminal branches of hepatic vein at either acinus.
- Along the plates of parenchymal cells, differences and cell ultrastructure and in enzyme activity can be demonstrated from zone to zone.
    - In zone-1, enzymes involved in oxidative metabolism and gluconeogenesis predominate, whereas in zone-3, the cells are especially rich in enzymes involved in glycolysis and lipid and drug metabolism.
    - Cells of zone-2 have a mixed complement of enzymes.
- All hepatocytes probably have the same potentialities, but they express differences in ultrastructure and function depending on the blood oxygen and solute concentration prevailing in their acinus.
- Their ability to alter the structure and function in response to a change in their microenvironment indicates that the cells in their zones are not intrinsically different.

CYTOLOGY OF HEPATOCYTES

- Hepatocytes make up approximately 80% of the cell population of the liver.
- Because they are polygonal and arranged in plates or trabeculae between sinusoids, they do not have surfaces that can appropriately be described as apical and basal.
- For descriptive purposes, the sides of the cell exposed to the sinusoids are called the **sinusoidal domain of plasmalemma**, and the sides in contact with neighboring hepatocytes are the lateral domain.
- A portion of the lateral membrane that forms the wall of the intracellular bile canaliculi is the bile canalicular domain.
- The sinusoidal and **bile canalicular domains** bear sparse microvilli.
- The other surfaces of the cell are planar.

NUCLEUS

- The **nucleus** is round, with peripheral clumps of heterochromatin and one or two prominent nucleoli.
- The **nuclei** vary somewhat in size, with 40 - 60% being polyploid.
- The majority of hepatocytes have a single nucleus, but as many as 25% are binucleate.
- The **perinuclear cisterna** has a thin, filamentous nuclear lamina on its inner surface.
- Examined with a light microscope, the cytoplasm contains conspicuous basophilic bodies that were traditionally referred to as ergastoplasm.
- In electron micrographs, these bodies are found to be aggregations of cisternae of the rough endoplasmic reticulum, and it is the ribosomes on its membranes that are responsible for its basophilia in histological sections.
- The **cisternae** are spread further than in comparable arrays of reticulum in pancreatic acinar cells.
- There are also meandering tubular elements of the reticulum and free polyribosomes are abundant throughout the cytoplasm.
- The r**ough endoplasmic reticulum** is the site of synthesis of protein constituents of the cytoplasm and the plasma proteins of the blood.

SMOOTH ENDOPLASMIC RETICULUM

- **Smooth endoplasmic reticulum** is present in varying abundance.
- It consists of a network at branching and anastomosing tubules, but the continuity of these elements is not always apparent in the thin sections required for electron microscopy.
- Smooth reticulum is not well developed in the cells of the peritoneal region (**zone-1**), but it is abundant in cells of **zone-3** which are active in lipid metabolism.
- **Very low-density serum lipoprotein (VLDL)** are synthesized in the liver and released into the blood as carrier of cholesterol.
  - Small, dense globules, 30-40 μm in diameter, are often present in its lumen.
- The membranes of this organelle are rich in a family of enzymes called **cytochromes-P450** that are involved in the synthesis of prostaglandins and other biologically active agents.
- They also have an important role in the catabolism of drugs and other potentially toxic exogenous compounds.

MITOCHONDRIA

- The **mitochondria** of hepatocytes are elongated with lamellar or tubular cristae projecting into their interior, which is occupied by a matrix of relatively low density containing a few dense matrix granules.
- Thus, the ultrastructure of the mitochondria is not unusual but there are striking regional differences in their size and number.
- In the cells of the periportal region (**zone-1**), they are fewer in number, but nearly twice the size of those in the centrilobular region (**zone-3** of the acinus).

GOLGI COMPLEX

- The **Golgi Complex** of the liver cells is not a single juxtanuclear organelle as in other glandular cells but consists of <u>multiple stacks of five to nine cisternae slightly expanded at their ends.</u>
- These are located along both sides of the cell near the bile canaliculi.
- Numerous small vesicles associated with the trans-Golgi cisterna transport constituents of the bile nearest the bile canaliculus.
- There are usually several membrane bound dense bodies, 0.2 - 0.5 μm in diameter, in the vicinity of Golgi bodies.
  - These give positive staining reactions for **acid hydrolases** and are, therefore, identified as **lysosomes**.
- Other membrane-lined spherical bodies, 0.2 - 0.8 μm in diameter, that are scattered through the cytoplasm are **peroxisomes**.
  - These contain catalase and other hydrogen peroxide generating oxidases.
- Nucleoids isolated from liver homogenates have been found to consist of the enzyme **uricase**.
  - The nucleoid is lacking in the peroxisomes of the human liver and the functional significance of liver peroxisomes is poorly understood.

CARBOHYDRATES

- In routine histological sections of the liver, many of the cells have irregularly shaped unstained areas of cytoplasm-free organelles.
- In preparations stained with a **periodic-acid-Schiff reaction** for carbohydrates, these areas are found to contain deposits of **glycogen** in electron micrographs; the glycogen is in the form of electron-dense particles of 0.1 μm in diameter called **α-particles**.
- These are aggregates of smaller subunits, 30 to 100 mm in diameter called β-particles.
- **Glycogen** is a storage form of carbohydrate that can be drawn on to maintain the normal glucose concentration in the blood.

LIPID

- Hepatocytes contain varying amounts of **lipid** in electron dense droplets that are not enclosed in a membrane.
  - They are few in number in the normal liver but are dramatically <u>increased after consumption of alcohol or other hepatotoxic substances.</u>
- Accumulation of lipid usually begins in cells of zone 3 in multiple small droplets that later coalesce, and in severely toxic states the liver cells may become distended by a single very large lipid drop.

CYTOSKELETON

- The **cytoskeleton** of hepatic cell consists of subplasmalemmal layer of **cytokeratin** and **actin filaments**.
  - This layer is identifiable around the entire periphery of the cell but it is <u>thicker under the bile canaliculi domain of the plasmalemma</u>, where it helps maintain the patency of bile canaliculus.
- Bundles of intermediate filaments extend inward from the cortex, converging on the centrosome and the pore complexes of the nuclear envelope to form a resilient cytoskeletal framework within the cytoplasm.

CELL MEMBRANE

- The **cell membrane** has the same ultrastructural appearance over the entire surface, but functionally distinct domains are identifiable by cytochemical methods.
- With labeled antibodies, receptors of sialoglycoproteins, mannose 6-phosphate and other substances taken up by receptor mediated endocytosis can be localized in the **sinusoidal domain.**
- The **bile canaliculi domain** contains amino peptidases and three glycoproteins that are not found elsewhere on the cell surface.
- Adenyl cyclase and Na+,K+-ATPase are found in both the **sinusoidal domain** and the **lateral domains** that interface with adjacent cells.
  - The functional significance of some of these membrane proteins is yet to be elucidated.

HEPATIC DUCTS

- A **bile canaliculus** is located midway along the interface between adjoining hepatic cells.
  - These minute channels, 0.5-1.5 μm in diameter, form a network within the plates of hepatocytes, with a single cell in each of its polygonal meshes.
  - Owing to the branching of anastomosis of cell plates, the network is continuous throughout the nobule and, in most species, into neighboring lobules.
  - Electron microscope revealed that the wall of the canaliculus is merely a specialization of the surfaces of a joining cells, and its lumen is a local expansion of the intercellular cleft.
- Over most of their length, the apposed lateral membranes of the contiguous cells are planar and separated by 15 nm.
- Near the middle of this interface, the membranes diverge to bind a wider intercellular space that constitutes the lumen of a bile canaliculus.
- Along either side of the lumen, the closely apposed membranes form a tight junction comparable to zonulae occludentes of other epithelia.
  - These junctions isolate the lumen of the canaliculus and prevent the escape of bile.
- A few short microvilli project into its lumen and the membrane bounding the canaliculus is reinforced by a thickening of the underlying cortical layer of cytoskeletal filaments.

PERIPHERY OF THE CLASSICAL HEPATIC LOBULE (AXIS OF THE ACINUS)

- At the periphery of the classical hepatic lobule (axis of the acinus), the **bile canaliculi** are confluent with the **terminal ductules (canals of Herring)** that drain into interlobular bile ducts associated with the branches of the hepatic artery and the portal vein in the portal areas.
- Their wall is initially made up of **squamous cells** as the ductules approach the interlobular ducts.
  - This transitional region of the duct system is seen clearly with a light microscope only when the ductules are distended, as they are following the occlusion of a bile duct.
- The interlobular ducts, 30-40 μm in diameter, continue into a system of progressively larger ducts that converge on the porta hepatis.
  - They are lined by cuboidal to low columnar epithelium and, in the larger ducts, the epithelium contains occasional clusters of mucus-secreting cells.
  - These ducts are enveloped by moderately dense connective tissue.

EXTRAHEPATIC PORTION OF THE DUCT SYSTEM

- The extrahepatic portion of the duct system consists of right and left hepatic ducts emerging from corresponding lobes of the liver and the common bile duct formed by the convergence.
- The **cystic duct** from the gallbladder joins the **common bile duct**, which continues to the duodenum.
  - These ducts are lined by columnar epithelium and have a moderately thick wall which includes a thin submucosa, muscularis, and adventitia.
- At intervals along their length, **tubular glands** extend down into the submucosa.
- **Lymphocytes** are common in the submucosa and migrate through the epithelium into the lumen.
- Bundles to smooth muscles first appear in the wall of the common bile duct.
  - They are oriented longitudinally and obliquely but do not form a complete layer.
  - Smooth muscle becomes more prominent as the common bile duct approaches the duodenum and in its intramural portion it forms a sphincter that exercises control over the flow of bile into the duodenum.

CONNECTIVE TISSUE STROMA

- The liver has remarkably little stroma for an organ of such a large size.
- Beneath the peritoneal mesothelioma that covers all but a small area of its diaphragmatic surface, there is a layer of dense connective tissue, 70-100 µm in diameter thick, called **Glisson's capsule.**
  - This is the thickest at the porta hepatis and from there connective tissue continues inward with the large vessels and ducts and ensheaths the intrahepatic branches of these structures in their arborization throughout the organ to the level of the interlobular portal tracts where it is continuous with the more delicate stroma of the classical hepatic lobules.
- With silver staining methods of light microscopy, the interlobular stroma appeared as a network of reticular fibers between the sinusoids and the plates of parenchymal cells.
- In the ultrathin sections required for electron microscopy, the stromal network is not apparent, but slender bundles of collagen can be seen in the **perisinusoidal space (space of Disse).**
- The three-dimensional organization of the interlopers trauma is more profitably studied and scanning electron micrographs of tissue, from which the cellular elements have been removed by maceration in strong alkali.
- Coarse bundles of 60 nm collagen fibrils in the portal areas are continuous with a network of very thin bundles of fibrils surrounding the sinusoids.
- The delicate networks of fibril surrounding the neighboring sinusoids are connected by larger bundles of collagen fibrils that cross the plates, passing between the parenchymal cells.
- The bundles of collagen and the portal areas are larger than those forming the perisinusoidal networks, but the unit fibrils of both are of the same diameter.
  - In view of this finding, their reason perpetuates the traditional distinction between "reticular fibers" and collagen fibers that were based on nonspecific silver staining methods for light microscopy.
- In the absence of typical fibroblast in the space of Disse, the origin of the collagenous framework of the liver lobules is a subject of debate. There is reason to believe that the fat-storing cells (Ito cells) may be involved.
- Endothelial cells have been implicated and liver cells in culture or reported to produce small amounts of collagen.
  - Thus, more than one cell type in the liver is a candidate, but which one is principally involved in the production of stroma is not known.
- The question is of some importance because of the prevalence of fibrosis and chronic liver disease.
- Excessive proliferation of connective tissue often impedes the flow of blood and bile and may interfere with the growth of monodulesdals of regenerating liver cells.

LYMPHATICS

- The Liver produces a large volume of lymph. From 1/4 to 1/2 of the lymph of the thoracic duct comes from the liver.
- Hepatic lymph differs from that of the other regions in containing a large amount of plasma protein.
- The ratio of albumin to globulin is somewhat **higher** than in the plasma.
- The network of lymphatics parallels the branches of the portal vein from the interlobular portal areas to the porta hepatis.
- Lymphatics have not been demonstrated within the hepatic lobules.
- Plasma escaping through fenestrations in the sinusoidal epithelium is believed to move along the spaces of Disse in a direction counter to the flow of blood seeping into the spaces around the terminal twigs of the portal vein and hepatic artery at the periphery of the classical lobules (axis of the acini).
- There it enters lymphatic capillaries that accompanied the blood vessels and ducts of the portal tracts.

GENERAL FUNCTIONS OF THE LIVER

- **Exocrine function** - production and secretion of bile
- **Endocrine functions** - metabolism of carbohydrates fat and protein
  - synthesis of glycogen and secretion of glucose
  - secretion of blood proteins (albumin, globulin, fibrinogen and etc)
  - secretion of lipoproteins
- **Detoxifying functions**
  - conversion of ammonia to urea
  - conversion of bilirubin conjugated bilirubin
- Blood filtering function, removal of bacteria & foreign body
- Site for blood storage

BILIARY DUCTS AND GALLBLADDER

COMMON BILE DUCT

- The main right and left hepatic ducts arise from the liver near the right end of the porta hepatis as the common hepatic duct which descends about 3 cm before being joined on its right at acute angle by the cystic duct to form the main bile duct.
- The common bile duct lies to the right of the hepatic artery and anterior to the portal vein.

GALLBLADDER

- The **Gallbladder** is a slate blue, pear-shaped partly sunk in a fossa in the right hepatic lobe's surface.
- It extends forward from a point near the right end of the porta hepatis to the inferior hepatic border.
- Its upper surface is attached to the liver by connective tissue; elsewhere it is completely covered by peritoneum continued from the hepatic surface.
- It is 7-10 cm long, 3 cm broad at its widest and 30-50 mL capacity.

PARTS OF THE GALLBLADDER

Fundus

- Expanded and then directed projects down, forward and to the right, extending beyond the inferior border to contact the anterior abdominal wall behind the ninth right costal cartilage.
- Posteriorly, it is related to the transverse colon, near its commencement.

Body

- Directed up, back and to the left, do the right end of the portal it is continuous with a gallbladder neck
- It is related above to the lever below to the transverse colon and, further back, to the first and second parts of the duodenum

Neck

- Narrow, curving up and forwards and then abruptly back and down, to become the cystic duct, at which there is a construction.
- The neck is attached to the liver by loose connective tissue containing the cystic artery.

CYSTIC DUCT

- This structure is 3 to 4 cm long, it passes back, down and to the left from the neck of the gallbladder, joining the common hepatic duct to form the bile duct.
- It is adherent to the common hepatic duct for a short distance before joining it, usually near the porta hepatis.
- It is usually S-shaped and descends in the right free margin of the lesser omentum.

BILE DUCT

- The bile duct is formed near the porta hepatis, by the junction of the cystic and common hepatic duct;
- It is usually about 7.5 cm long and 6 mm in diameter.
- It descends posteriorly and slightly to the left, **anterior** to the epiploic foramen, at the **right border** of the lesser omentum, **in front** and to the **right** of the portal vein and to the **right** of the hepatic artery proper.
- It passes behind the right (superior) part of the duodenum, with the gastroduodenal artery to its left, and then runs in a groove on the superolateral part of the posterior surface of the head of the pancreas, anterior to the inferior vena cava and sometimes embedded in the pancreatic tissue.

VESSELS

- The **cystic** artery, a branch of the right hepatic artery supplies the gallbladder and also supplies branches to the hepatic ducts into the upper part of the common bile duct.
- Veins from the upper part of the bile duct and from the gallbladder and cystic duct usually enter the **liver**, while those from the lower part of the bile duct enter the **portal vein**.

INNERVATION

- Sympathetic and parasympathetic innervation are from the **coeliac plexus** along the hepatic artery and its branches.
- Autonomic plexuses exist in the muscular and submucous layers, and ganglion cells.
- Fibers from the **right phrenic nerve**, through communications between the phrenic and coeliac plexuses appear to reach the gallbladder via the **hepatic plexus**, thus explaining referred **"shoulder pain"** in gallbladder pathology.

HISTOLOGY

- The **gallbladder** is a pear-shaped hollow organ occupying a shallow fossa on the inferior surface of the liver
- All but the hepatic surface of the gallbladder is covered by a serosa continuous with that covering the liver.
- Its wall consists of a thin subserosal layer of connective tissue overlying a layer of smooth muscle.
- Deep to this is the **mucosa**, composed of the epithelium and its highly vascular lamina propria.
  - The mucosa is plicated into convoluted folds of varying height that delimit narrow bays or clefts.
- The mucosal folds are tall and closely spaced in the contracted gallbladder but are short and more widely spaced when the organ is distended.
- These differences are most dramatically revealed in surface views with the scanning electron microscope.
  - In the contracted gallbladder, the folds follow a generally parallel course.
  - In the distended state, the folds are reduced to low ridges and it becomes apparent that they branch and anastomose to form a network outlining shallow polygonal recesses.
- A loose organization of the collagenous and elastic fibers of the lamina propria provides flexibility to accommodate these changes in surface topography.

EPITHELIUM

- The epithelium is a single layer of tall columnar cells with the oval nuclei and a faintly eosinophilic cytoplasm.
- In histological sections, an inconspicuous **striated border** is detected, but in electron micrographs, the **microvilli** are shorter and less regular in their orientation than are those of the striated border of the intestine.
- The tips of the microvilli bear minute filiform appendages similar to those comprising the glycocalyx on other absorptive at epithelia.
- The lateral cell boundaries are relatively straight in their apical portion but may be plicated and interdigitated from the level of the nucleus to the basal lamina.
- The intercellular cleft and the **upper half** of the epithelium is 15 to 20 nm wide and sealed, near the lumen, by a zonula occludens.
- The width of the intercellular cleft in the **lower half** of the trillium depends on the functional state of the gallbladder.
- It is narrow in the inactive condition but distended when bile is being concentrated by transport of water across the epithelium.

LAMINA PROPRIA

- Near the neck of the gallbladder, there are **simple tubuloalveolar glands** in the **lamina propria** and extending into the muscular layer.
- Their epithelium is cuboidal with an unstained apical region and nucleus that is compressed at the base by accumulated secretion, which is a form of mucus.
- **Larger inpocketings** of the mucosa in this region have sometimes been mistaken for glands.
- They extend through the lamina propria and muscular layer, with a lining that is continuous with the surface epithelium.
- They are called **Rokitansky-Aschoff sinuses** and may represent a pathological change in the gallbladder wall that permits evagination of the mucosa through enlarge measures of submucosal smooth muscle.

MUSCULARIS LAYER

- The **muscle layer** of the gallbladder wall is an irregular loose network of longitudinal transverse, and oblique bundles of smooth muscle cells.
- Spaces between bundles are occupied by **collagen and elastic fibers** and occasionally **fibroblasts**.
- External to the muscularis is a fairly dense connective tissue layer rich in collagen and elastin and containing fibroblasts, macrophages and occasional clusters of adipose cells.
- The blood vessels, nerves, and lymphatics of the organ run in this layer and send branches through the muscular layer of the mucosa.

LUSCHKA DUCTS

- Not infrequently, peculiar duct-like structures may be found on the hepatic surface of the gallbladder near its neck.
- They can be traced in the connective tissue for a considerable distance but none open into the lumen.
- Some appear to connect with the bile ducts.
- They are called **Luschka ducts** and may be aberrant bile ducts formed during embryonic life and persisting in the adult.

STRUCTURES FROM THE CYSTIC DUCT

- The **cystic duct** continues from the neck of the gallbladder for 3 to 4 cm and joins the **common hepatic duct (common bile duct)** which courses downward behind the head of the pancreas, approaching the pancreatic duct.
- The two passes together with the muscularis of the duodenum.
- In their oblique course to the mucosa, the two ducts unite to form the **ampulla of Vater (hepatopancreatic ampulla)** which opens into the lumen of the duodenum at the tip of a small papilla.
- In the wall of the duodenum, the bile and pancreatic ducts are encircled by a band of smooth muscle called **sphincter of Oddi**.

MUSCLE COMPLEX

- This muscle complex consists of four parts:
  - A strong circular band of smooth muscle, the sphincter choledochus around the terminal portion of the bile duct;
  - A corresponding sphincter pancreaticus around the pancreatic duct;
  - Longitudinal bundles of smooth muscle, the fasciculus longitudinalis in the space between the duct; and
  - A meshwork of muscle fibers around the ampulla, the sphincter ampullae.

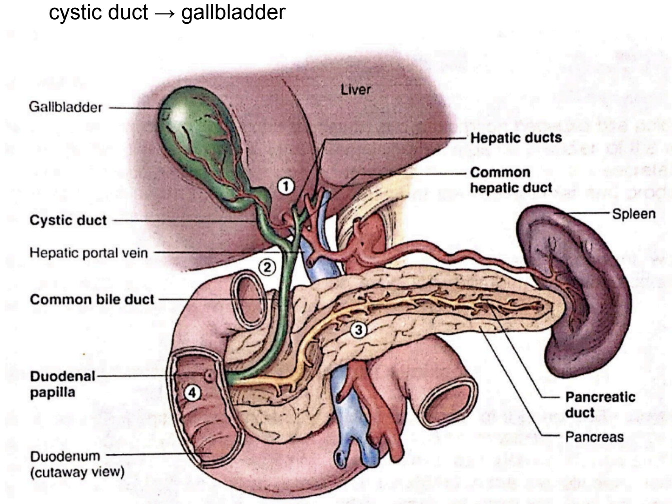
- The degree of development of these components of the sphincter of Oddi is subject to great individual variation.
- Normally, contraction of the sphincter choledochus stops the flow of bile.
- The longitudinal fasciculi shorten the intramural portion of the docks and probably facilitate the flow of bile into the duodenum.
- When the sphincter ampulla is unusually well developed, it's contraction may have the undesirable effect of causing reflux of bile into the pancreas, resulting in pancreatitis.

PHYSIOLOGIC ANATOMY OF BILIARY SECRETION AND ITS REGULATION

- Bile is secreted in two stages by the liver:
  - the initial portion is secreted by the principal metabolic functional cells of the liver, the hepatocytes;
    - This initial secretion contains large amounts of bile acids, and other organic constituents.
    - It is secreted into the bile canaliculi.
    - Next, the biles flows in the canaliculi toward the interlobular septa, where the canaliculi empty into terminal bile ducts and then into progressively larger, finally reaching the hepatic duct and the common bile duct.
    - From these the bile either empties into the duodenum or is diverted through the cystic duct into the gallbladder.
  - In its course through the bile ducts, a second portion of secretion is added to the initial bile.
    - This additional secretion is a watery solution of sodium and bicarbonate ions secreted by secretory epithelial cells that line the ductules and ducts.
    - This second secretion sometimes increases the total quantity of bile by as much as additional 100%.
    - The second secretion is stimulated by secretin, which causes release of increased quantities of bicarbonate ions to supplement for neutralizing acid that empties into the duodenum.

OUTLINE

- Initial secretion of bile in the hepatocytes → bile canaliculi → interlobular septa → terminal bile ducts → larger ducts → hepatic duct and common bile duct → duodenum
  ↓
  cystic duct → gallbladder



1. The hepatic ducts from the liver lobes combine to form the common hepatic duct.
2. The common hepatic duct combines with the cystic duct from the gallbladder to form the common bile duct.
3. The pancreatic duct carries secretions from the pancreas.
4. The common bile duct and the pancreatic duct combine and empty into the duodenum at the duodenal papilla.

BILE

FUNCTIONS

- Bile plays an important role in **fat digestion and absorption** because bile acids in the bile do two things:
  1. They help emulsify the large fat particles of the food into many minute particles that can be attacked by lipase enzymes secreted in pancreatic juice and
  2. They aid in absorption of the digested fat end products through the intestinal mucosal membrane.
- Second, bile serves as a means of **excretion of several important waste products** from the blood.
  - These include especially bilirubin, an end product of hemoglobin destruction and excesses of cholesterol.

STORAGE AND CONCENTRATION OF BILE IN THE GALLBLADDER

- Bile is secreted continually by the liver cells, but most of it is normally stored in the gallbladder until needed in the duodenum.
- The maximum volume of the gallbladder is only **30 - 60 milliliters**.
- Nevertheless, as much as 12 hours of bile secretion (usually about 450 milliliters) can be stored in the gallbladder because water, sodium, chloride, and most of their small electrolytes are continually absorbed by gallbladder mucosa, concentrating the remaining bile constituents including the bile salts, cholesterol, lecithin, and bilirubin.
- Most of this gallbladder absorption is caused by active transport of sodium to the gallbladder, absorption of chloride ions, water, and most other highly diffusible constituents.
- Bile is normally concentrated in this way about 5-fold, but it can be concentrated up to a maximum of 20-fold.

COMPOSITION OF BILE

	LIVER BILE	GALLBLADDER BILE
Water	97.50 g/dl	92.0 g/dl
Bile Salts	1.10 g/dl	6.0 g/dl
Bilirubin	0.04 g/dl	0.3 g/dl
Cholesterol	0.10 g/dl	0.3 - 0.9 g/dl
Fatty Acids	0.12 g/dl	0.3 - 0.12 g/dl
Lecithin	0.04 g/dl	0.3 g/dl
Na^+	145 mEq/L	140 mEq/L
K^+	5 mEq/L	12 mEq/L
Ca^{2+}	5 mEq/L	12 mEq/L
Cl^-	100 mEq/L	25 mEq/L
HCO_3	28 mEq/L	10 mEq/L

- The table above shows that by far the most abundant substance secreted in the bile is **bile salts**, accounting for about one-half of the total solutes of bile;
- Also secreted or excreted in large concentrations are **bilirubin**, cholesterol, lecithin, and the usual electrolytes of plasma.
- In the concentrating process in the gallbladder, water and large amounts of **electrolytes** (except calcium ions) are reabsorbed by the gallbladder mucosa;
- Essentially all the other constituents, especially the **bile salts** and lipid substances, **cholesterol** and **lecithin**, are not reabsorbed and therefore become highly concentrated in the **gallbladder bile**.

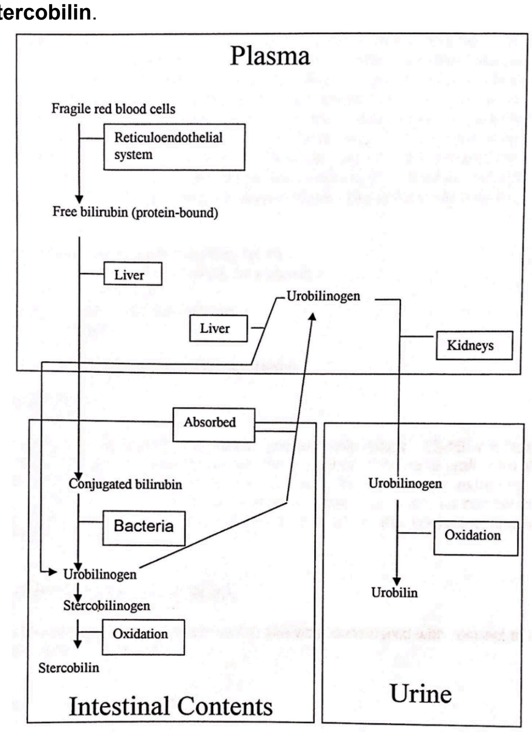
EMPTYING THE GALLBLADDER

- The cause of gallbladder emptying is rhythmical contractions of the wall of the gallbladder, but effective emptying requires simultaneous relaxation of the sphincter of Oddi, which guards the exit of the common bile duct into the duodenum.
- The most potent stimulus for causing gallbladder contraction is the hormone cholecystokinin.
  - **Cholecystokinin** causes increased secretion of digestive enzymes by the pancreas.

    - The stimulus for cholecystokinin secretion into the blood from the duodenal mucosa is mainly **fatty foods** themselves that enter the duodenum.
- The gallbladder is stimulated less strongly by **acetylcholine secreting nerve fibers** from both vagi and the intestinal enteric nervous system.
    - They are the same nerves that promote motility and secretion and other parts of the upper gastrointestinal tract.

BILIRUBIN FORMATION AND EXCRETION

- When red blood cells have lived out their lifespan, their cell membrane rupture, and the released hemoglobin is phagocytized by tissue macrophages (also called the reticuloendothelial system) throughout the body.
    - Here, the hemoglobin is first split into globin and heme, and the heme ring is opened to give:
        1. free iron that is transported in the body by heme ring
        2. a straight chain of four pyrrole nuclei, which is the substrate from which bilirubin will eventually be formed.
- The first substance formed is biliverdin, but is rapidly reduced to free bilirubin, which is gradually released from macrophages into the plasma.
- The **free bilirubin** immediately combines strongly with the plasma **albumin** and is transported in this combination throughout the blood and interstitial fluid. Even when bound to plasma protein, this bilirubin is still called "free bilirubin".
- Within hours, the free bilirubin is absorbed through the hepatic cell membrane.
- In passing to the insides of the hepatic cell, it is released from the plasma albumin and then conjugated about 80% with **glucuronic acid** to form **bilirubin glucuronide**, about 10% would **sulfate** to form **bilirubin sulfate**, and the 10% with other substances.
- In this form the bilirubin is excreted from the hepatocytes by an active transport process into the bile canaliculi and then into intestines.
- Once in the **intestine**, about one half of the **"conjugated" bilirubin** is converted by *bacterial action* into **urobilinogen**.
- Some of the urobilinogen is reabsorbed through the **intestinal mucosa** back into the blood.
- Most of this is *re-excreted* by the liver back into the **gut**, and about **5%** is *excreted* by the **kidneys** into the urine.
- After exposure to air in the urine, the urobilinogen becomes oxidized to **urobilin**, or in the feces, it becomes oxidized to form **stercobilin**.



PANCREAS

- The pancreas is a soft lobulated, grayish-pink gland, 12-15 cm long, extending nearly transversely across the posterior abdominal wall from the duodenum to the spleen, behind the stomach.
- Its broad, right extremity or head is connected to the body by a slightly constricted neck; its **narrow**, left extremity is the tail.
- It ascends slightly to the left in the epigastric and left hypochondriac region.

RELATIONS OF THE PANCREAS

- The structures related to the pancreas are best considered with respect to its different parts as follows:

HEAD

- Flattened anteroposteriorly, it lies within the duodenal curve.
- Its upper border is overlapped by the superior segment of the duodenum, the other borders being grooved by the adjacent margin of the duodenum, which they invariably overlap in front and behind.
- Sometimes a small part of the head is actually embedded in the wall of the descending part of the duodenum.
- From the lower and left part of the head the hook-like uncinate process projects upwards and to the left behind the superior mesenteric vessels.
- In or near the groove between the duodenum and the right and lower borders of the head are the anastomosis superior and inferior pancreaticoduodenal arteries.

ANTERIOR SURFACE

- From the pancreatic head's anterosuperior aspect the neck just forwards, upwards and to the left merging with the body.
- The boundary between head and neck, on the right and in front, is a deep incisure containing the union of the superior mesenteric and splenic veins to form the portal vein.
- Below and the right of the neck, the head's anterior surface is at first in contact with the transverse colon, separated only by loose connective tissue;
- Still lower the surface is covered by peritoneum continuous with the inferior layer of the transverse mesocolon, and is in contact with the jejunum.
- The uncinate process is crossed anteriorly by the superior mesenteric vessels.

POSTERIOR SURFACE

- The head is related posteriorly to the inferior vena cava which ascends behind it and covers almost all of this aspect;
- It is also related to the terminal parts of the renal veins and the right crus of the diaphragm.
- The uncinate process lies in front of the aorta.
- The bile duct is lodged either in a superolateral groove on the posterior surface or in a canal within the gland's substance.

NECK

- About 2 cm long, it projects forwards, upwards and to the left from the head, merging into the body.
- Its anterior surface, covered with peritoneum, adjoins the pylorus, with part of the omental bursa intervening, the gastroduodenal and anterior superior surface pancreaticoduodenal arteries descend in front of the gland to the right of the junction of the neck and head
- The posterior surface is related to the superior mesenteric vein and the beginning of the portal vein.

BODY

- Prism like in section, it has three surfaces:
    - Anterior
    - Posterior
    - Inferior
        - More precisely anterosuperior, posterior and anteroinferior; they are obliquely set

Anterior Surface

- This faces anteroposteriorly, is covered by peritoneum continuous antero-inferiorly with the anterior ascending layer of the greater omentum and is separated from the stomach by the omental bursa.
- On reaching the taenia mesocolica, the greater omentum's posterior ascending layer fuses with anterosuperior surface of the transverse mesocolon, while the anterior layer continuous up to the mesocolon's root and is then reflected up over the anterior surface of the pancreas.

Posterior Surface

- Devoid of peritoneum, it is in contact with the aorta and the origin of the superior mesenteric artery, the left crus of the diaphragm, left suprarenal gland and with the left kidney and renal vessels, particularly the vein.
- It is closely related to the splenic vein which courses from the left to right and separates it from the structures mentioned.
- The left kidney is also separated from the perirenal fascia and fat.

Inferior Surface

- This is narrow on the right but broadens to the left and is covered by the peritoneum of the posteroinferior layer of the transverse mesocolon; inferior to it are the duodenojejunal flexure and coils of the jejunum; its end rest on the left colic flexure.

Superior Border

- This is blunt and flat to the right, but narrow and sharp to the left near the tail.
- An omental tuberosity usually projects from the right end of the superior border above the level of the lesser curvature of the stomach, in contact with the posterior surface of the lesser omentum.
- The border is related above to the coeliac artery, its common hepatic branch coursing to the right just above the glands, while its sinuous splenic ramus runs to the left along this border.

Anterior Border

- This separates the anterior from the interior surfaces and along this border the two layers of the transverse mesocolon diverge, one passing up over the anterior surface, the other backwards over the inferior surface.

Inferior Border

- This separates the posterior from the interior surfaces, the superior mesenteric vessels emerging from under its right extremity.

TAIL

- Narrow, usually reaching the inferior part of the gastric surface of the spleen, it is contained between the two layers of the splenorenal (lienorenal) ligament, together with the splenic vessels.

MAIN PANCREATIC DUCT

- It traverses the gland from left to right, being nearer its posterior than its anterior surface.
- It begins by the junction of the lobular ducts in the tail and, running to the right in the body, receives further lobular ducts which join it almost at the right angles **(the 'herringbone' pattern)**.
- Much enlarged, it reaches the neck of the gland, turning down, backwards and right towards the bile duct, which lies on its straight side.
- The **two ducts** enter the wall of the descending part of the duodenum obliquely and unite in a short dilated **hepatopancreatic ampulla or ampulla of the bile duct**;
  - The narrow distal end of this opens on the summit of the major duodenal papilla, which lies posteromedial in this part of the duodenum and 8-10 cm distal to the pylorus.
  - Usually, the two ducts do not unite until very near the orifice of the major papilla. Sometimes they open separately.
- Frequently an **accessory pancreatic duct** drains the lower part of the head, ascending in front of the main duct, with which it communicates, and opening on a small rounded minor duodenal papilla, about 2 cm anterosuperior to the major.
  - The duodenal end of the accessory duct may fail to expand; secretion is then diverted along the connecting channel into the main duct.

SURFACE ANATOMY

- The **head** of the pancreas lies within the duodenal curve.
- The **neck** is situated in the transpyloric place, behind the pylorus.
- The **body** passes obliquely up and left to about 10 cm, its
- left part lying a little above the transpyloric plane.
- The **tail** is a little above and to the left of the intersection of the transpyloric and left lateral planes.

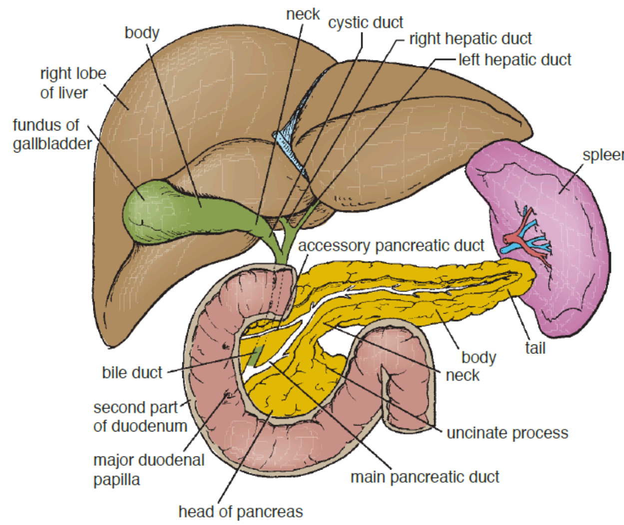


FIGURE 5.58 Different parts of the pancreas dissected to reveal the duct system.

PANCREATIC MICROSTRUCTURE

- The pancreas is composed of two different types of glandular tissues in intimate association with each other.
- The main mass is **exocrine**, embedded in which are pancreatic islets of endocrine cells.

EXOCRINE PANCREAS

ACINAR TISSUE

- The exocrine pancreas is a compound acinous gland made up of many small lobules bound together by loose connective tissue, through which course the blood vessels, nerves and interlobular ducts.
- The **acini** are round or slightly elongated and consist of 40 to 50 pyramidal epithelial cells around a narrow lumen.
- The size of the lumen varies with the physiological state of the gland becoming somewhat wider during active secretion.
- In histological sections, the **cytoplasm** near the base of the acinar cells is strongly basophilic owing to its high concentration of *ribonucleoproteins*.
- The spherical **nucleus** has a prominent nucleolus and peripheral clumps of heterochromatin.
- There is a less deeply stained supranuclear Golgi region that varies in size in different phases of the secretory cycle.
- The **cytoplasm** is filled with large numbers of secretory granules containing the precursors of the pancreatic digestive enzymes.
  - These zymogen granules are most abundant in acinar tissue fixed during fasting and are noticeably reduced in number after the copious secretion induced by a meal.
  - After depletion of the zymogen granules, the Golgi region enlarges while new secretory granules are being formed.
- The intensely basophilic lower portion of the acinar cell is found, in electron micrographs, to be crowded with closely spaced parallel cisternae of granular endoplasmic reticulum.
- In morphometric studies, this organelle has been shown to occupy about 20 percent of the cell volume and to present a surface area of some 800 um2.
- The surrounding cytoplasm is rich in free polyribosomes.

- Here and there, the cisternae diverge to accommodate long **mitochondria** that have numerous cristae and many matrix granules.
- The **supranuclear Golgi complex** consists of several short stacks of parallel cisternae that have numerous small vesicles associated with the convex cis-face.
- At the concave trans-face of the stacks, there are a few larger **vesicles** and condensing **vacuoles** with a homogenous content of low density. These represent formative stages of new secretory granules.
- Occasional **lipid droplets** and **lysosomes** may also be found in this region.
- **Dense membrane bounded-zymogen granules** completely fill the apical region of the cell. In actively secreting cells, these may be found in the process of discharging their content into the lumen of the acinus.
- Although the term **zymogen "granule"** implies solid or semisolid consistency, it is evident in electron micrographs that their content is fluid at time of release because it appears to flow through the opening formed by fusion of the lining membrane with the plasmalemma.
- No granules are seen in the lumen, only diffuse material of moderate density.
- **Secretory vesicle** might be a more appropriate descriptive term than secretory granule.
- However closely these crowded together in the apical cytoplasm, they normally remain discrete, but during very active secretion, a second zymogen vesicles may fuse with one engaged inexocytosis, and a third may fuse with the second, so that a series of intercommunicating secretory vesicles is formed that extends some distance down into the apical cytoplasm.

DUCT SYSTEM

- The pancreas is unique among compound acinous glands in that low cuboidal or squamous cells lining the duct extend a short distance into the acinus.
- These so-called **centroacinar cells** are easily identified by their pale staining in histological sections and by their very low density and paucity of cytoplasmic organelles in electron micrographs.
- The centroacinar cells are continuous with the lining epithelium of slender intercalated ducts that drain the acinus.
- These slender tubed converge to form large **intralobular ducts** that are, in turn, tributaries of **interlobular ducts** in the connective tissue septa between lobules.
- The latter are lined by a low columnar epithelium containing occasional goblet cells.
- The smaller ducts of the gland are not simply conduits for the secretory products of the acini.
  - Their lining epithelium is active in transporting water and bicarbonate ions into lumen, and they make a major contribution to the volume of pancreatic secretion.
- The interlobular ducts join the main pancreatic ducts, of which there are two.
- The larger, the **duct of Wirsung**, begins in the tails and runs through the length of the gland, gradually increasing in diameter as it is joined by numerous interlobular ducts.
  - In the head of the pancreas, it runs parallel to the common bile duct (ductus choledochus) with which it may have a common opening into the duodenum at the **ampulla of Vater.**
- The opening and closing of this common outlet is controlled by the sphincter of Oddi in its wall.
- An accessory duct of Santorini is nearly always present. It lies cranial to the duct of Wirsung and is about 6 cm in length.
- These larger pancreatic ducts are lined by a low columnar epithelium containing a moderate number of goblet cells and occasional argentaffin cells.
- They are enveloped in a substantial layer of connective tissue, containing some smooth muscle fiber and many mast cells.

EXOCRINE BLOOD VESSELS

- The pancreas receives its blood supply from numerous branches of the **splenic artery** and from **pancreaticoduodenal branches of the hepatic** and **superior mesenteric arteries.**
- The larger vessels course through the interlobular septa and give off branches that arborize into a rich capillary network surrounding the acini.
- The walls of the capillaries in the exocrine pancreas have a continuous endothelium, whereas the capillaries of the islets of the endocrine pancreas are **fenestrated**.
- The capillary bed of the gland is drained by veins that join the portal, splenic, and superior mesenteric veins.

EXOCRINE LYMPHATICS

- There are lymphatic capillaries that end blindly among the acini and drain via larger lymphatics that follow the course of the blood vessels to reach pancreaticosplenic lymph nodes distributed along the upper border of the gland.

EXOCRINE NERVE SUPPLY

- The nerve supply is from the vagus and splanchnic nerves via the **splenic nerve plexus**.
- Small clusters of **autonomic ganglion cells** are sometimes encountered in histological sections of the acinar tissue.
- In electron micrographs, axons are occasionally observed penetrating the basal lamina and ending in intimate contact with the base of an acinar cell.
  - These are probably termination of branches of the vagus nerve because stimulation of the vagus results in exocytosis and accumulation of secretion in the lumen of the acini and in small ducts.
  - However, there is little outflow of secretion from the gland under these circumstances because only very small amounts of water and electrolytes are added to the secretion.
- Nervous regulation of pancreatic secretion is thought to be of less importance than its hormonal regulation.

ENDOCRINE PANCREAS

- This consists of **pancreatic islets** or **insulae (of Langerhans),** composed of spheroidal or ellipsoidal clusters of cells dispersed in the exocrine tissue, together with scattered, often solitary, endocrine cells.
- The human pancreas may contain more than a million islets, usually most numerous in the tail.
- Each is a mass of polyhedral cells pervaded by fenestrated capillaries and a rich autonomic innervation.
- Staining procedures distinguish three major types of cells, designated **A, B** and **D**.
- Immunofluorescence microscopy and immuno-electron microscopy have confirmed the identity of their secretory products and revealed other types of endocrine cells.

ENDOCRINE BLOOD VESSELS

- Arteries are rami of the **splenic and pancreaticoduodenal arteries.**
- Venous drainage is into the **portal, splenic and superior mesenteric veins.**
- Larger blood and lymph vessels travel with the exocrine ducts and nerves in the interlobular connective tissue, supplying lobular branches.
- Bunnag et al. (1963) have shown that in mice one to three afferent arterioles arise from arterial rami to supply each islet, before which they may supply the acini.
- In each islet they feed a capillary network almost as dense as in a renal glomerulus; the network is drained by one to six venules which join to enter an interlobular vein.

ENDOCRINE NERVE SUPPLY

- This comes from the **coeliac plexus** and enters along with the arteries of supply.
- Little is known of the afferent nerves; the efferents consists of sympathetic postganglionic fibers from the coeliac ganglion and parasympathetic preganglionic from the right vagus.

- These fibers, mainly non-myelinated are **vasomotor (sympathetic)** and **parenchymal (sympathetic and parasympathetic)** in their distribution.
- Fine branches ramify among the cells, from peri-insular plexuses.
- Fibers frequently synapse with acinar cells before innervating the islets, suggesting a close linkage between neural control exocrine and endocrine components.
- Many fibers enter the islets with the arterioles.
- **Parasympathetic ganglia** lie in the inter- and intralobular connective tissue, and in the latter case are frequently associated with insular cells, forming neuro-insular complexes.
- **Three types of nerve terminal are noted in islets:**
    - **Cholinergic** (with 30 - 50 nm diameter agranular vesicles),
    - **Adrenergic** (with 30-50 nm dense-cored vesicles)
    - **Uncharacterized type** (with 60-200 nm dense-cored vesicles).

FUNCTIONS OF THE PANCREAS

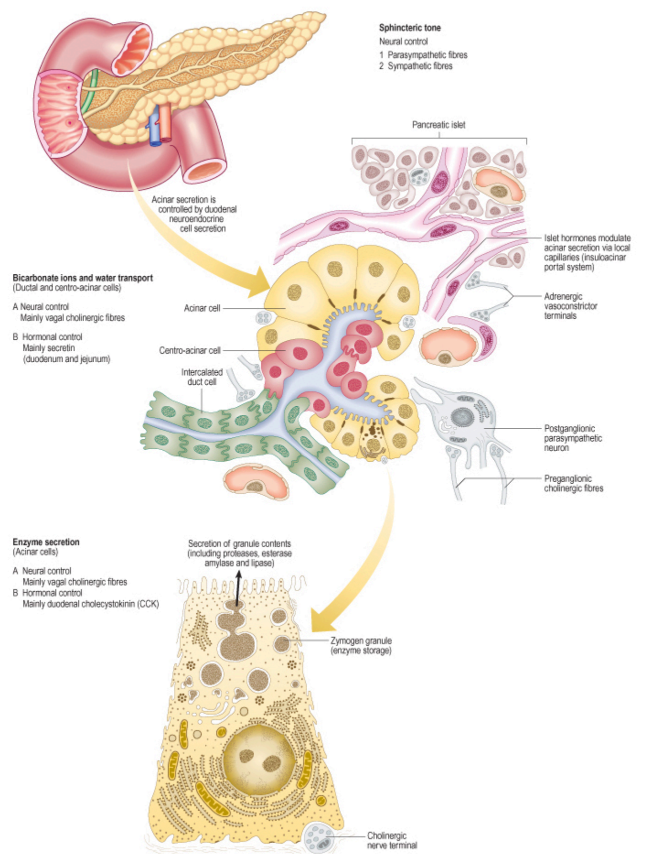
- The **exocrine secretion** of the pancreas include bicarbonate ions, which neutralize the acidic chyme that enters the small intestine from the stomach.
- The increased pH resulting from the secretion of bicarbonate ions stops pepsin digestion but provides the proper environment for the function of pancreatic enzymes.
    - **Pancreatic enzymes** are also present in the exocrine secretions and are important for the digestion of all major classes of food.
    - Without the enzymes produced by the pancreas, lipids, proteins, and carbohydrates are not adequately digested.
    - The major proteolytic enzymes are **trypsin** and **chymotrypsin**, which continue the protein digestion that started in the stomach.
    - **Pancreatic amylase** continues the polysaccharide digestion that was initiated in the oral cavity.
    - The pancreatic enzymes also include a group of lipid-digesting enzymes called **pancreatic lipases**.
    - **Nucleases** are pancreatic enzymes that reduce DNA and RNA to their component nucleotides.
- The **endocrine part** of the pancreas consists of **pancreatic islets (islets of Langerhans)**.
    - The islet cells produce insulin and glucagons, which are very important in controlling blood levels of nutrients, such as glucose and amino acids.

DIGESTIVE ENZYMES AND ITS REGULATION

- Pancreatic secretion contains enzymes for digesting all **three major types of food**: proteins, carbohydrates, and fats.
- It also contains large quantities of **bicarbonate ions,** which play an important role in neutralizing the acid chyme emptied from the stomach into the duodenum.
- The more important of the pancreatic proteolytic enzymes are **trypsin**, **chymotrypsin**, and **carboxypeptidase**.
- Less important are several elastates and nucleases.
- By far, the most abundant of all these is trypsin.
- The trypsin and chymotrypsin split whole and partially digested proteins into peptides of various sizes but do not cause release of individual amino acids.
- Conversely, carboxypeptidase does not split some peptides into individual amino acids, thus completing the digestion of some of the proteins all the way to the amino acid state.
- The pancreatic digestive enzyme for carbohydrates is **pancreatic amylase**, which hydrolyzes starches, glycogen and most other carbohydrates (except cellulose) to form disaccharides and a few trisaccharide.
- The **main enzymes for fat digestion** are:
    - **Pancreatic Lipase** - capable of hydrolyzing neutral fat into fatty acids and monoglycerides
    - **Cholesterol Esterase** - causes hydrolysis of cholesterol esters
    - **Phospholipase** - splits fatty acids from phospholipids
- When first synthesized in the pancreatic cells, the proteolytic enzymes are in the inactive forms trypsinogen, chymotrypsinogen, and procarboxypolypeptidase, which are all inactive enzymatically. They become activated only after they are secreted into the intestinal tract.
- **Trypsinogen** is intestinal mucosa when chyme comes in contact with the mucosa.
    - Also, trypsinogen can be autocatalytically activated by trypsin that has already been formed from trypsinogen can be autocatalytically activated by trypsin that has already been formed from trypsinogen.
- **Chymotrypsinogen** is activated by trypsin to form **chymotrypsin** and **procarboxypolypeptidase** is activated in a similar manner.

SECRETION OF TRYPSIN INHIBITOR PREVENTS DIGESTION OF THE PANCREAS ITSELF

- It is important that the proteolytic enzymes of the pancreatic juice do not become activated until after they have been secreted into the intestine because the trypsin and other enzymes would digest the pancreas itself.
- Fortunately, the same cells that secrete the proteolytic enzymes into the acini of the pancreas secrete simultaneously another substance called **trypsin inhibitor.**
    - This substance is formed in the cytoplasm of the glandular cells and prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas.
    - Because it is trypsin that activates the other pancreatic proteolytic enzymes, trypsin inhibitor prevents the subsequent activation of the others as well.
- When the pancreas becomes severely damaged or when a duct becomes blocked, large quantities of pancreatic secretion sometimes become pooled in the damaged areas of the pancreas.
    - Under these conditions, the effect of trypsin inhibitor is sometimes overwhelmed, in which case the pancreatic secretions rapidly become activated and can literally digest the entire pancreas within a few hours, giving rise to the condition called **acute pancreatitis**.
- This often is lethal because of accompanying circulatory shock; even if not lethal, it usually leads to a subsequent lifetime of pancreatic insufficiency.



BASIC MECHANISMS INVOLVED IN THE FUNCTIONS OF THE SMALL INTESTINE

SECRETORY FUNCTION AND ITS REGULATION

SECRETION OF MUCUS BY BRUNNER'S GLANDS

- The **Brunner's glands** are located in the first few centimeters of the **duodenum**, mainly between the **pylorus** and the **papilla of Vater** where the pancreatic juices and bile empty into the duodenum.
- These glands secrete a large amount of **alkaline mucous** in response to:
  - Tactile stimuli or irritating stimuli of the overlying mucosa
  - Vagal stimulation, which causes increased Brunner's glands secretion concurrently with increase in stomach secretion
  - Gastrointestinal hormones, especially secretin
- The function of the mucus secreted by Brunner's glands is to protect the duodenal wall from the digestion by the highly acid **gastric juice**.
- The mucus contains a **large excess of bicarbonate ions**, which add to the bicarbonate ions from the pancreatic secretion and liver bile in neutralizing the hydrochloric acid entering the duodenum from the stomach.
- Brunner's glands are inhibited by sympathetic stimulation; therefore, such stimulation is likely to leave the duodenal bulb unprotected and is perhaps one of the factors that cause this area of the GIT to be the site of peptic ulcers in about 50% of ulcer patients.

SECRETION OF THE INTESTINAL DIGESTIVE JUICES BY THE CRYPTS OF LIEBERKUHN

- The **intestinal surfaces of both the crypts and the villi** are covered by an epithelium composed of **two types of cells**:
  - a moderate number of goblet cells, which secrete mucus that lubricates and protects the intestinal surfaces
  - a large number of enterocytes in the crypts, secrete large quantities of **water and electrolytes** and reabsorb the water and electrolytes along with end products of digestion over the surfaces of the villi.
- The intestinal secretions are formed by the **enterocytes of the crypts** at a rate of about 1800mL/day.
- The secretions are almost pure extracellular fluid and have a slightly alkaline pH in the range of **7.5 to 8.0**.
- The secretions are also rapidly reabsorbed by the **villi**.
  - This circulation of fluid from the crypts to the villi supplies a watery vehicle for absorption of substances from the chyme as it comes in contact with the villi.

DIGESTIVE ENZYMES IN THE SMALL INTESTINE

- When secretions of the small intestine are collected without cellular debris, they have almost no enzymes.
- However, the **enterocytes of the mucosa**, especially those that cover the villi, do contain digestive enzymes that digest specific food substances while they are being absorbed through the epithelium.
- These enzymes are the following:
  - **peptidases** for splitting small peptides into amino acids
  - four enzymes for splitting disaccharides into monosaccharides – **sucrase, maltase, isomaltase**, and **lactase**
  - small amounts of **intestinal lipase** for splitting neutral fats into glycerol and fatty acids.
- Most if not all of these digestive enzymes are located mainly in the **brush border** of the enterocytes.

REGULATION OF SMALL INTESTINAL SECRETION

- **Local Stimuli**
  - The most important means for regulating small intestinal secretion are various local enteric nervous reflexes, especially reflexes initiated by **tactile or irritative stimuli** and by **increase in enteric nervous activity** associated with the GI movement.
  - Secretion in the small intestine occurs in response to the **presence of chyme in the intestine** – the greater the amount of chyme, the greater the secretion.
- **Hormonal Regulation**
  - **Secretin** and **Cholecystokinin** increase small intestinal secretion.

DIGESTION OF VARIOUS FOOD

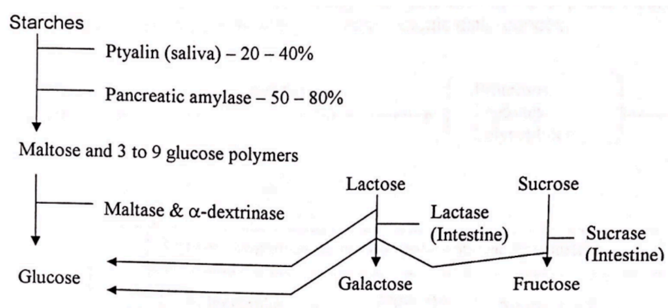
DIGESTION OF CARBOHYDRATE IN THE SMALL INTESTINE

DIGESTION BY PANCREATIC AMYLASE

- Pancreatic secretion contains a large quantity of **a-amylase** that is almost identical in its function with the α-amylase of saliva.
- Within **15 – 30 minutes** after the chyme empties from the stomach into the duodenum and mixes with pancreatic juice, virtually all the starches will have been digested.
- Starches are almost totally converted into **maltose** and other **very small glucose polymers** before passing beyond the duodenum or upper jejunum by intestinal epithelial enzymes.

HYDROLYSIS OF DISACCHARIDES AND SMALL GLUCOSE POLYMERS INTO MONOSACCHARIDES

- The enterocytes lining the villi of the small intestine contain four enzymes **(lactase, sucrase, maltase, and α-dextrinase)**, which are capable of splitting the disaccharides lactose, sucrose, and maltose, plus other small glucose polymers, into their constituent monosaccharides.
  - These enzymes are located in the enterocytes covering the intestinal microvilli brush border, so the disaccharides are digested as they come in contact with these enterocytes.
    - **Lactose** splits into a molecule of galactose and a molecule of glucose.
    - **Sucrose** splits into a molecule of fructose and a molecule of glucose.
    - **Maltose** and other small glucose polymers all split into multiple molecules of glucose.
  - Thus, the final products of carbohydrate digestion are all monosaccharides.
  - They are all water soluble and are absorbed immediately into the portal blood.
- In the ordinary diet, which contains far more starches than all other carbohydrates combined, glucose represents more than 80 percent of the final products of carbohydrate digestion, and galactose and fructose each seldom represent more than 10 percent.



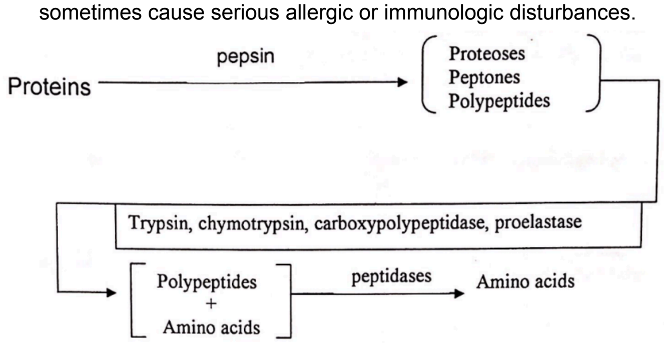
DIGESTION OF PROTEINS

BY PANCREATIC SECRETIONS

- Most protein digestion occurs in the upper small intestine, in the **duodenum** and **jejunum**, under the influence of proteolytic enzymes from pancreatic secretion.
- Immediately upon entering the small intestine from the stomach, the partial breakdown products of the protein foods are attacked by the major proteolytic pancreatic enzymes trypsin, chymotrypsin, carboxypolypeptidase, and proelastase.
- Both trypsin and chymotrypsin split protein molecules into small polypeptides;
- **Carboxypolypeptidase** then cleaves individual amino acids from the carboxyl ends of the polypeptides.
- **Proelastase**, in turn, is converted into **elastase**, which then digests elastin fibers that partially hold meats together.
- Only a small percentage of the proteins are digested all the way to their constituent amino acids by the pancreatic juices.
- Most remain as dipeptides, tripeptides, and some even larger.

BY PEPTIDASES IN THE ENTEROCYTES

- The last digestive stage of the proteins in the intestinal lumen is achieved by the **enterocytes that line the villi of the small intestine**, mainly in the duodenum and jejunum.
  - These cells have a brush border that consists of hundreds of microvilli projecting from the surface of each cell.
- In the membrane of each of these microvilli are multiple **peptidases** that protrude through the membranes to the exterior, where they come in contact with the intestinal fluids.
- **Two types of peptidase enzymes:**
  - Aminopolypeptidase
  - dipeptidases
- They split the remaining larger polypeptides into tripeptides and dipeptides and a few into amino acids.
- The amino acids, dipeptides, and tripeptides are easily transported through the microvillar membrane to the interior of the enterocyte.
- Inside the cytosol of the enterocyte are multiple other peptidases that are specific for the remaining types of linkages between amino acids.
- Within minutes, virtually all the last dipeptides and tripeptides are digested to the final stage to form single amino acids, which then pass on through to the other side of the enterocyte and thence into the blood.
- More than 99 percent of the final protein digestive products that are absorbed are individual amino acids, with only rare absorption of peptides and very rare absorption of whole protein molecules.
- Even these few absorbed molecules of whole protein can sometimes cause serious allergic or immunologic disturbances.



DIGESTION OF FATS

DIGESTION OF FATS IN THE INTESTINE

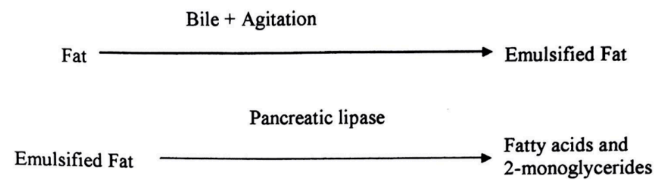
- A small number of triglycerides is digested in the stomach by **lingual lipase** secreted by **lingual glands** in the mouth and swallowed with the saliva.
  - This amount of digestion is less than 10 percent and is generally unimportant. Instead, essentially all fat digestion occurs in the small intestine as follows.

EMULSIFICATION OF FAT BY BILE AND LECITHIN

- The **first step in fat digestion** is to break the fat globules into small sizes so that the water-soluble digestive enzymes can act on the globule surfaces.
  - This process is called **emulsification of the fat.**
    - It is achieved partly by agitation in the stomach along with the products of stomach digestion but mainly in the duodenum under the influence of **bile**–the secretion of the liver that does not contain any digestive enzymes.
- Bile contains a large quantity of bile salts as well as the phospholipids lecithin, both of which, but especially the lecithin, are extremely important for the emulsification of fat.
- The polar parts of the bile salts and lecithin molecules are highly soluble in water, whereas most of the remaining portions of their molecules are highly soluble in fat.
- Therefore, the fat-soluble portions of these liver secretions dissolve in the surface layer of the fat globules, with the polar portions projecting outward; and, the polar parts' being soluble in the surrounding watery fluids, this effect greatly decreases the interfacial tension of the fat.
- A major function of the bile salts and lecithin, especially **lecithin** in the bile is to make the fat globules readily fragmentable by agitation of the water in the small bowel.
- The lipases are water-soluble compounds and can attack the fat globules only on their surfaces.

DIGESTION OF TRIGLYCERIDES BY PANCREATIC LIPASE

- The most important enzyme for digestion of the triglycerides is **pancreatic lipase**, present in enormous quantities in pancreatic juice, enough to digest within 1 minute all triglycerides that it can reach.
- The enterocytes of the small intestine contain additional lipase, known as **enteric lipase**.
- Most of the triglycerides of the diet are split by pancreatic lipase into **free fatty acids** and **2-monoglycerides**.
  - Minute portion remain in the diglyceride state.

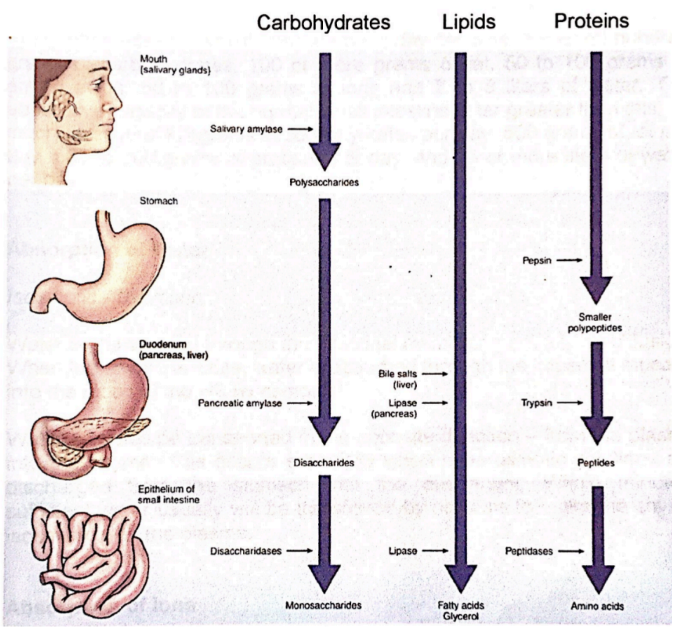


ROLE OF BILE SALTS IN ACCELERATING FAT DIGESTION - FORMATION OF MICELLES

- The hydrolysis of triglycerides is a highly reversible process; therefore, accumulation of monoglycerides and free fatty acids in the vicinity of digesting fats quickly blocks further digestion.
- However, the bile salts play the additional important role of removing the monoglycerides and free fatty acids from the vicinity of the digesting fat globules almost as rapidly as these end products of digestion are formed.
- When bile salts are of a high enough concentration in water, they have the propensity to form **micelles**, which are small spherical, cylindrical globules 3 to 6 nanometers in diameter composed of 20 to 40 molecules of bile salt.
  - These micelles develop because each bile salt molecule is composed of a sterol nucleus that is highly fat-soluble and a polar group that is highly water-soluble.
- The sterol nucleus encompasses the fat digestate, forming a small fat globule in the middle of a resulting micelle, with polar groups of bile salts projecting outward to cover the surface of the micelle.
- Because these polar groups are negatively charged, they allow the entire micelle globule to dissolve in the water of the digestive fluids and to remain in stable solution until the fat is absorbed into the blood.
- The bile salt micelles also act as a transport medium to carry the monoglycerides and free fatty acids, both of which would otherwise be relatively insoluble, to the brush borders of the intestinal epithelial cells.
- There the monoglycerides and free fatty acids are absorbed into the blood, as discussed later, but the bile salts are released back into the chyme to be used again and again for this **"ferrying" process.**

DIGESTION OF CHOLESTEROL AND PHOSPHOLIPIDS

- Most cholesterol in the diet is in the form of **cholesterol esters**, which are combinations of free cholesterol and one molecule of fatty acid.
- **Phospholipids** also contain fatty acid within their molecules.
- Both the cholesterol esters and the phospholipids are hydrolyzed by two other lipases in the pancreatic secretion that free the fatty acids—the enzyme **cholesterol ester** hydrolase to hydrolyze the cholesterol ester, and **phospholipase** A2 to hydrolyze the phospholipid.
- The bile salt micelles play the same role in "ferrying" free cholesterol and phospholipid molecule digestates that they play in ferrying monoglycerides and free fatty acids.
- Indeed, essentially no cholesterol is absorbed without this function of the micelles.



BASIC MECHANISMS OF ABSORPTION

- Absorption through the GI mucosa occurs by active transport, by diffusion, and possibly by solvent drag.
- **Active transport** imparts energy to transport the substance to the other side of the membrane.
- Transport by **diffusion** means simply transport of substances through the membrane as a result of random molecular movement.
- Transport by **solvent drag** means that any time solvent is absorbed because of physical absorptive forces, the flow of the solvent will "drag" dissolved substances along with the solvent.

ABSORPTION IN THE SMALL INTESTINE

- Absorption from the small intestine each day consists of several hundred grams of carbohydrates, 100 or more grams of fat, 50 to 100 grams of amino acids, 50 to 100 grams of ions, and 7 to 8 liters of water.
- The absorptive capacity of the normal small intestine is far greater than this; each day as much as several kilograms of carbohydrates, 500 grams of fat, 500 to 700 grams of proteins, and 20 or more liters of water can be absorbed.
- The large intestine can absorb still more water and ions, although it can absorb very few nutrients.

ABSORPTION OF WATER

ISOSMOTIC ABSORPTION

- Water is transported through the intestinal membrane entirely by **diffusion**. Furthermore, this diffusion obeys the usual laws of osmosis.
- Therefore, when the chyme is dilute enough, water is absorbed through the intestinal mucosa into the blood of the villi almost entirely by osmosis.
- Water can also be transported in the opposite direction—from plasma into the chyme. This type of transport occurs especially when hyperosmotic solutions are discharged from the stomach into the duodenum.
- Within minutes, sufficient water usually will be transferred by osmosis to make the chyme isosmotic with the plasma.

ABSORPTION OF IONS

ACTIVE TRANSPORT OF SODIUM

- **20 to 30 grams of sodium** are secreted in the intestinal secretions each day.
  - In addition, the average person eats 5 to 8 grams of sodium each day.
- Therefore, to prevent net loss of sodium into the feces, the intestines must absorb **25 to 35 grams of sodium** each day, which is equal to about one seventh of all the sodium present in the body.
- Normally, less than 0.5 percent of the intestinal sodium is lost in the feces each day because it is rapidly absorbed through the intestinal mucosa.
- **Sodium** also plays an important role in helping to absorb sugars and amino acids.
  - The motive power for sodium absorption is provided by active transport of sodium from inside the epithelial cells through the basal and side walls of these cells into the paracellular spaces.
  - Part of the sodium is absorbed simultaneously with chloride ions; in fact, the negatively charged chloride ions are passively "dragged" along with the positive electrical charges of the sodium ion.

ABSORPTION OF CHLORIDE IONS IN THE DUODENUM AND JEJUNUM

- In the upper part of the small intestine, **chloride ion absorption** is rapid and occurs mainly by **diffusion** (i.e., absorption of sodium ions through the epithelium creates electronegativity in the chyme and electropositivity in the paracellular spaces between the epithelial cells).
- Chloride ions then move along this electrical gradient to "follow" the sodium ions.

ABSORPTION OF BICARBONATE IONS IN THE DUODENUM AND JEJUNUM

- Often large quantities of bicarbonate ions must be reabsorbed from the upper small intestine because large amounts of bicarbonate ions have been secreted into the duodenum in both pancreatic secretion and bile.
  - The bicarbonate ion is absorbed in an indirect way.
- When **sodium ions** are absorbed, moderate amounts of hydrogen ions are secreted into the lumen of the gut in exchange for some of the sodium.
- These **hydrogen ions**, in turn, combine with the **bicarbonate ions** to form **carbonic acid (H_2CO_3)**, which then dissociates to form water and carbon dioxide.
- The water remains as part of the chyme in the intestines, but the **carbon dioxide** is readily absorbed into the blood and subsequently expired through the lungs.
  - This process is the so-called **"active absorption of bicarbonate ions."**

ABSORPTION OF OTHER IONS

- **Calcium ions** are actively absorbed into the blood, especially from the duodenum, and the amount of calcium ion absorption is exactly controlled to supply the daily need of the body for calcium.
- One important factor controlling calcium absorption is **parathyroid hormone** secreted by the parathyroid glands, and another is **vitamin D.**
- **Parathyroid hormone** activates vitamin D, and the activated vitamin D, in turn, greatly enhances calcium absorption.
- **Iron ions** are also actively absorbed from the small intestine.
- Potassium, magnesium, phosphate, and probably other ions can also be actively absorbed through the intestinal mucosa.
- **Monovalent ions** are absorbed with ease and in great quantities while bivalent ions are normally absorbed in only small amounts.

ABSORPTION OF NUTRIENTS

ABSORPTION OF CARBOHYDRATES

- Essentially all the carbohydrates in food are absorbed in the form of monosaccharides;
- Only a small fraction is absorbed as disaccharides and almost none is absorbed as larger carbohydrate compounds.
- By far the most abundant of the absorbed monosaccharides is glucose, which usually accounts for more than 80 percent of the carbohydrate calories absorbed.
  - The reason for this high percentage is that glucose is the final digestion product of our most abundant carbohydrate food, the starches.
  - The remaining 20 percent of absorbed monosaccharides is composed almost entirely of **galactose** and **fructose**—the galactose derived from milk and the fructose as one of the monosaccharides digested from cane sugar.

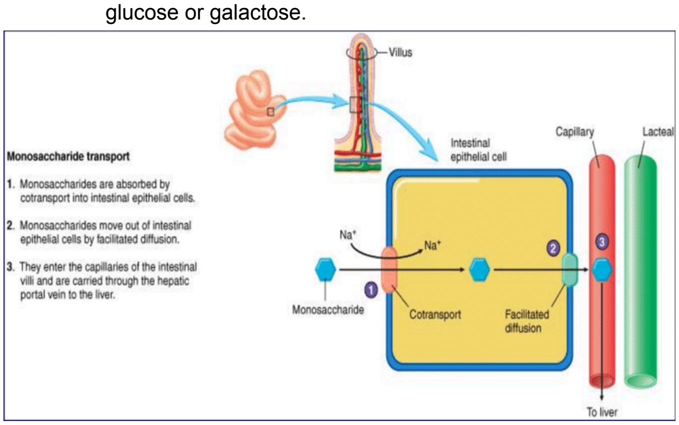
- Virtually all the monosaccharides are absorbed by active transport process.

Glucose Transport By Sodium Co-Transport Mechanism

- Glucose absorption occurs in a **co-transport mode** with the **active transport medium**.
- There are **two stages in the transport of sodium** through the intestinal membrane:
    - **Active transport of sodium ions** through the basolateral membranes of the intestinal epithelial cells into the interstitial fluid, thereby depleting sodium inside the epithelial cells.
    - Decrease of sodium inside the cells causes sodium from the intestinal lumen to move through the brush border of the epithelial cells to the cell interiors by a process of **secondary active transport** – that is, a sodium ion combines with a transport protein, but the transport protein will not transport the sodium to the interior of the cell until the protein also combines with some other appropriate substance such as glucose.
        - Therefore, intestinal glucose also combines simultaneously with the same transport protein and both the sodium ion and glucose molecule are then transported together to the interior of the cell.

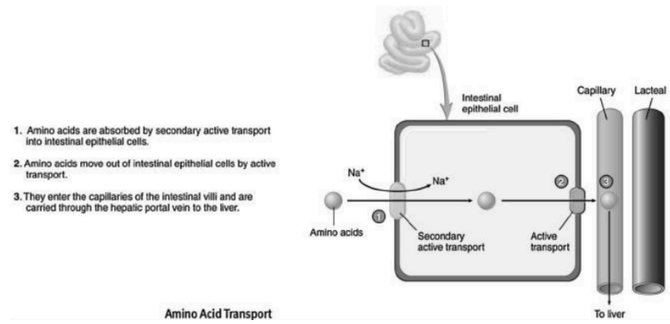
ABSORPTION OF MONOSACCHARIDES

- **Galactose** is transported by almost exactly the same mechanism as glucose.
- **Fructose** is transported by facilitated diffusion all the way through the intestinal epithelium and is not coupled with sodium transport.
    - That is, on entering the cell, becomes phosphorylated.
    - It is then converted to glucose and finally transported in the form of glucose the rest of the way into the blood.
    - Because fructose is not co-transported with sodium, its overall rate of transport is only about one half that of glucose or galactose.



ABSORPTION OF PROTEINS

- Most proteins are absorbed through the luminal membranes of the intestinal epithelial cells in the form of dipeptides, tripeptides, and a few free amino acids.
- The energy for most of this transport is supplied by a **sodium co-transport mechanism.**
- Most peptide or amino acid molecules bind in the cell's microvillus membrane with a specific transport protein that requires sodium binding before transport can occur.
- After binding, the sodium ion then moves down its electrochemical gradient to the interior of the cell and pulls the amino acid or peptide along with it.
    - This process is called **co-transport** (or **secondary active transport**) of the amino acids and peptides
- A few amino acids do not require this sodium co-transport mechanism but instead are transported by special membrane transport proteins in the same way that fructose is transported, by **facilitated diffusion**.



ABSORPTION OF FATS

- **Monoglycerides** and **free fatty acids**, **digestive end products**, become dissolved in the central lipid portion of the bile micelles.
- Monoglycerides and free fatty acids are carried to surfaces of the **microvilli** of the intestinal cell brush border and then penetrate into the recesses among the moving, agitating microvilli.
- Here, both the monoglycerides and the fatty acids diffuse immediately from the micelle and then through the membrane of the microvilli to the interior of the cell.
- After entering the epithelial cells, the fatty acids and monoglycerides are taken up by the cell's **smooth endoplasmic reticulum**, and here they are mainly used to form **new triglycerides** that are subsequently transported mainly in **lymph chylomicrons**, flowing upward through the **thoracic lymph duct** to empty into the circulatory blood.

Direct Absorption of Fatty Acids Into the Portal Blood

- Small quantities of *short- and medium-chain fatty acids*, such as those from **butterfat**, are absorbed directly into the portal blood rather than being converted into triglycerides and absorbed by way of the lymphatics.
    - The cause of this difference between short- and long chain fatty acid absorption is that the short-chain fatty acids are more water soluble and mostly are not reconverted into triglycerides by the endoplasmic reticulum.
    - This phenomenon allows direct diffusion of these short chain fatty acids from the intestinal epithelial cells directly into the capillary blood of the intestinal villi.