National Higher Agronomic School
Food Technology Department

Digestion and absorption

For 4th year, Food and Human Nutrition students

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Introduction:

The process of digestion involves a combination of mechanical and chemical actions that transform the food we eat into nutrients that our body can absorb and use as a source of energy to build and maintain itself. Our digestive system is made up of a tube-like structure, known as the gastrointestinal (GI) tract, which extends from our mouth to our anus. This includes our oral cavity, pharynx, esophagus, stomach, and small and large intestines. Additionally, our digestive system includes other organs such as the teeth, tongue, oral glands, liver, gallbladder, and pancreas.

The digestive system performs four main functions, which are interdependent and flow from one another.

- The first function is ingestion, where food is introduced into the body through the mouth.
- The next function is digestion, which occurs through both mechanical and chemical processes and results in the production of simple, directly absorbable molecules known as nutrients.
- The third function is absorption, where these nutrients are absorbed into the body's internal environment via the bloodstream and circulatory systems.
- Lastly, elimination occurs, where the remains of the digestive process and unabsorbed waste, known as feces, are eliminated from the body via the anus.

The order of these functions is crucial, as any anomaly in one of them can lead to anomalies in the whole digestive system.

Chapter I.
Anatomy and physiology of the digestive tract

Anatomy refers to the examination of the shape and structure of the body and its various parts, as well as how they relate to one another. Physiology, on the other hand, studies how the body and its parts function, and how they contribute to the maintenance of life.

The human digestive tract consists of three main parts.

- Firstly, the upper aerodigestive tract, which includes the oral cavity and pharynx, is used to ingest food.
- Secondly, the digestive tract, which comprises hollow organs, is where digestion takes place. This part begins with the esophagus and continues through the stomach, small intestine, and colon, ending with the rectal ampulla, a more dilated part that opens to the outside through the anus.
- Finally, there are annexed glands, exocrine glands, which discharge their secretions into the lumen of the digestive tract. These secretions are essential for digestion and absorption and include the salivary glands, liver, and pancreas.

Histologically, the digestive tract is composed of 4 layers, or tunics, from the inside out:

➢ **The mucosa,** or inner lining of the digestive tract, is a mucous membrane. It is delimited by a lining epithelium in contact with the food, the type of which corresponds to the function of the segment, situated above a chorion composed of a loose, highly vascularized connective tissue, rich in immune cells organized in lymphoid formations of varying size and arrangement, and provided with exocrine glands whose structure varies according to the segments considered. The mucosa ends in the muscularis mucosae, which is made up of smooth muscle cells. The mucosal epithelium protects against the abrasive effect of the food bolus as it passes through. It also protects underlying tissues and provides mechanical protection. It generally forms a sound barrier against the entry of pathogens.

➢ **The submucosa** is made up of denser connective tissue containing blood vessels and a network of sympathetic nerves, the Meissner plexus, which controls the motility of the digestive tract. This layer includes the lymphoid follicles of the lymphoid organs annexed to the digestive tract (Peyer's patches of the ileum and appendix) and the glands of the duodenum.

➢ **The muscularis:** The muscularis of the mouth, pharynx, and upper esophagus is the partly skeletal muscle responsible for voluntary swallowing. The same applies to the external sphincter of the anus, which enables voluntary control of defecation. In the rest of the digestive tract, the muscular comprises smooth muscle, usually arranged in two layers: an inner layer of circular fibersand an outer layer of longitudinal fibers. In between, the muscularis contains most of the autonomic nervous tissue of the digestive tract, the nerve plexus (Auerbach's plexus), which primarily regulates the motility of the digestive tract.

➢ **The serosa, or adventitia**, is a layer of dense, vascularized connective tissue containing numerous adipocytes. This layer ends in a mesothelium, the visceral layer of the peritoneum.

Cell renewal in the digestive mucosa is as follows:
- esophagus: migration time and lifespan = 8 days
- stomach: acid-secreting parietal cells: lifespan = 1 year
- small intestine: migration time = 3 to 5 days
- colon: migration time = 4 to 6 days

1.1. Upper aerodigestive tract

➢ Oral cavity

The oral cavity is the first segment of the digestive tract. It is divided into two parts:
- the vestibule, between the teeth and the inside of the cheeks and lips ;
- the oral cavity proper, bounded at the front and sides by the teeth, at the back by the isthmus of the gullet, at the top by the bony and membranous palate, and at the bottom by the tongue and floor of the mouth;

The teeth, implanted in the maxillary and mandibular arches, play a significant role in chewing food. During childhood, the dental arches are composed of 20 decidual teeth. These teeth fall out from the age of 6, and are gradually replaced by 32 permanent teeth in adulthood:
- milky teeth, per arch: 4 incisors (central and lateral), 2 canines, and 4 molars;
- definitive dentition, per arch: 4 incisors, 2 canines, 4 premolars, and 6 molars, the last of which are called "wisdom teeth" and grow during adolescence.

The palate comprises a bony front part, covered with mucous membrane, on which the tongue can block food during chewing, marked by the median raphe, a slightly wrinkled protrusion in the middle; and a soft posterior part, mobile during swallowing, which is extended behind by the uvula, a finger-shaped appendage, and on the sides by two pillars, folds, which frame the tonsils.

The tongue, a musculomucosal organ, its fleshy part is a set of muscles oriented in three dimensions, which allows all possible movements during mastication, participates in phonation or sound formation (speech, singing), and in some ancillary activities such as moistening the lips. The tongue is also responsible for taste via the taste buds.
The tongue brake, located below the tip of the tongue, connects it to the maxilla and limits its backward movement: it is impossible to swallow one's tongue.
The pharyngeal part of the tongue, at the very back, has no taste buds but has a bumpy appearance.
The tongue's surface is bristling with taste buds, the organs of perception of the four fundamental tastes: salty, sweet, sour, and bitter. They give the tongue a roughness that is useful for chewing pasty foods.
The main excretory ducts (parotid, submaxillary, and sublingual) and accessory salivary glands lead into the oral cavity. The tongue is then used to mix food with saliva.

Saliva consists of 99.5% water and 0.5% solutes. Solutes include ions such as sodium, potassium, chloride, and bicarbonate. Saliva also contains several dissolved gases and various organic substances (urea, uric acid, serum albumin, globulin, mucin, lysozyme, a bacteriolytic enzyme, and salivary amylase).

The absence of glands in the lips means they must be regularly moistened with saliva to prevent them from drying out.

When swallowing, the tongue propels the food bolus backward through the pharynx towards the esophagus.

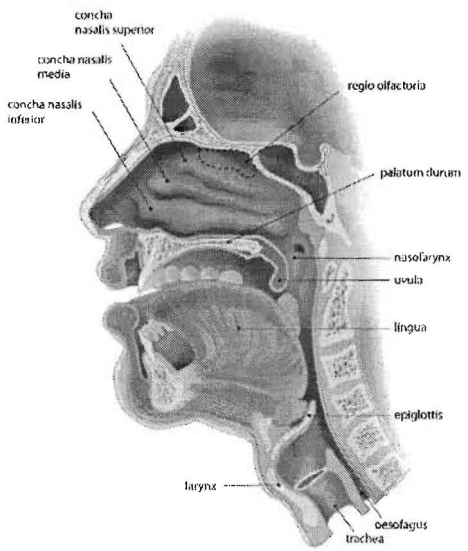
The oral microbiota consists mainly of bacteria. Over 800 species colonize the oral mucosa, 1,300 share the sheltered crevice separating the gum from the tooth, and almost 1,000 make up the biofilm more exposed to salivary flow that is dental plaque. Saliva is a medium rich in hundreds of species of bacteria, with concentrations ranging from 10 to 1,000 million germs per milliliter.

➢ Pharynx

The pharynx (from ancient Greek φάρυγξ (fárynx): "throat") is a funnel-shaped musculomembranous duct extending from the base of the skull at the top to the sixth cervical vertebra at the bottom (to the esophagus and trachea). This fundamental organ is unique and familiar to the upper respiratory tract and the initial part of the digestive system.

It is involved in the digestive and respiratory systems, hearing and phonation.

The contractility of its muscular structure plays a significant role during swallowing, propelling the food bolus while protecting the nasal and laryngeal airways.



The sagittal section of the head

(*Epiglottis:* small organ that covers the trachea during swallowing to prevent food from entering.)

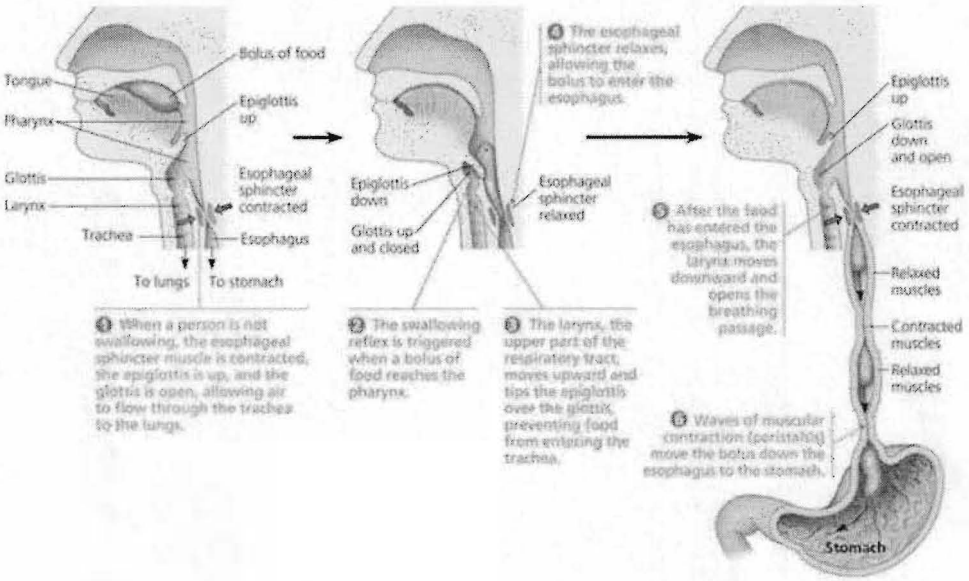
1.2. Digestive tract

➢ Oesophagus

The oesophagus (from the Greek οισοφάγος, literally "that which carries what is eaten") is a flexible musculo-membranous duct located behind the trachea, mainly thoracic and communicating with the pharynx in the neck and the stomach in the abdomen. The orifice that joins the oesophagus to the stomach is the cardia (sphincter).

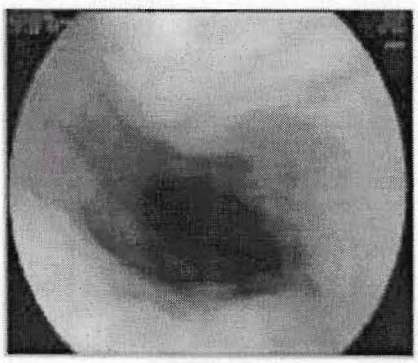
The oesophagus is a vertical tube 25 to 30 cm long in adults and 5 cm long in newborns.

It transports swallowed solid and liquid foods to the stomach, thanks to muscular contractions of its wall. These movements are known as peristaltic.



Food mixed in the mouth with amylase (a salivary enzyme) continues to be broken down in the oesophagus (transforming starch into sugar).

The lining of the oesophagus follows the classic pattern of the gastrointestinal tract: a mucosa that resists damage from the alimentary bolus, a submucosa containing the vessels, a muscular with muscle fibers that allow the alimentary bolus to progress, and an external tunica (adventitia or serosa).



Walls of the esophagus

(Mini atlas of upper digestive endoscopy)

- Stomach

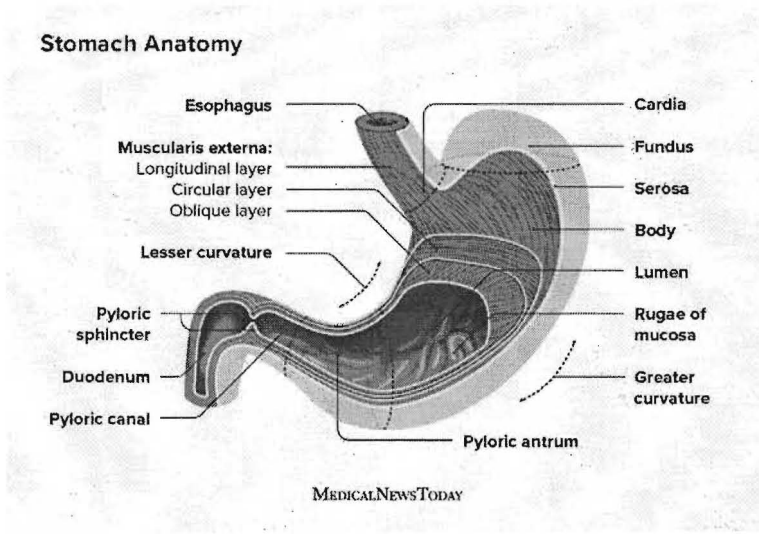
Physiologically, the stomach is a glandular pouch that follows the oesophagus (reservoir between the oesophagus and intestine), starting at the cardia and ending at the pylorus (2 orifices).

The stomach is a thoracoabdominal organ (in the abdomen, touching the wall of the thorax) located under the diaphragm and above the transverse colon. On average, it is 25 cm long and 10 cm wide, with an average capacity of 1.5 L.

The stomach receives the food bolus from the oesophagus; mixes the food bolus and gastric juice to form chyme; initiates protein digestion; limited absorption (Certain molecules are absorbed here: slow, little absorption of alcohol and aspirin); sends the chyme to the duodenum (gastric emptying).

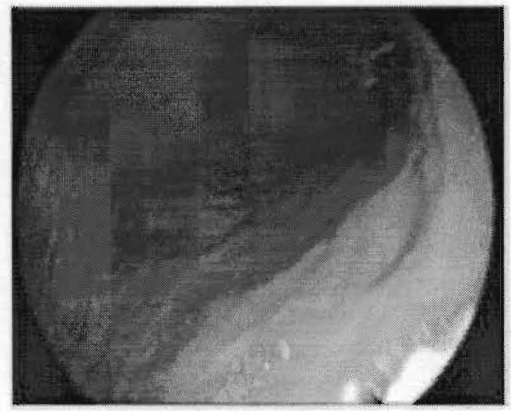
Anatomically, several parts are described:

- the junction with the esophagus is ***the cardia***;
- ***the body***: the vertical part, the upper part of which is called ***the fundus***;
- ***The pyloric part***: the horizontal part, consisting of the antrum and ending in the pylorus (connected to the duodenum). The pylorus is often considered the pyloric orifice itself (and its mighty sphincter); alternatively, the term is used to designate the orifice, the sphincter and the short pyloric duct that extends the antrum.



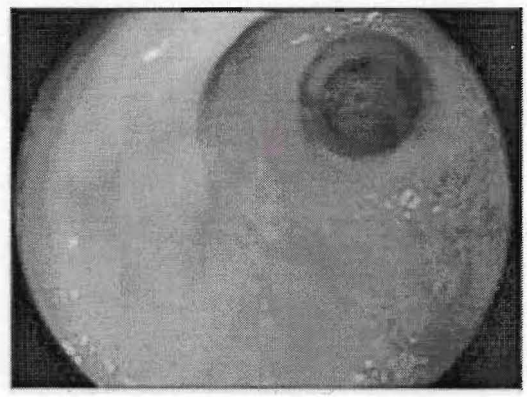
The stomach

Structurally, the stomach is made up of many glandular formations that generate gastric juice (2 to 3 liters per day) and a mucous membrane (acid and alkaline secretion) that forms the gastric folds:



Greater curvature of the stomach

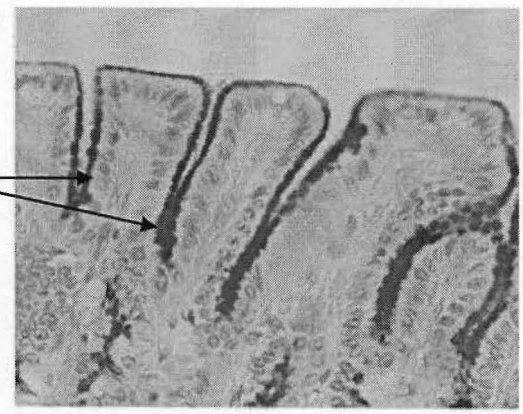
(Mini upper digestive endoscopy atlas)



Pylorus of the stomach

(Mini upper digestive endoscopy atlas)

Glandular cells
(sheet glands)



Gastric folds

(gastric epithelium)

- ***At the fundus level***: the glands are composed of 3 types of cells: parietal (or bordering) cells, which will secrete hydrochloric acid thanks to a proton pump (secretion stimulated by histamine and can be slowed down by antihistamines), and the intrinsic factor, which is used for the absorption of vitamin B12; main cells, which secrete pepsin (an enzyme transforming proteins into peptides and polypeptides) and gastric lipase (an enzyme of lesser importance); and mucous cells, which protect the mucous membrane against acid secretions.

  These first three types of cells discharge their secretions into the lumen of the stomach;

- ***The mucous membrane of the antrum:*** mucus cells, gastrin G cells (gastrin serves to stimulate acid secretion), and endocrine cells. G cells secrete the hormone gastrin into the blood;

- It is also made up of ***a submucosa*** (composed of loose muscle fibers); ***of a muscular*** It has three layers of smooth muscle cells: in addition to the inner circular layer and the outer longitudinal layer, there is a more internal oblique layer. The middle circular layer is very thick around the pyloric canal and forms the pyloric sphincter; and ***a serosa*** (which covers the anterior and posterior surfaces of the stomach).

Table 1: Composition of gastric juice

Compound	Origin	Function
Hydrochloric acid (average: 2 liters/day)	Parietal cells	Converts pepsinogen to pepsin; Kills pathogens; Partially denatures proteins present in food; Stimulates the secretion of hormones which promotes the secretion of bile and pancreatic juice
Pepsinogen	Main cells	Pepsin precursor
Pepsin	Produced from pepsinogen in the presence of HCl which ensures a very acidic environment of the stomach (pH 2).	Protease; Breaks certain peptide bonds between amino acids that form proteins; Ensures coagulation and digestion of milk proteins
Mucus	Mucus Cells	Protects the mucous membrane
Intrinsic factor	Parietal cells	Promotes the absorption of vitamin B_{12}
Serotonin and histamine	Endocrine cells	Autocrine regulation
Gastrin (hormone)	G cells	Stimulates the secretion of HCl and pepsin

➢ Small intestine

Physiologically, the small intestine follows the stomach at the level of the pylorus, it measures approximately 6 to 7 m long. It receives chyme from the stomach, gastric juice, and bile produced by the liver; it ensures the chemical and mechanical degradation of chyme into **chyle**; it absorbs nutrients; and it carries waste to the large intestine.

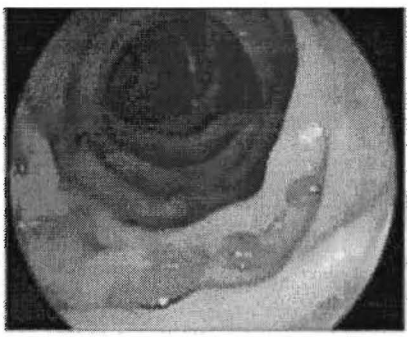
The small intestine divides into the short ***duodenum***, located around the pancreas, into ***the jejunum*** which corresponds to approximately 2/5 of the small intestine, and ***the ileum***, which represents the distal 3/5.

The transition between each portion is gradual.

The outer wall of the small intestine shows numerous circular folds whose muscular activity allows the chyme to rotate on itself. It contains numerous smooth, involuntary muscle fibers that ensure the mixing and progression of chyme throughout the small intestine.

The internal surface of the small intestine has thousands of projections of approximately 1 mm, the intestinal villi, which give it a downy appearance and multiply the internal surface five to six times:

- Each villi is the seat of microvilli, visible only with an electron microscope. The density of the villi decreases between the jejunum and the ileum, as we progress towards the colon.
- In total, the absorption surface of the small intestine reaches 200 m ^{2}.



Duodenum

(Mini upper digestive endoscopy atlas)

Table 2: Absorption surface area per digestive tract organ (cm ^{2})

	Length (cm)	Diameter (cm)	Absorption surface (m ^{2})
Mouth	15-20	10	0.07
Esophagus	25	2.5	0.02
Stomach	25	15	0.11
Duodenum	25	5	0.09
Jejunum	300	5	60
Ileon	60	5	60
Caecum	10	7	0.05
Colon	150	5	0.15
Rectum	20	2.5	0.015

Anatomically, the parts described are:

- **The duodenum:** extends from the pyloric sphincter of the stomach to the duodenojejunal angle(approximately 30 cm long). it includes 4 parts:
  - **DI(or duodenal bulb):** almost horizontal, dilated, 5 cm long, preferred site of ulcers;
  - **DII:** vertical, 10 cm long, joins the common bile duct (brings bile from the liver) and pancreatic ducts. The bile duct and pancreatic ducts join to form the hepatopancreatic ampulla which opens into the duodenum.
  - **DIII:** horizontal, 9 cm long, it crosses the spine at the level of L4;
  - **DIV:** slightly vertical, 6 cm long, ends at the duodenojejunal angle.

- The jejunum

approximately 2.5 m long, the jejunum generally occupies the center of the abdominal cavity which it travels through in numerous folds called loops. The jejunum appears redder than the rest of the small intestine due to its rich vascularization. It continues with the ileum without clear limits.

- The ileum

Along with the jejunum, they constitute the mobile parts of the small intestine. 3.6 m long, the ileum occupies the lower part of the abdominal cavity, between the ascending and descending parts of the colon. It is also arranged in the form of handles. It ends at the level of the cecum, where it opens through the Bauhin valve (ileo-cecal), an anti-return system that prevents any return of waste from the colon to the small intestine. It is the circular component of the muscularis that is reinforced to constitute this sphincter.

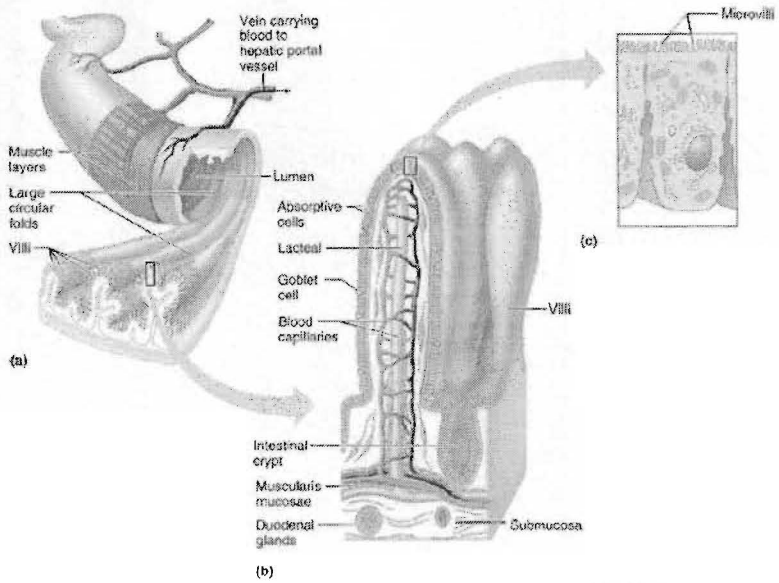
The jejunum and the ileum are formed by around fifteen loops, each measuring 20 to 40 cm long and are attached to the posterior plane by a serous membrane composed of 2 layers = the mesentery (composed of arteries which are ramifications of the superior mesenteric artery arising from the aorta).

Structurally , the four tissue layers are present in the small intestine:

- The mucous membrane:

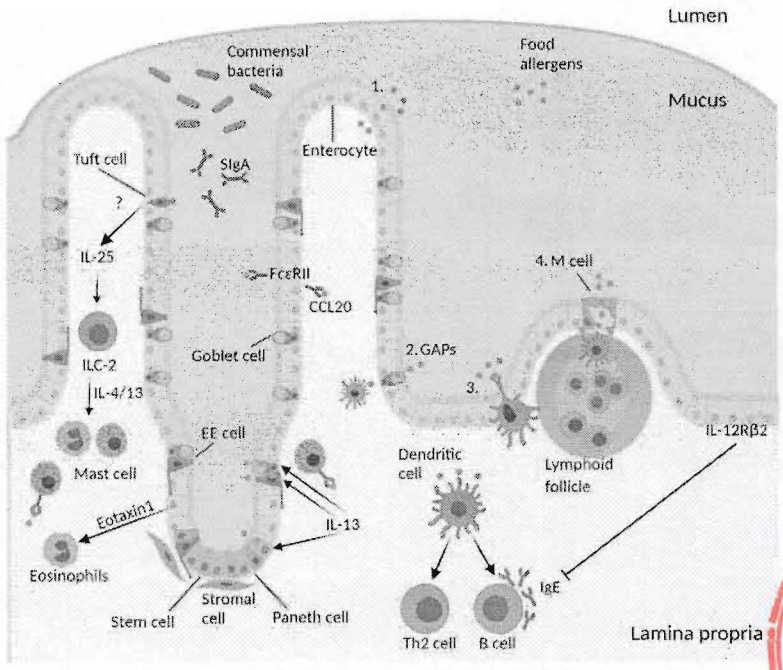
The increase in the exchange surface to increase the absorption of nutrients is made possible by several structures: the great length of the organ; the presence of *circular folds* especially present at the level of the jejunum, *villi*(narrow structures involving the very long mucosa at the level of the duodenum and the proximal jejunum) and *microvilli* of the apical pole (i.e. 350 m^2 of exchange surface).

Each villus contains a network of capillaries and a lymphatic vessel (chyliferous vessel). *Absorption* corresponds to the passage of molecules resulting from digestion, in these vessels, through the microvilli.



Folds, villi, and microvilli of the small intestine

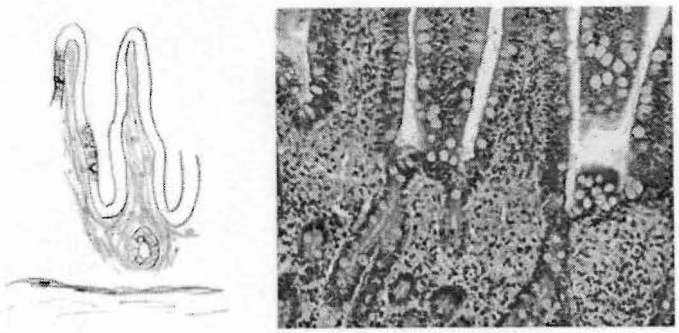
The epithelium of the mucosa of the entire small intestine is simple, prismatic composed of a single cell layer with 4 cell types: prismatic cells with a ridged plate called ***enterocytes*** (absorb nutrients), ***goblet cells*** (goblet cells secrete mucus to help the chyme slide), ***endocrine*** cells (secrete various hormones), and ***paneth cells*** (defense role against bacteria).



Epithelium of the mucosa of the small intestine

➢ Enterocytes:

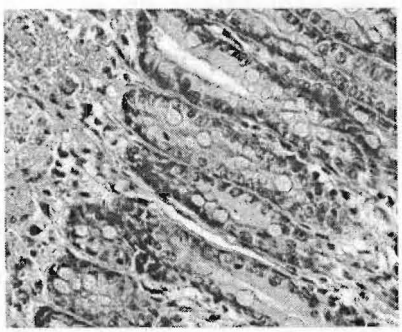
The striated plate of enterocytes corresponds in electron microscopy to microvilli: regular cytoplasmic extensions arranged parallel to each other and containing actin microfilaments.



Enterocytes

➢ Goblet cells:

They produce mucus and are said to have an open pole. The secretory grains accumulate at the apical pole and push the nucleus into the basal region which is narrower.



Goblet cells

➢ Endocrine cells :

At the base of the villi are the *intestinal glands* which secrete digestive enzymes:

- In the duodenum, Brunner's glands secrete mucus which protects the lining against the acidity of the chyme and gastric enzymes.
- In the jejunum and ileum, the Lieberkühn glands secrete protective mucus, produce digestive hormones, and produce digestive enzymes and antibodies.

The intestinal enzymes secreted are:

- **Peptidase:** Breaks down proteins into amino acids.
- **Glycosidase:** Breaks down disaccharides into monosaccharides (maltase and lactase).
- **Lipase:** Breaks down lipids into fatty acids and glycerol.
- **Amylase:** Breaks down starch and glycogen into disaccharides.
- **Nuclease:** Breaks down nucleic acids into nucleotides.
- **Enterokinase:** Activates trypsin secreted by the pancreas.

➢ Paneth cells:

They are grouped at the base of the Lieberkühn glands. They have a basophilic cytoplasm and produce secretion granules containing lysozyme, an enzyme capable of destroying the bacterial cell wall. Their cytoplasm is rich in lysosomes.

The ileum is characterized by the increasing abundance of goblet cells and Lieberkühn glands. In addition, at the level of the ileum, there are Peyer's patches, a lymphoid organ annexed to the digestive tract formed of lymphoid follicles which are located in the chorion of the mucosa and extend into the submucosa.

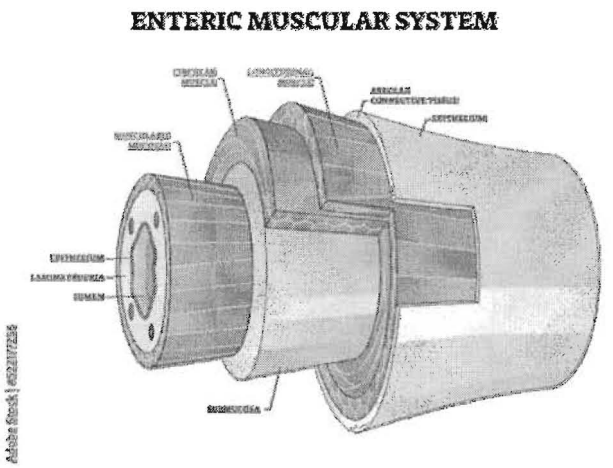
All cells of the epithelium are short-lived and are constantly renewed from pluripotent stem cells located in the neck of the Lieberkühn glands. Cells differentiated into enterocytes or goblet cells migrate along the villi.

- The submucosa :

It is unremarkable except in the duodenum where it contains Brunner's glands. The secretory product is an alkaline mucin that protects the duodenal mucosa from gastric acidity and raises the pH of the intestinal contents to an optimal value for the action of pancreatic enzymes.

- The muscular one :

Sheis thin throughout the small intestine made up of a few smooth muscle cells arranged concentrically.



Smooth muscle layers of the small intestine

- The peritoneum (peri: around; tonos: tension)

The peritoneum is a serous membrane that entirely lines the walls of the abdominopelvic cavity, and which envelops in whole or in part the organs contained therein, i.e. the digestive system.

This serous membrane is called the " *Parietal sheet of the peritoneum* " when it covers the wall of the abdominopelvic cavity" and the " *Visceral sheet of the peritoneum* " when it covers an organ.

Serous membranes are formed of a layer of simple squamous epithelium, called mesothelium, and an underlying layer of connective tissue serving as support.

The visceral peritoneum covers some of the organs and forms their serous tunic.

The peritoneal cavity, a virtual space between the parietal and visceral parts of the peritoneum, contains a serous fluid.

The Mesentery

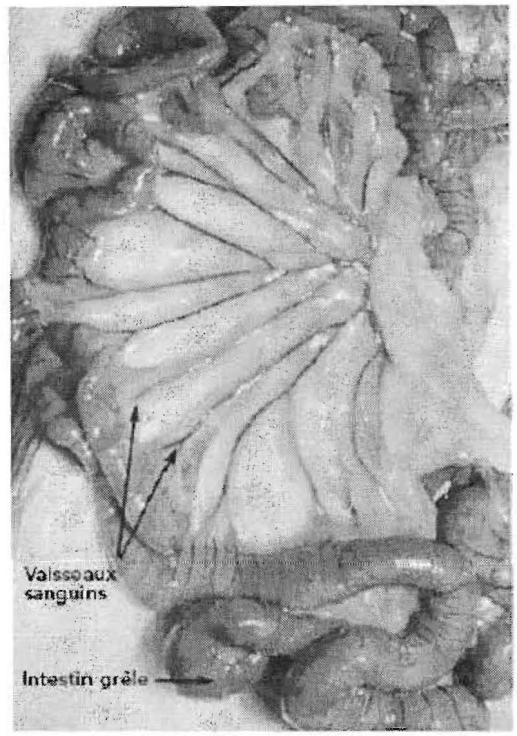
(meso: middle; enteron: intestine)

It is a sheet of peritoneum. The intestinal mesentery connects the small intestine to the back of the abdominal wall.

It contains the arteries which bring fresh blood, the portal veins which carry blood loaded with nutrients toward the liver, and the vegetative nerve fibers which regulate the functioning of the intestine.

An identical fold of the parietal peritoneum, the **mesocolon,** connects the colon to the posterior wall of the body.

It also contains the blood and lymphatic vessels of the intestines.

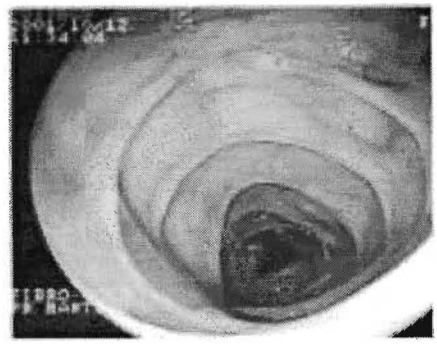


Intestinal mesentery and blood supply of the small intestine

Colon

Physiologically, the colon, or large intestine, follows the small intestine at the ileocaecal angle. It then describes a frame route, covering almost the entire abdomen.
It ends at the rectosigmoid junction and continues through the rectum. It is approximately 1.5 m long and 5 cm wide. The colon presents an appearance due to the alternation of dilated, bumpy areas (hustrations) and areas tightened by the muscular tone of its wall. Haustrations are also visible inside the colon during a colonoscopy.

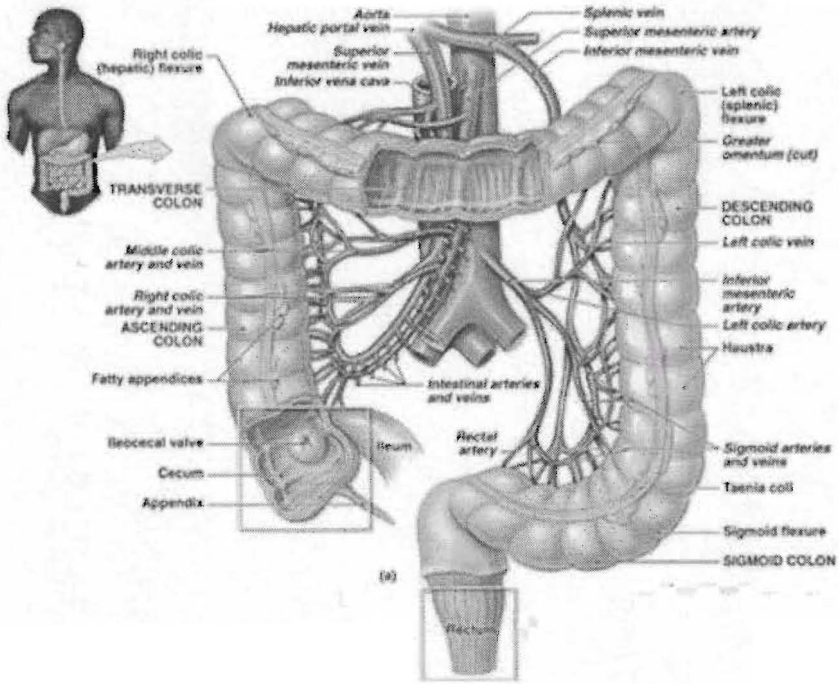
Between two muscular layers, the colonic wall contains an autonomic nervous system, the Auerbach plexus. It also has numerous lymphatic vessels connected to nodes which filter bacteria and possible toxins.



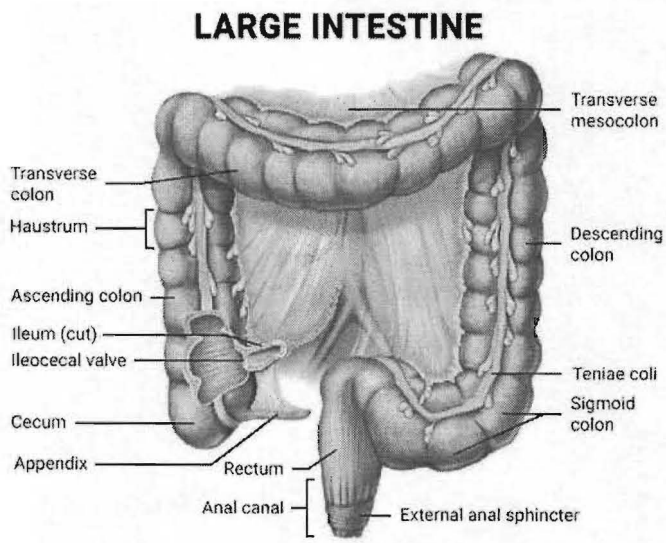
Colic haestrations

On an anatomical level, we distinguish:

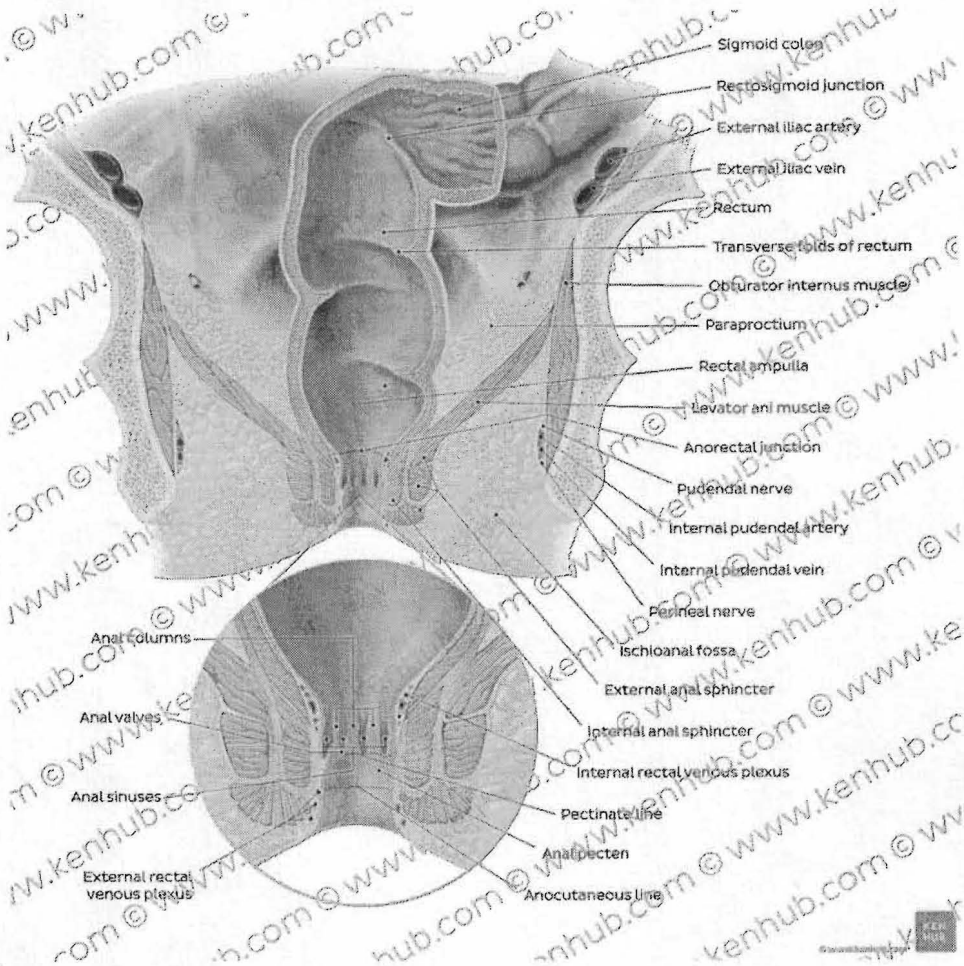
- **the cecum** is the initial part of the colon which begins with the junction with the ileum: ileo-caecal valve (Bauhin valve) whose shape prevents any reflux of fecal matter towards the intestine. It looks like a dilated pocket and has an atrophied extension: the vermicular appendix (vermiform), if this is inflamed there may be peritonitis. The appendix is a cylindrical, hollow lymphoid formation 6 to 8 cm long and 4 to 8 mm in diameter. The junction between the cecum and appendix is called Mac Burney's point, an area carefully palpated by the doctor looking for appendicitis;
- **The ascending colon** extends in the upper right part of the abdomen, from the cecum to the hepatic angle of the colon, at the level of the liver. It is vascularized by the superior mesenteric artery;
- **The transverse colon** passes through the upper part of the peritoneal cavity. It extends from the right colic angle to the left colic angle;
- **The descending colon** extends in the lower left part, from the splenic flexure to the pelvis. It is vascularized by the inferior mesenteric artery;
- **The sigmoid colon:** Terminal segment of the large intestine. It has an "S" shape and is mobile. It ends with the **rectum** (which means "right"), which ensures the storage of stools before their evacuation through the anus. The rectum measures on average 15 cm long. Its diameter varies with its degree of filling. The lower part of the rectum is wider than the upper part and forms the rectal bulb, surrounded by the levator ani muscles. Only its lower end narrows to form the anal canal which passes through the pelvic floor muscles. The anus is the terminal opening of the digestive tract. It begins when the rectum reaches the pelvic floor muscles, attached to the bony pelvis, and opens onto the outside of the body. The anus includes the anal canal and the sphincters:
  - The anal canal, is 3 cm long on average. It is closed apart from defecation or gas emission.
  - The internal sphincter is a circular muscle made up of smooth fibers, the automatic control of which escapes the will. It seals the anal canal except at the time of defecation or incontinence due to illness.
  - The external sphincter is a circular striated muscle, controlled by will. It also closes the anal canal which opens at the time of defecation.



The large intestine



The colon

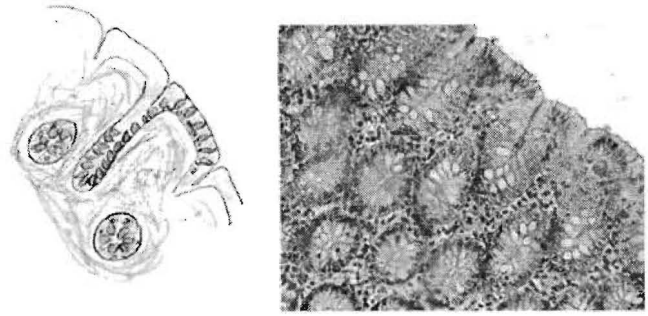


Structure of the anal canal in a frontal section

Structurally,all its segments have the same histological structure. Its surface is devoid of all folds and all villi.

The epithelium of the mucosa is simple, essentially composed of *mucus cells* that secrete mucus intended to facilitate the progression of intestinal contents and to protect the epithelium from materials, and a few *enterocytes* that play a role in the absorption of mucus. water and salts to concentrate the feces.

The muscularis is formed of a thin internal circular layer and an external longitudinal one whose thickness is not uniform forming the strips of the colon. At the level of the anus, the internal circular is thickened and forms the internal anal sphincter. A circular ring composed of striated muscle cells forms the external sphincter.



The epithelium of the colon mucosa

On each side, the ascending and descending colons are fixed due to the adjoining of the mesocolons with the posterior parietal peritoneum. The transverse colon is mobile and attached by a mesocolon posteriorly along an oblique root above and to the left.

The wall of the rectum does not have any haustration or banding like the wall of the colon. It has three furrows, the transverse folds of the rectum whose role is to separate gas and fecal matter. The need to have a bowel movement appears when the pressure exerted by gas and stool reaches 30 mm of mercury on the wall of the rectal ampulla.
The wall of the rectum contains numerous nerve fibers that flood the brain with sensory information and play a major role in defecation.

The mucosa of the anal canal has numerous folds arranged in a crest, the anal columns.
It differs from the mucous membrane of the rectum by the presence of several layers of cells which give it better resistance to the mechanical and chemical action of stools.
A brief transition zone ensures the transformation of the mucous membrane into skin, with its usual hairiness.
The wall of the anal canal includes an important venous system, the internal and external hemorrhoidal plexuses, the dilation of which is responsible for hemorrhoidal crises.

Colon longer than normal = dolichocolon;
Colon wider than normal = megacolon.

1.2. Accessory glands

The accessory glands produce the substances (enzymes, bile salts) necessary for the chemical digestion of food, and discharge them into the digestive tract through ducts. The most important are:

- the salivary glands which discharge their secretions into the mouth;
- the liver, one of the innumerable functions of which is to secrete bile, stored in the gallbladder between two digestions and released into the duodenum when food passes;
- the pancreas, the juice of which is discharged into the duodenum.

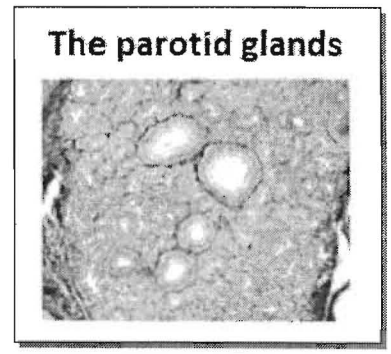
1.3.1. The salivary glands

The mucous membrane lining the mouth contains numerous small glands, the salivary glands, which discharge their secretion product into the oral cavity through ducts, and the mixture of which constitutes saliva. In total, the salivary glands secrete between 1 and 1.5 L of saliva per day.
The continuous secretion of saliva permanently moistens the mouth (the oral and pharyngeal mucous membranes), facilitates speaking, allows chewing and swallowing, it has an antiseptic role, and a protective role for the esophagus. It initiates the digestion of starches, cleans the mouth, and moistens the food bolus. It increases suddenly with the arrival of food in the mouth. The smell, sight, or sometimes just the thought of food also stimulates saliva secretion.
It is the parotid glands, not the ear, that are inflamed during a once-common viral illness, mumps.

There are two groups of salivary glands:

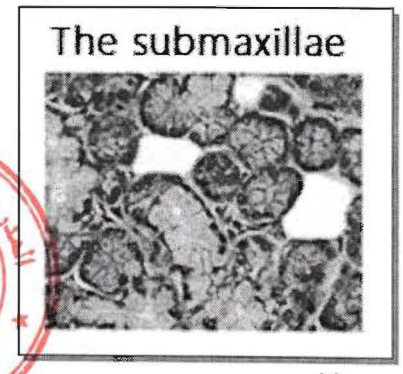
- ***the main glands,*** compound, comprising numerous secretory elements and excretory ducts, represented by the parotid glands (duct of Stensen), the submaxillary (or submandibular) glands (ducts of Wharton), and the sublingual glands (ducts of Rivinus);

- ***accessory glands,*** formed of a few clusters of secretory elements arranged in the chorion of the oral cavity and in the connective trabeculae which separate the muscles of the tongue (thousands of tiny glands located on the internal surface of the cheeks).



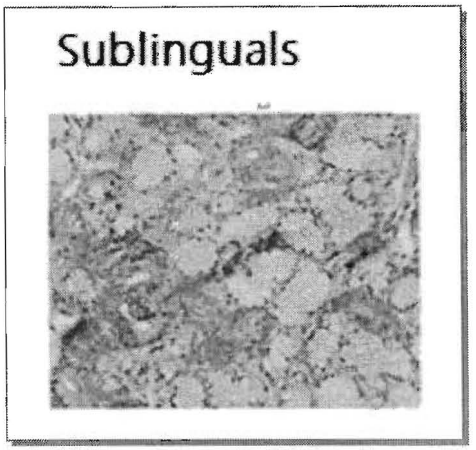
- The parotid glands:

The largest of the salivary glands, they are placed on each side of the face in front of the ears. In each cell of this gland are the secretion grains (enzymatic proteins: amylase, maltase, ribonuclease).
The excretory ducts end in a single duct on each side (Stenon's duct) which opens into the oral cavity.



- The submaxillae:

Smaller than the parotid glands, they are located under the mandible (under the lower jaw) on either side of the midline.
They discharge saliva through the Wharton canal.



- Sublinguals:

The smallest of the main salivary glands are located in front of the submaxillary glands on the dorsum of the tongue. They secrete a digestive enzyme called lingual lipase, which initiates the digestion of triglycerides into fatty acids and mono-glycerides.

1.3.2. liver

Physiologically, it is a large dark red organ, which weighs at autopsy 1500 g in adults (i.e. 2.5% of body weight) but can reach 2500 g in the living when it is full of blood. It measures on average 28 cm wide, 16 cm deep, and 8 cm high.

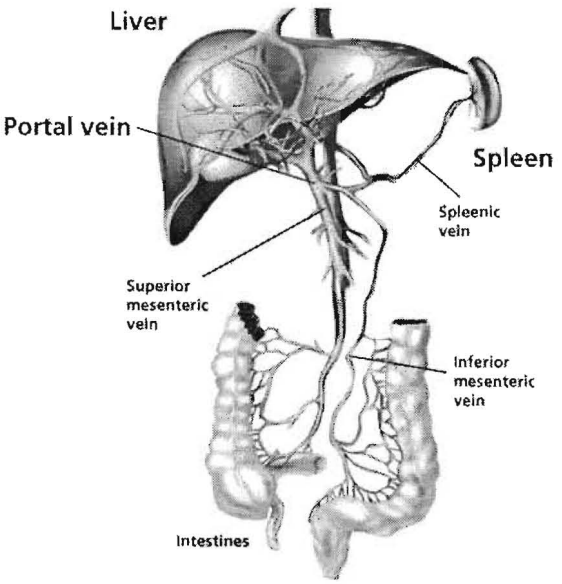
Located at the top and to the right of the abdomen, placed under the diaphragm and in front of the stomach, it is largely hidden under the last right ribs.

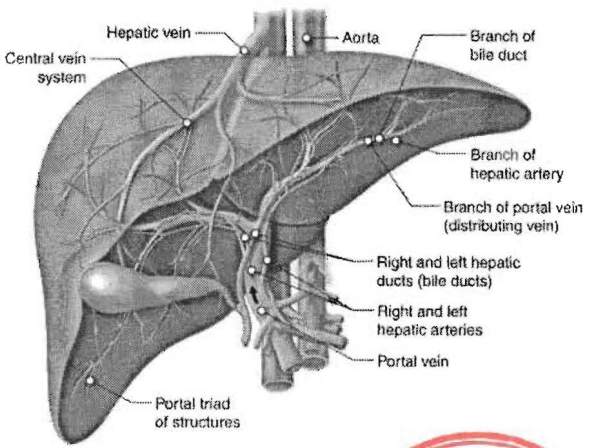
It is an extremely vascularized organ, which gives it this dark red color, and has a double afferent and an efferent vascularization.

The afferent vascularization is composed of two major vessels: the hepatic artery itself which brings oxygen and the portal vein which constitutes the functional vascularization of the organ since it drains the blood coming from the digestive tract and provides various substances (nutrients but also toxins, drugs or xenobiotics) which will be transformed during their passage through the liver.

Once filtered, the blood arrives at the centrilobular vein and then returns to the heart via the suprahepatic veins which flow into the inferior vena cava (*efferent vascularization*).

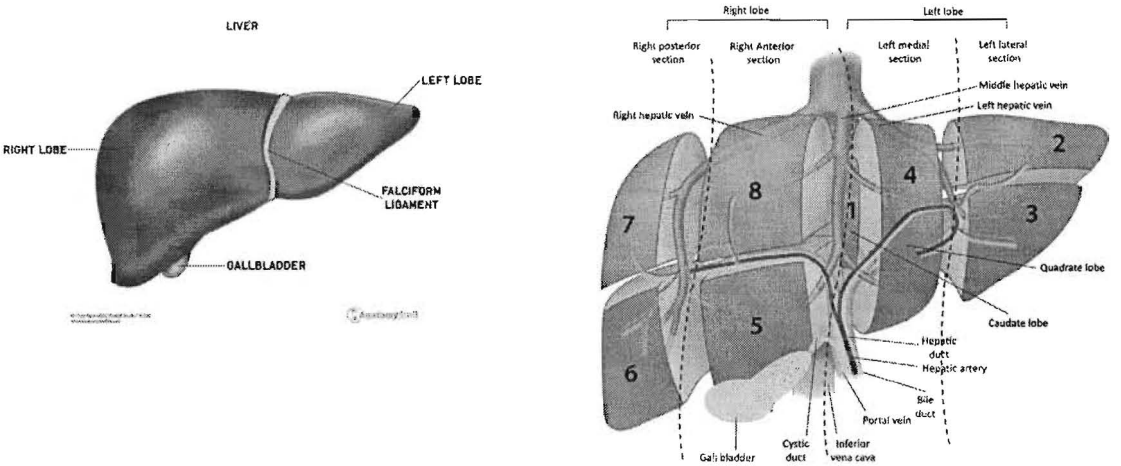
The liver is also crossed by numerous bile ducts which collect the secreted bile and carry it into the hepatic duct to drain it out of the organ.





Vascularization of the liver

Anatomically, the liver is surrounded by a connective envelope, called Glisson's capsule, whose invaginations make it possible to delimit two main lobes, the right lobe (the largest) and the left lobe (the narrowest, placed in front of the stomach) as well as two annexed lobes, the caudate lobe and the square lobe (significantly smaller, are only visible if you look at the liver from below). The latter two are separated by a ligament called the falciform suspensory ligament, which suspends the liver from the diaphragm and abdominal wall.

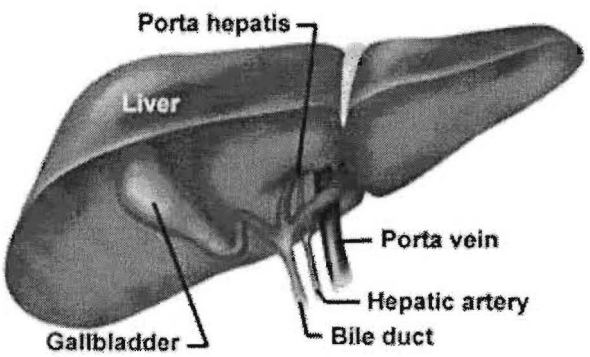


Liver Anatomy

The gallbladder, areservoir of bile, is attached to the liver at the border of the square lobe and the right hepatic lobe. The square lobe and the caudate lobe are separated by a furrow called the hilum of the liver. It is at the hilum that the portal vein and hepatic artery enter the liver, and where major bile ducts pass.

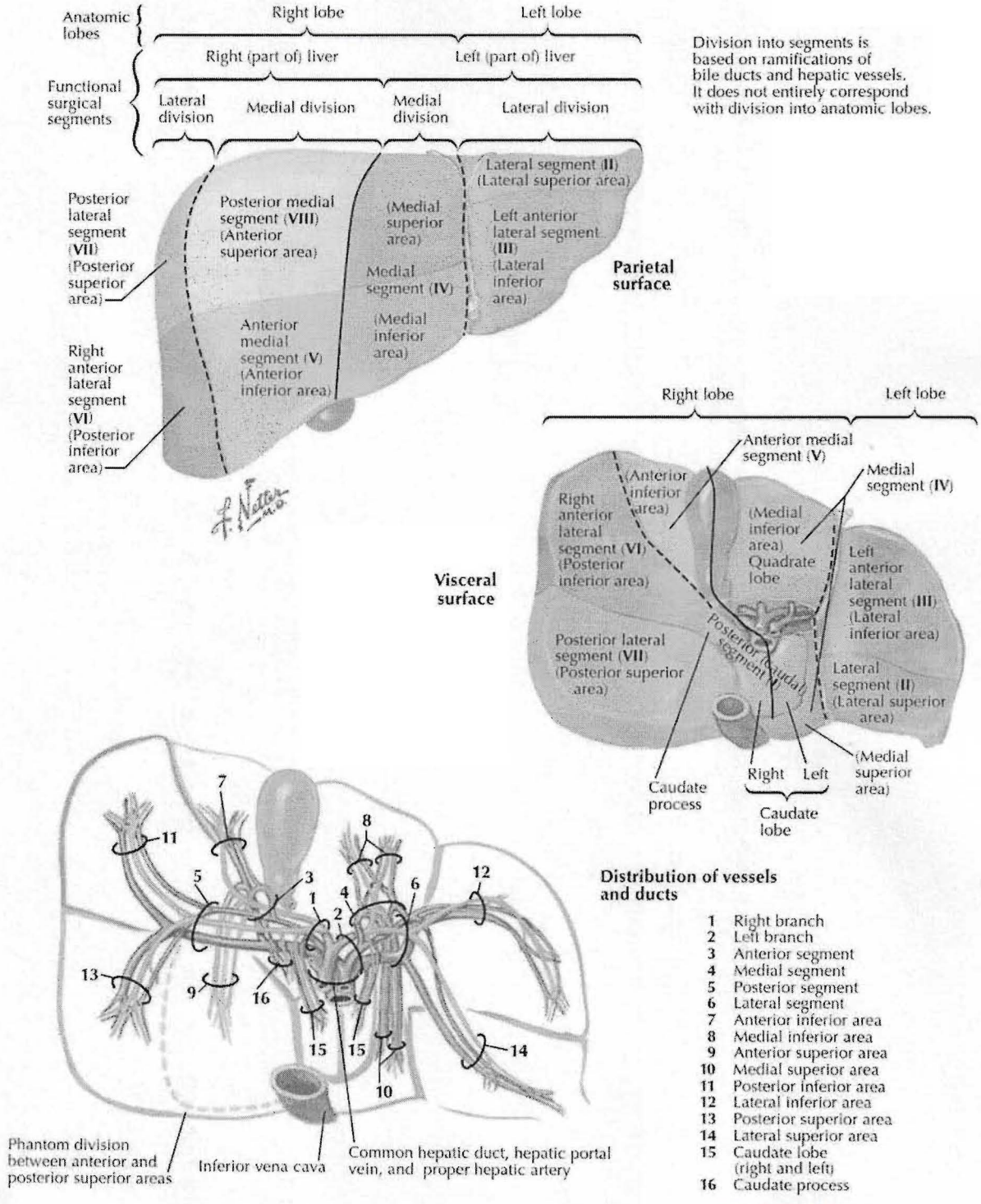
The hilum of the liver, located under its lower surface, has a pedicle comprising:

- the hepatic artery which supplies the liver with oxygenated blood;
- the portal vein which drains all the blood coming from the digestive tract;
- the bile duct which drains all the internal canaliculi of the liver where bile is formed;
- three suprahepatic veins that return blood to the heart.



The hilum of the liver

The liver is also divided into eight segments which correspond to the eight venous branches originating from the portal vein. It is thanks to this segmentation, more than by the division into lobes, that the surgeon can operate on part of the liver without threatening the entire organ.

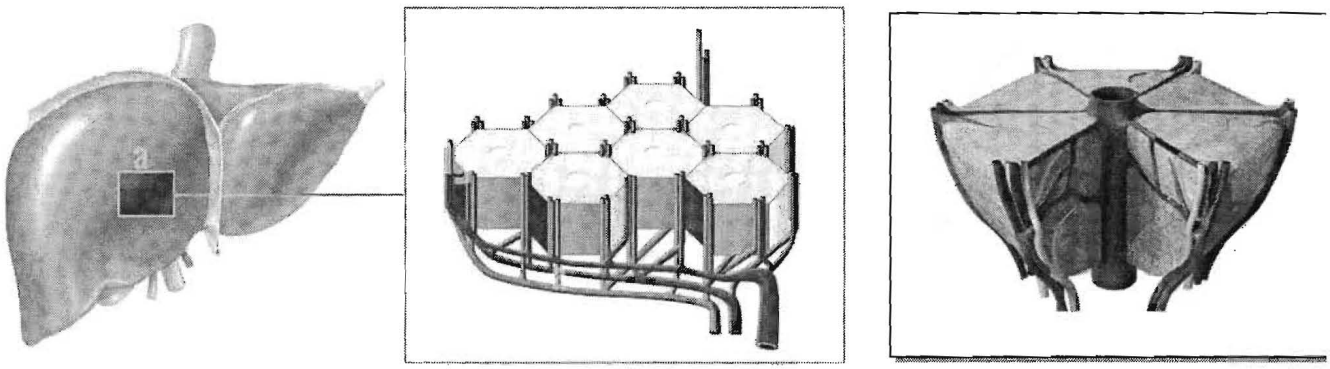


Liver segmentation and lobes

Structurally, the liver contains approximately 300 billion hepatic cells, hepatocytes, organized into small functional units: hepatic lobule, polyhedral in shape. The latter is organized around the centrilobular vein.

At each of the six angles of the lobule is a portal space (or portal triad) which contains a portal vein, a feeding capillary from the hepatic artery, and a bile canaliculus.

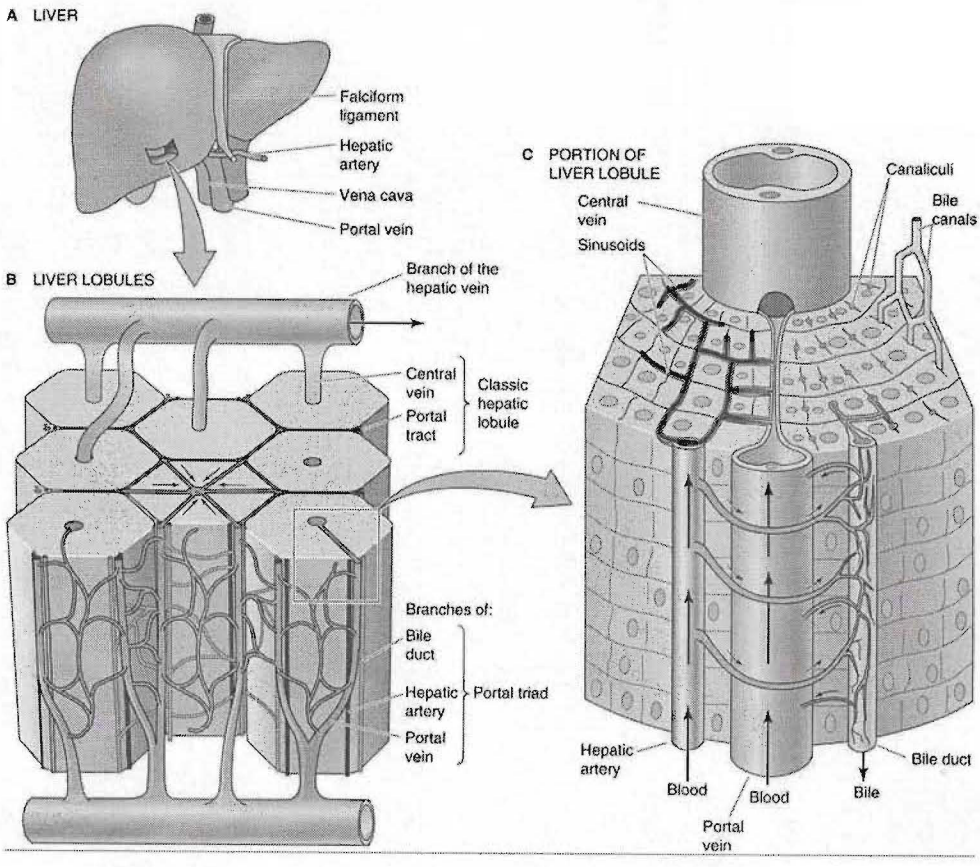
Each element emits extensions into the lobule to deliver nutrients, recover their production, or drain bile.



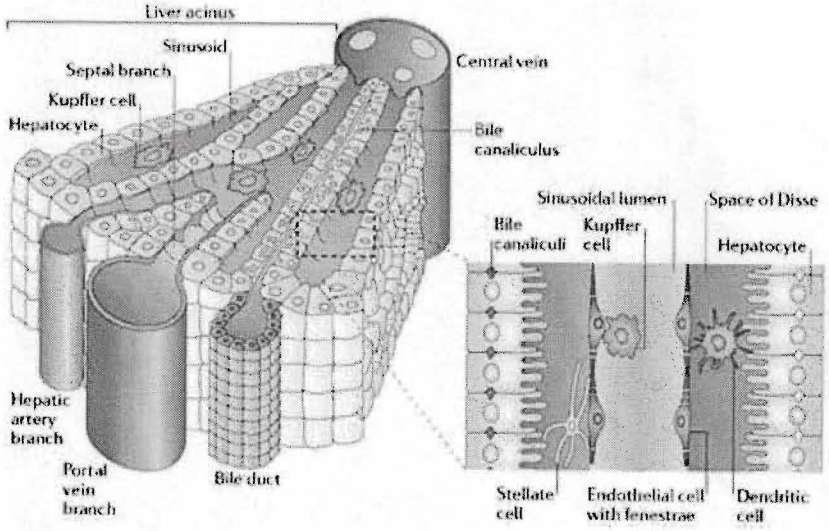
Hepatic organization in lobules Hepatic lobule

The parenchyma of these lobules is mainly composed of hepatocytes organized into single-cell sections separated by blood capillaries or sinusoids. Bile canaliculi drain bile into the bile duct against the direction of blood flow.

The bile canaliculi join to form the bile duct at the hilum.



Structure of liver lobules



Lobular circulation

The adult liver is composed of two distinct cellular categories: hepatocytes or parenchymal cells and non-parenchymal cells, themselves subdivided into 5 different cell types interacting with each other for the proper functioning of the organ.

1. Hepatocytes:

Polygonal epithelial cells represent 60% of the total number of liver cells and 80% of the liver mass. They are involved in a large number of hepatic functions such as metabolism, synthesis, or even storage and are polarized according to three poles ensuring particular functions:

- The sinusoidal pole is in contact with the space of Disse (space located between hepatocytes and blood vessels) and the endothelial cells of the sinusoids. It represents an exchange surface with the blood, thus ensuring the secretion and absorption of hormones and other metabolites as well as the uptake of xenobiotics;
- The bile pole allows the secretion of bile acids into the bile canaliculi. They constitute the starting point of the bile collection and evacuation system;
- The lateral pole ensures cohesion between neighboring hepatocytes and inter-hepatocyte exchanges.

2. Cholangiocytes:

Epithelial cells that line the extra- and intrahepatic bile ducts as well as the gallbladder, and cholangiocytes represent 3 to 5% of the liver mass. Through the expression of various proteins (transporters, ion channels, or exchangers), they control the composition, pH, and transport of bile outside the liver.

3. Küpffer cells:

Located in the lumens of the sinusoids, Küpffer cells represent 20% of non-parenchymal cells and serve as hepatic macrophages for potentially toxic organisms such as viruses or bacteria originating from the digestive tract.

4. Ito's cells:

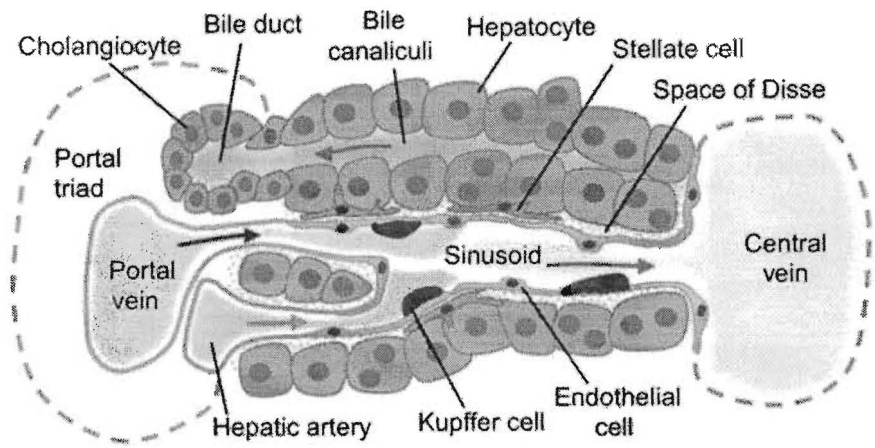
Also called hepatic stellate cells, Ito cells are located in the space of Disse. With a stellate morphology, they are mainly responsible for the synthesis of numerous extracellular matrix proteins such as certain types of collagens. They also have an important role in the storage of fats and vitamin A via their cytoplasmic lipid droplets.

5. Endothelial cells:

Liver sinusoidal endothelial cells line sinusoidal capillaries. Flat in shape, their cytoplasm is fenestrated and they do not have a basement membrane. These two features facilitate the exchange of metabolites between the blood and the underlying hepatocytes.

6. The "pit cells":

Natural-killer lymphocytes, pit cells, are present in small quantities in the liver at the level of the sinusoids and the space of Disse. Through their strong cytotoxic power, they act in synergy with Küppfer cells to eliminate tumor or necrotic cells or cells infected by viruses.



The different types of liver cells

The privileged anatomical position of the liver the blood circulation and its very structured histological organization allow it to accomplish its specific metabolic functions of synthesis, catabolism, and storage of numerous compounds and nutrients.

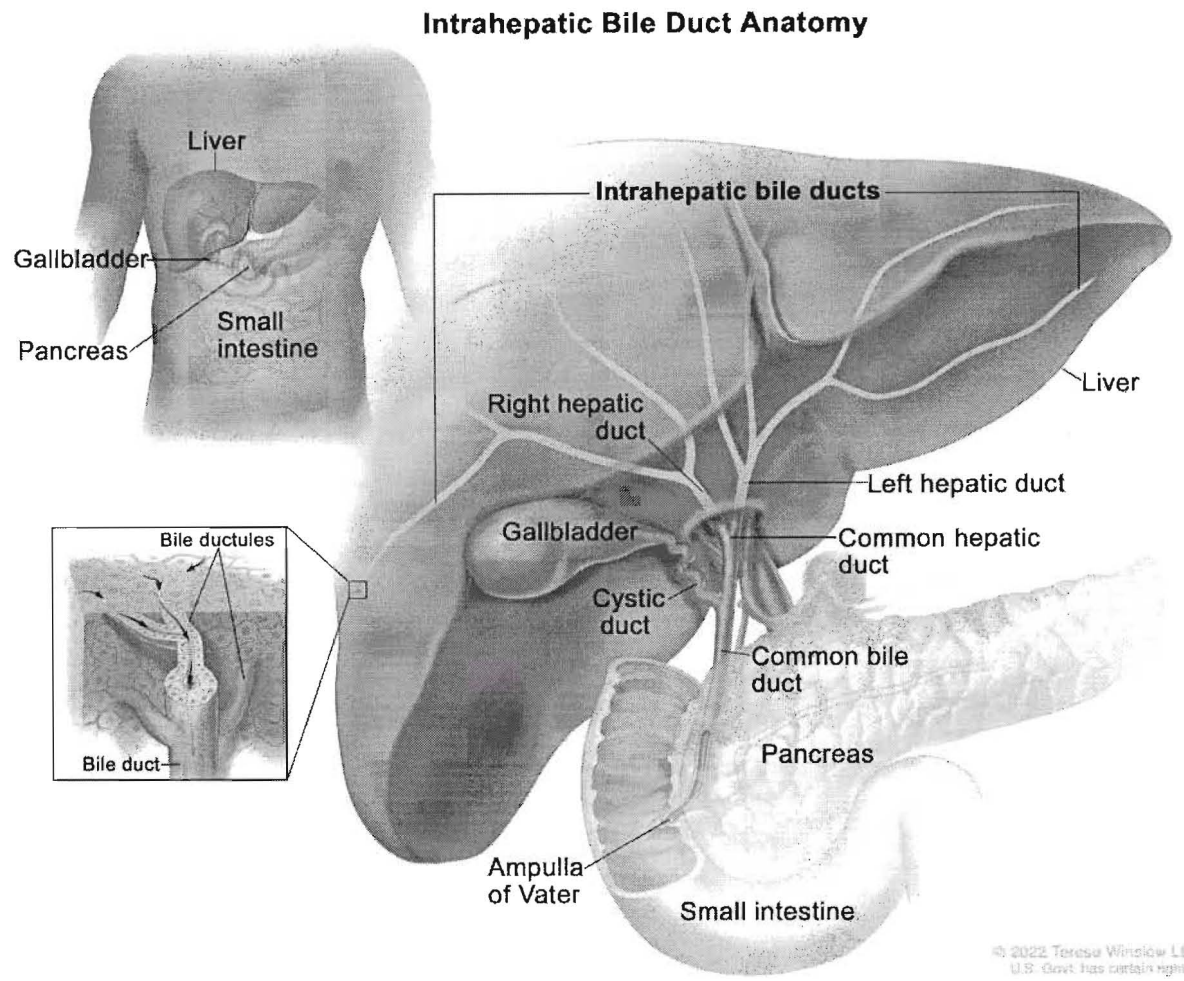
It thus ensures the metabolism of numerous proteins (synthesis of plasma proteins, albumin, and coagulation factors, degradation of ammonia from amino acids into urea), carbohydrates (glucose and glycogen, maintenance of blood sugar), and lipids (cholesterol). It is also the reserve of a multitude of substances such as vitamin A, iron, or copper.
The liver produces bile, which emulsifies fats in the duodenum.

Finally, being equipped with a very rich enzymatic system, it is the organ of detoxification of all toxic substances (xenobiotics or harmful endogenous metabolites) which arrive in particular through the circulation of the digestive tract, preventing them from passing into the general circulation. For this, different types of reactions are implemented such as oxidation, hydrolysis, or even conjugation.

1.3.3. The gallbladder

The bile ducts connect the liver to the duodenum:

- They have three ducts and a reservoir, the gallbladder.
- Their function is the storage and transport of bile according to the needs of digestion.



The bile ducts

- *The gallbladder* is a pear-shaped bag that is green in color. It measures 8 to 10 cm long by 3 cm wide, for a maximum capacity of 50 ml. Between two digestions the gallbladder receives the primitive bile produced by the liver, which it concentrates up to ten times by reabsorbing water. At the start of a meal, the fine muscle fibers in the wall of the gallbladder contract to move concentrated bile toward the duodenum and common bile duct. The gallbladder has two parts:
  - a narrow part or neck, which detaches from the liver to continue into the cystic duct;
  - a part called "the body" or bottom of the pocket which remains under the liver while adhering to it.

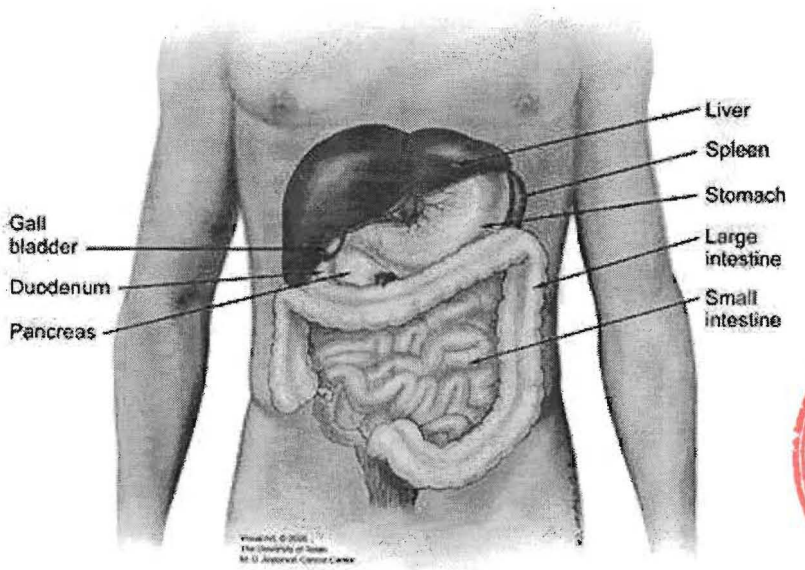
- *The hepatic duct* brings together, under the hilum of the liver, the right and left bile canaliculi arising from the lobes of the liver. It plunges 2 or 3 centimeters before joining the cystic duct to form the common bile duct.
- *The cystic duct*, 2 to 4 cm long, connects the hepatic duct and the gallbladder:
  - The bile constantly excreted by the liver goes up the cystic duct to be stored there between two digestions.
  - It follows the opposite path as soon as food enters the stomach.
- *The common bile duct* joins the hepatic duct and the cystic duct:
  - 5 cm long, it plunges behind the pylorus of the stomach and crosses the head of the pancreas where it joins the Wirsung duct which drains pancreatic juices.
  - On contact with the wall of the duodenum, they pass through a muscular ring, the sphincter of Oddi, and form a slight bulge, the ampulla of Vater, whose papilla opens into the intestinal lumen.

With a diameter of 5 to 6 mm, the bile ducts can be easily blocked by a stone formed in the gallbladder by the crystallization of cholesterol.

1.3.3. The pancreas

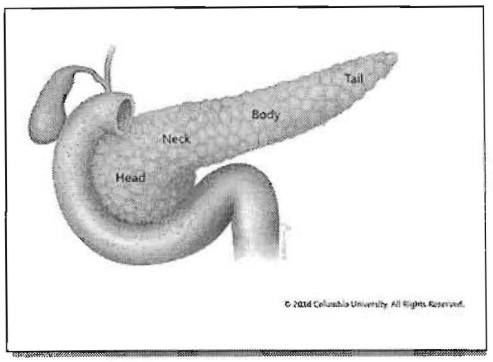
Physiologically, the pancreas is an exocrine and endocrine gland located in front of the lumbar spine. It is connected to the duodenum by its excretory ducts. It is tadpole-shaped, smooth in appearance, pale pink in color, and firm in consistency, but crumbly under the finger.

Lying transversely from right to left and flattened from front to back, the pancreas extends from the duodenal frame to the spleen. It measures on average 15 cm long, 4 cm wide, and 2 cm high, for a weight of approximately 80 grams.



Anatomically, the pancreas is divided into 4 parts:

- The head of the pancreas (right), the widest part, around which the C-shape of the duodenum wraps, emits at its lower part a transverse extension, the hook of the pancreas;
- The neck of the pancreas or the pancreatic isthmus, a short-narrowed portion visible between the head and the body;
- the body of the pancreas, generally rectangular and continues with the tail;
- the tail of the pancreas (left), tapered end in contact with the spleen.

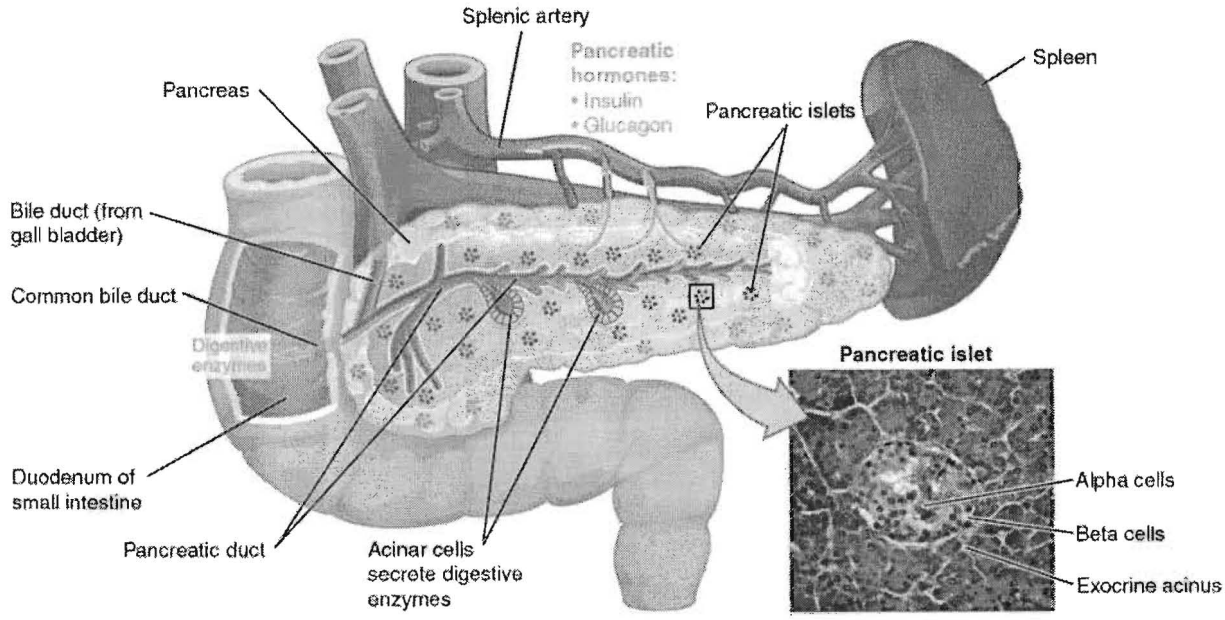


The head and body of the pancreas are separated in the fetus and are only joined by the isthmus shortly before birth.

The pancreas has two excretory ducts (ducts):

- *The main pancreatic duct* (called the duct ofWirsung), which runs the entire length of the pancreas, draining pancreatic juices from the tail to the head. At the head of the pancreas, the duct of Wirsung expands slightly to form the ampulla of Vater. It is joined there by the common bile duct: pancreatic secretions and bile mix before flowing into the second duodenum. As intestinal chyme enters the duodenum, the contents of the ampulla of Vater pass through a muscular ring, the sphincter of Oddi, which opens reflexively;
- *The accessory pancreatic duct* (called the duct ofSantorini), This channel only runs through and drains the head of the pancreas. It flows into the second duodenum through an independent orifice.

There are small glands in these ducts (main and accessory) that will secrete mucus to lubricate and protect the epithelium.



The pancreas

Structurally, the pancreas is made up of lobules, arranged in clusters around the excretory ducts; the lobule is the elementary unit of the pancreas, and each contains exocrine tissue and endocrine tissue:

- on the one hand, the exocrine pancreasproduces and excretes into the second duodenum enzymes essential for the digestion of fats, proteins, and starches. It is made up of lobules (the serous acini) arranged along the Wirsung canal like grapes on a bunch. These acini are formed by two types of cells: glandular cells (or acinar cells) and centroacinar cells which secrete a fluid rich in sodium bicarbonate.

- on the other hand, the endocrine pancreas synthesizes and secretes into the blood several hormones, the two main of which are insulin, which lowers the blood glucose level, and glucagon which raises the same glucose level. It is made up of a million Langerhans islets (discovered in 1869 by Langerhans who gave them his name) arranged near the blood vessels which irrigate the interior of the gland. These islets are scattered throughout the pancreas in the middle of the pancreatic acini. These are spherical clusters which do not exceed 300 µm. They are richly vascularized, and made up of 5 types of cells:

  - *alpha cells* (15 to 20%), located on the periphery, secrete glucagon, a hyperglycemic hormone that promotes glycogenolysis in the liver and exerts lipolytic activity.

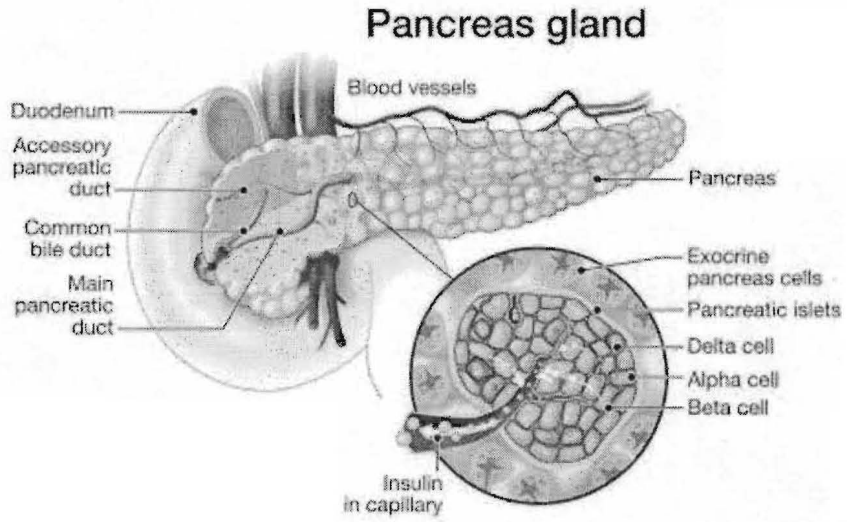
- *beta cells* (65 to 70%), abundant throughout the islet secrete insulin, a hypoglycemic hormone, which promotes the penetration of plasma glucose into cells, particularly into hepatocytes and muscle cells.

- *delta cells* (<5%), in the periphery secrete somatostatin which inhibits the secretion of insulin and glucagon;

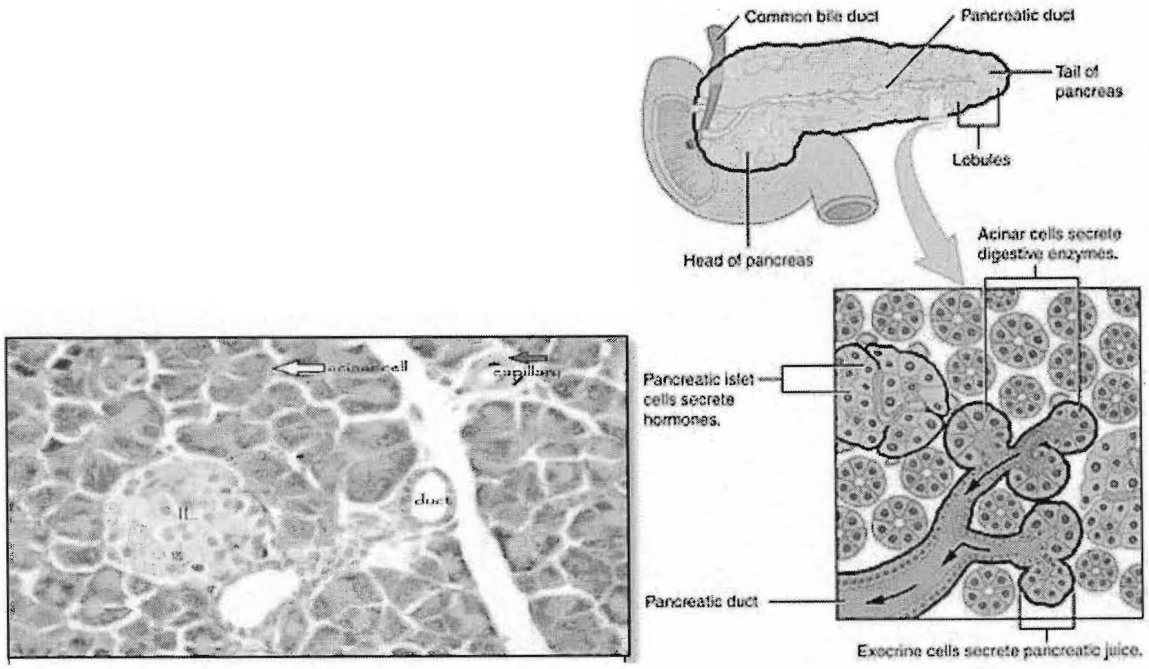
- *pp cells*, very few, and secrete the pancreatic polypeptide which inhibits somatostatin and stimulates gastric secretion and hepatic glycogenolysis.

- *epsilon cells* secrete ghrelin which stimulates the appetite.

It is possible to live without a pancreas with treatment with insulin which is then essential and injected subcutaneously and pancreatic enzymes taken orally.



Structure of the pancreas



Cross section of the pancreas

2. Food in the mouth and swallowing phenomena

In the mouth, digestive processes involve several stages:

2.3. Ingestion:

It is the starting point of the digestive process, which consists of the voluntary introduction of food into the mouth before being transformed. It is an active process.

The food will undergo several actions (mechanical digestion andchemical).

2.4. Mechanical digestion:

Chewing food is the first mechanical step of mechanical digestion. The teeth act thanks to the contraction of the muscles which forcefully tighten, on each side of the mouth, the lower jaw against the upper jaw:

- the incisors cut food into large pieces;
- the incisors tear animal (meat) or plant (fruit, vegetables) fibers;
- the premolars and molars grind food by crushing it between their flattened faces.

During this time:

- the saliva released by the salivary glands moistens the contents of the mouth;
- the tongue kneads the different pieces by pushing them against the palate and passes them from one jaw to the other until the formation of a pasty ball: the bolus) easy to swallow.

Chewing promotes the emergence of flavors (sweet, salty, sour, bitter) and aromas of food, which stimulates the secretions of the different digestive organs.

During chewing, an enzyme in saliva, amylase, begins the digestion of starches.

It is essential to have good teeth to chew well and therefore to digest well.
Chewing sends information messages to the brain about the volume of food ingested: good chewing accelerates satiety and facilitates weight loss.

2.5. Chemical digestion:

Salivary amylase breaks certain chemical bonds between glucose units in starch, to reduce polysaccharides to maltose (disaccharide), maltotriose (trisaccharide), and short-chain glucose polymers (dextrins).
Salivary amylase initiates the breakdown of starch. It continues to transform starch for 15 to 30 minutes in the stomach until the acidity of the latter inactivates it.
Lingual lipase, which is active in the stomach, can convert up to 30% of dietary triglycerides into fatty acids and monoglycerides.

2.6. Swallowing:

This food bolus subsequently undergoes propulsion from the mouth towards the stomach (another mechanical action), which imposes an involuntary action (≈10 sec). Swallowing is a complex mechanism that involves the coordination of the tongue, the soft posterior palate, the epiglottis in the pharynx, and the wall of the esophagus. It is facilitated by saliva and mucus (secreted by the esophagus) and involves the mouth, pharynx, and esophagus.
Initially controllable by will, the tongue pushes the food bolus against the palis and then contracts to propel it backward. What happens next is entirely reflexive and uncontrollable by will.
the epiglottis closes the airways of the larynx, which opens the orifice of the esophagus (it is impossible to speak or breathe while swallowing without causing a false food route);
the soft palate rises to close the opening to the nasal cavity;
the food bolus is propelled into the esophagus, through the pharynx, by the contractions of muscles in the throat;
the muscles of the esophageal wall create a wave that continues to propel the food bolus throughout the esophagus: peristalsis (succession of circular contraction then relaxation of the smooth muscles of the digestive tract which occurs from top to bottom allowing progression bolus).

Swallowing proceeds in three stages:

- **the voluntary oral stage**, in which the bolus is moved toward the oropharynx; it also concerns the action of swallowing saliva, which does not follow chewing, after the occlusion of the dental arches (physiological swallowing). It occurs on average 3,000 times/day in men (twice per minute).

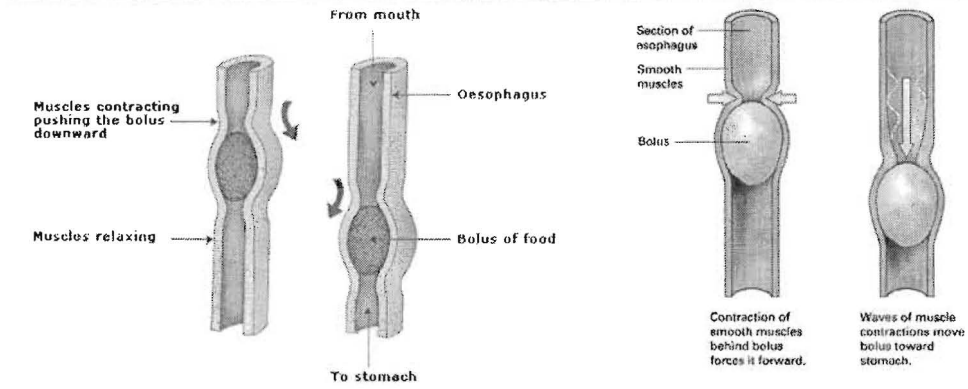
A slightly higher empty swallow frequency was observed in male subjects. In adults, a little less than half a ton of saliva is swallowed per year, or 1.5 liters of saliva per day. It is also the most frequent, energy-intensive, and most important function of the mouth, which allows for the humidification of the oral and pharyngeal mucous membranes, the drainage of secretions from

the nasal cavity and nasopharynx, and ventilation. of the middle ear by opening the Eustachian tube (which allows pressure to be balanced on each side of the tympanic membrane).

- **the pharyngeal stage,** or involuntary passage of the food bolus from the pharynx into the esophagus.
- **the esophageal stage,** orinvoluntary passage of the food bolus along the esophagus (upper sphincter) to the stomach (cardia) thanks to a peristaltic wave that travels through the esophagus from top to bottom. Esophageal peristalsis is slower than pharyngeal peristalsis: the speed of the esophageal wave is 3 cm/s in the proximal esophagus and up to 5 cm/s in the lower third.

Unlike the pharyngeal phase, gravity plays a role in the transfer of the food bolus into the esophagus. Fluids may reach the cardia several seconds before the peristaltic wave. Esophageal contractions are greater in the subject lying down than in the standing subject.

The duration of the esophageal time is much greater than the previous two: 2 seconds for liquids, 7 to 9 seconds for solids.



The esophagus secretes mucus and carries food into the stomach. The passage of food from the laryngopharynx to the esophagus is regulated by a sphincter (thick ring of muscle that is usually contracted so that there is no opening in the center) at the mouth of the esophagus, the upper esophageal sphincter; formed by the cricopharyngeal muscle attached to the cricoid cartilage.

Elevation of the larynx during the pharyngeal stage of swallowing causes relaxation of the sphincter and allows entry of the food bolus into the esophagus. The sphincter also relaxes during expiration.

Microscopic examination of the mucosa reveals a simple columnar epithelium (superficial mucus cells) containing a large number of narrow ducts, called gastric pits, which extend to the chorion.

3. Gastric secretion and motility

3.1. Mechanical digestion:

The arrangement of the muscularis in three layers of muscle fibers (an outer longitudinal layer, a middle circular layer, and an inner oblique layer) allows the stomach to contract (contractions independent of will) in various ways to mix food (mixing the food bolus), transforming them into small particles, and mixing them with gastric juice. The bolus becomes **chyme** (whitish liquid mush).

These contractions are moderate, undulating peristaltic movements. They will spread along the stomach every 15 to 25 seconds, a few minutes after food enters.

These muscles are stimulated by the arrival of food in the stomach pouch, by excess acidity or by prolonged fasting (causing a gurgling sensation).

Their activity ceases during swallowing, to prevent food from moving up through the esophagus.

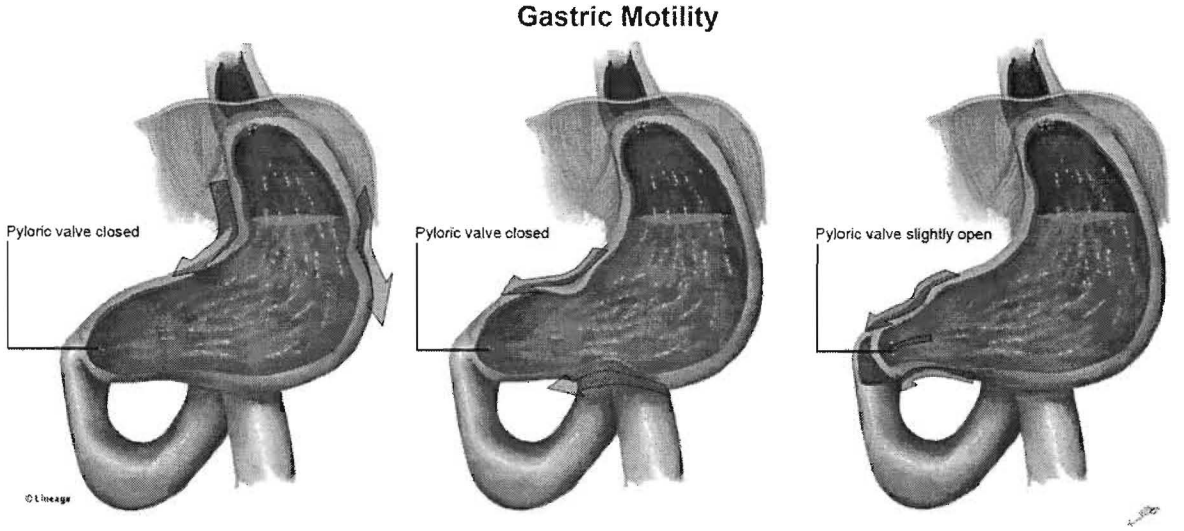
The fundus mainly serves as a place of reserve (few contractions). Food can remain in the fundus for more than an hour without being mixed with gastric juice. During this time, digestion due to lingual lipase and saliva continues.

During digestion, stronger mixing waves begin in the body of the stomach and intensify upon reaching the pylorus. The pyloric sphincter normally remains partially open.

When food reaches the pylorus, each wave of mixing pushes a small amount (the volume never exceeds 3 ml) of the gastric contents into the duodenum through the pyloric sphincter which opens briefly: gastric emptying. Most of the food is pushed back into the body of the stomach where mixing continues. The next wave pushes the contents of the stomach forward again to force some more food into the duodenum.

This process is repeated countless times to evacuate an entire meal, which usually takes 3 to 4 hours.

This back-and-forth movement alone ensures almost all the mixing of food in the stomach.



Gastric emptying

3.2. Chemical digestion:

The glands of the gastric wall secrete gastric juice (approximately 2 L/day) which is an acidic liquid used for the digestion and assimilation of food. Its role is to divide large molecules into smaller molecules that the intestine can absorb and to destroy the microorganisms present in the food bolus.

Its flow and composition varies depending on food intake:

- low flow and low acidity outside of meals;
- high flow and high acidity during digestion.

Gastric juice is 99% water. Its acidity comes mainly from hydrochloric acid (HCl), which can lower the pH of gastric juice to 1. To protect the stomach from the acidity of gastric juice, goblet cells produce mucin, which adheres to the wall of the intestine and maintains a pH above 4.

Gastric juice also contains many enzymes :

- pepsin, synthesized in the form of pepsinogen, serves to degrade the peptide bonds of proteins ;
- gastric lipase, which hydrolyzes triglycerides (fatty acids) ;
- chymosin or rennin, mainly present in newborns and which is used to digest breast milk ;
- intrinsic factor, necessary for the absorption of vitamin B12 .

All these secretions are controlled by a complex biological process triggered by receptors sensitive to odors and contact with food.

3.3. Absorption:

The wall of the stomach is impermeable to the passage of most substances into the blood; most of these substances can therefore only be absorbed when they reach the small intestine. However, it is true that the stomach participates in the absorption of a certain quantity of water, electrolytes, certain medications (particularly aspirin) and alcohol.

4. Biliopancreatic secretion

1.1. Bile:

Bile is a greenish-yellow fluid produced by hepatocytes (0.8 to 1 L/day), essential for the digestion of food and the detoxification of our body. Its pH is between 7.6 and 8.6.

Bile is a mixture of several elements:

- a large proportion of water: 97.5%;
- bile salts, made from cholesterol , which will be reabsorbed in the ileum before reaching the liver (recycling);
- bile pigments, resulting in particular from the destruction of hemoglobin in red blood cells:
  - ✓ bilirubin, yellow-brown in color, which gives their color to urine and stools;
  - ✓ biliverdin, green in color.

- cholesterol;
- phospholipids, which notably make it possible to solubilize cholesterol;
- mineral salts in the form of ions: sodium, bicarbonates, potassium, calcium, chlorine, etc.

After passing through the intestine, a very large part of the bile salts is recycled and returns to the liver; only a very small part is eliminated with the stools.

Bile plays several roles within the body:

- It is involved in the digestion of fats, thanks to the presence of bile salts;
- It ensures the elimination of waste. Excess cholesterol is, for example, evacuated through the bile, as well as bilirubin, which is toxic to the body. It also makes it possible to eliminate medications, but also alcohol or drugs;
- It helps maintain the duodenum at an appropriate pH.

Cholestasis (poor bile flow), a bile-related disease, occurs when bile can no longer flow normally ; it causes jaundice (bilirubin passes into the blood and gives the skin and mucous membranes a yellowish tint), discoloration of the stools, and itching.

It may be linked to the presence of an obstacle in the channels that carry bile:

- it is most often a ***gallstone***, a sort of small stone which forms within the gallbladder, too large to pass towards the intestine;
- the development of a tumor within the bile ducts, or in surrounding organs, which compresses the ducts as it grows.

It can also be linked to a failure in the production of bile by liver cells, in cases of hepatitis or cirrhosis. Depending on its origin, treatment is based on the prescription of medication, the use of surgery or biliary endoscopy: a flexible tube is inserted through the mouth to the bile ducts, to eliminate a stone for example.

1.2. Pancreatic juice:

Pancreatic juice is an alkaline fluid secreted by the exocrine pancreas (1.2 to 1.5 L/day), and drains into the duodenum. It constitutes one of the main agents of digestion.

Sodium bicarbonates and enzymes:

- Bicarbonates, salts whose high content makes the juice slightly alkaline (pH 7.1 to 8.2), which buffers the acidic gastric juice from the chyme, interrupts the pepsin activity of the stomach and creates a pH adapted to the action of digestive enzymes of the small intestine;
- enzymes (*endopeptidases* and *exopeptidases*) which hydrolyze proteins into amino acids;
- enzymes (amylolytic) which hydrolyze sugars into oses;
- enzymes which hydrolyze triglycerides, diglycerides and monoglycerides into glycerol and fatty acids;
- enzymes capable of digesting nucleic acids.

The pancreas secretes an impressive quantity of enzymatic proteins, the largest per gram of tissue in the entire body, i.e. approximately 2 to 20 g of digestive enzymes per day in a volume of 2.5 L. Several elements combine to provide pancreatic cells with effective protection against enzymatic digestion:

- the enzymes are secreted as inactive zymogens. They are sequestered by the lipoprotein membranes of the granules;
- the activating enzyme, trypsin, is released from trypsinogen in the intestine and not in the pancreatic ducts.

1.2.1. Enzymes :

1.2.1.1. Endopeptidases:

These are ***trypsin***, ***chymotrypsin***, ***elastase*** and ***kallikrein***. There are large homologies in the amino acid sequence of these enzymes which are termed endopeptidases since they cleave proteins at specific sites within the peptide chain. They are characterized by the reactivity of a serine group in the active site of the enzyme.

- **Trypsin:**

It plays a key role in the digestion processes to the extent that it is responsible for the cascade activation of all the other enzymes. In normal subjects, trypsinogen (its precursor) is inactive in pancreatic juice. The most important pathway for trypsinogen activation is when chyme comes into contact with the activating enzyme, intestinal enterokinase, secreted by the intestinal mucosa in the duodenum. Enterokinase is, in fact, much more effective than trypsin. Trypsin cleaves proteins at lysine or arginine residues.

- **Chymotrypsin:**

Its precursor, chymotrypsinogen, is activated by trypsin, it is then capable of specifically cleaving the bonds involving the carboxyl groups of the aromatic amino acids phenylalanine, tyrosine, and tryptophan. Tryptic inhibitors are not active on chymotrypsin.

- **Elastase:**

Its precursor is proelastase. Elastase has the specificity of hydrolyzing elastin.

- **Kallikrein** :

its precursor is Kallikreinogen. It is a minor component whose physiological function is unclear. Its main function would be to release kinin from kininogen.

1.2.1.2. Exopeptidases:

Their characteristic is to cleave the carboxyl or amino groups from the terminal residues of amino acids.

- **Carboxypeptidases:**

They include procarboxypeptidases A and B. They are metalloenzymes, comprising a Zn atom in their active site. They cleave the C-terminal amino acids of proteins at the level of aromatic amino

acids (carboxypeptidase A) or basic amino acids (carboxypeptidase B). They are activated by trypsin. Procarboxypeptidase B exists in two forms and requires significant amounts of trypsin to be activated.

1.2.2. Lipolytic enzymes

- Prophospholipase A2:

It cleaves fatty acid groups in position 2 of phosphoglycerides.

- Pancreatic lipase:

It participates with gastric lipase and intestinal lipase in the hydrolysis of long-chain triacylglycerols provided by the diet. The pancreatic enzyme secreted in active form is by far the most important enzyme in fat digestion. Lipase acts on all fatty acid esters. When the substrate is associated with bile salts and phospholipids, the lipase is inactive or inhibited. Colipase restores this activity.

- Colipase:

Secreted in inactive form (procolipase), it is activated by trypsin to generate active colipase. Colipase is the only agent known to date to remove the inhibition exerted by bile salts on the hydrolysis of triglycerides by lipase.

- Carboxylester hydrolase:

Carboxylester hydrolase or carboxylester lipase, lysophospholipase, cholesterolester hydrolase, unlike lipase, hydrolyzes a large quantity of substrates. It hydrolyzes mono-, di-, triglycerides, cholesteryl- and retinyl esters, lysophosphatidyl glycerol. It acts whether the substrate is in micellar, emulsified or soluble form. Bile salts serve as activators for the hydrolysis of long-chain emulsified triacylglycerols.

A new enzyme has recently been isolated from the pancreas, pancreatic fatty acid ester synthase. Structurally related to triglyceride lipase, this enzyme catalyzes the synthesis and hydrolysis of ethyloleate from oleic acid and ethanol, properties which could explain the disturbances in lipid metabolism in the event of ethanol ingestion.

1.2.3. Amylolytic enzyme

- Pancreatic α-amylase:

It is the most important source of amylase. It plays a vital role in human nutrition and its serum dosage is used for the diagnosis of pancreatic disease. It catalyzes the hydrolytic degradation of starch, amylose and amylopectin of plant origin or glycogen of animal origin. It hydrolyzes 1,4-branched amylopectins to produce short-chain polysaccharides called dextrins. An intestinal enzyme, ***1-6 glucosidase***, cuts the 1,6 bonds of dextrin to form maltotetraose, then maltose and isomaltose. The disaccharides are cleaved into glucose by ***intestinal maltase.***

1.2.4. Other enzymes:

These include ***deoxyribonuclease*** (DNAse I), which pancreatic tissue is rich in, ***ribonuclease*** and ***lysosomal enzymes.***

5. Intestinal transit and motility in the small intestine

5.1. Mechanical digestion:

The contents of the stomach are expelled into the duodenum through the pyloric sphincter. Small motility stirs food with digestive enzymes and ensures controlled progression of intraluminal contents to allow absorption of nutrients.

Small intestine movements are of three types:

- **Segmentation movements:** crushing chyme;
- **Pendulum movements:** slow, they ensure the progression of the chyme and its impregnation with digestive juices (intestinal and pancreatic juices) and bile. They also bring nutrients into contact with the mucous membrane for absorption (repeats 12 to 16 times per minute).
- **Peristaltic movements:** rapid progress, they propel the chyme forward along the small intestine (3 to 5 hours). They are facilitated by the presence of fibers (cellulose);

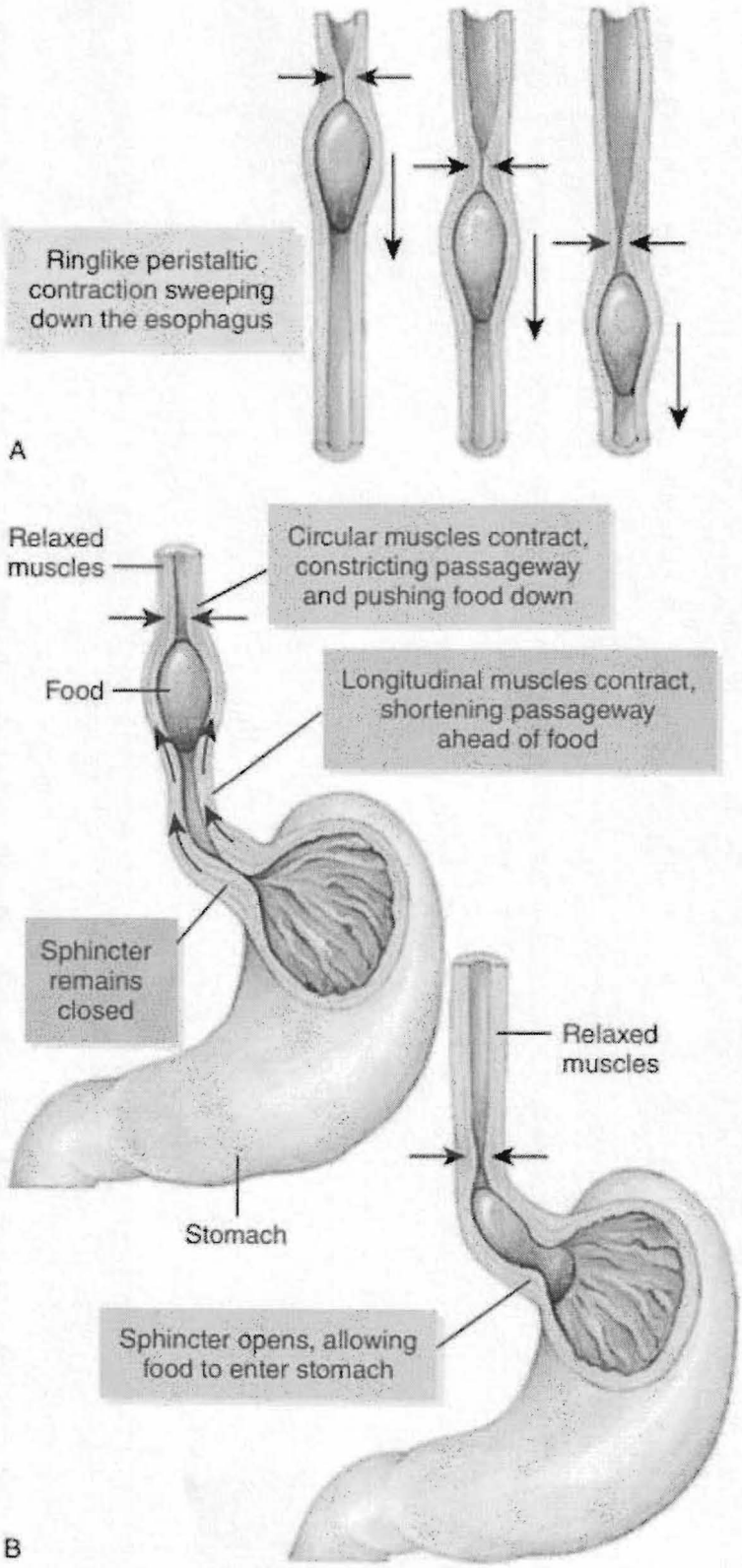


FIGURE 24-4 Peristalsis.

Intestinal motor movements

5.2. Chemical digestion:

Chemical digestionconsists of mixing chyme with digestive juices (bile, pancreatic and intestinal juice) in order to degrade large molecules (carbohydrates, proteins and lipids) into basic units by enzymes (monosaccharides, amino acids, monoglycerides and fatty acids).

Intestinal juice is a light-yellow liquid secreted at a rate of 1 to 2 L/day. It is slightly alkaline (pH 7.6) and contains water, mucus and several digestive enzymes, called brush border enzymes, secreted by the absorptive epithelial cells that line the villi:

- four enzymes ensure the digestion of carbohydrates: dextrinase, maltase, sucrase (saccharase) and lactase;
- enzymes capable of digesting proteins, peptidases (aminopeptidases and dipeptidases);
- two types of enzymes capable of digesting nucleotides, nucleosidases and phosphatases.

Pancreatic juice, bile, and *intestinal juice* together provide a vehicle for the absorption of substances contained in chyme when they come into contact with the villi.

In the small intestine, pancreatic enzymes continue the digestion of fats and proteins.

3.1. Absorption:

It is the passage of digestion products (monosaccharides, amino acids, fatty acids and monoglycerides) from the intestinal lumen to the blood or lymph through the intestinal mucosa by active or passive transport mechanisms.

Absorption occurs in the small intestine and a little in the oral cavity (trinitrin), the stomach (aspirin, alcohol) and the colon (water, ions, vitamin K).

4. Digestive hormones

- Ghrelin

Ghrelin is a hormone produced primarily by the stomach. Ghrelin is secreted when the stomach is empty (fasting). It stimulates hunger in fasting conditions and increases food intake.

Ghrelin stimulates physical activity and food-seeking motivation. It increases the anxiety and nervousness of unfed animals. Ghrelin secretion is stimulated by pancreatic polypeptide (PP), and is inhibited by meals.

- Obestatin

It is a "derivative" of ghrelin. Preproghrelin is cut into 2 pieces: one is ghrelin, the other is obestatin. It binds to a ghrelin receptor. Obestatin has actions opposite to those of ghrelin: reduction of hunger and reduction of food intake. It also has an inhibitory action on gastric emptying and propagated jejunal contractions.

- Pancreatic polypeptide (PP)

It is a peptide synthesized by pancreatic endocrine cells. It would be anorexigenic.

It is thus secreted during the cephalic phase of the meal. It stimulates exocrine pancreatic secretion.
In humans, acute administration of PP reduces food intake in healthy or obese subjects.

- The CCK

CCK (cholecystokinin) is a hormone secreted by the duodenum that stimulates exocrine pancreatic secretion. CCK is also strongly anorexigenic. CCK slows down the ingestion of a meal, reduces the quantity consumed and reduces the feeling of hunger.

- Leptin

Leptin is produced mainly by adipose tissue (> 95% of overall leptin secretion) and (a little) by the stomach and duodenum. The plasma concentration of leptin is higher in women than in men, probably due to the greater mass of adipocytes in women.
Leptin released by adipose tissue is strongly anorexigenic in acute situations (intravenous injection) in rats and to a lesser degree in humans. Adipocyte leptin is anorexigenic.

- Endorphin

Endorphin is synthesized by specific endocrine cells located in the jejunum and ileum. Their actions aim above all to reduce the luminal pressure in the intestine and thus to oppose the pain generated by the pressure. Intestinal endorphin clearly has a role in regulating food intake by modulating the sensation of peripheral hunger, particularly due to its inhibitory action on motor skills.

- Serotonin

Serotonin is a neuropeptide derived from tryptophan. It is a peptide released by endocrine cells and, above all, by neurons located in the small intestine and the colon. There is also a lot of serotonin in the duodenum.
In the digestive tract, serotonin and its receptors are involved above all in the stimulation of circular and longitudinal smooth muscles), which induces a slowdown in gastric emptying and earlier satiation, an increase in pancreatic secretion and discomfort. digestive which could contribute to satiation, or even, in the event of stronger stimulation, to nausea and vomiting.
Serotonin and its receptors are thought to be involved in anorexia nervosa, bulimia, and compulsive eating.

- Dopamine

Dopamine is derived synthetically from tyrosine.

- Motilin

Motilin is a hormone synthesized mainly by endocrine cells of the duodenal mucosa. Motilin increases the tone of the lower esophageal sphincter and stimulates gastric, antral and duodenal motility.

- GLP-1

Glucagon -Like Peptide (GLP-1 or enteroglucagon). It would have a satiating role. GLP-1 levels were negatively correlated with feelings of hunger.

- Adiponectin

It is a hormone secreted by adipose tissue. Administration of adiponectin has been shown to stimulate the phosphorylation of tyrosine residues of the insulin receptor and increase the action of insulin on muscle and liver. Adiponectin also stimulates muscle oxidation of fatty acids, reduces concentrations of free fatty acids and triglycerides and produces a reduction in body fat without changing dietary intake.

- Resistin

Resistin is secreted by adipose tissue. It induces severe insulin resistance in mice.
Resistin could therefore be one of the mechanisms by which obesity promotes type 2 diabetes.

5. Physiology of the large intestine

After remaining in the large intestine for approximately 3 to 10 h, the chyme forms a solid or semi-solid mass. At this stage, it is called feces; formed from water, inorganic salts, debris from the epithelial cells of the lining of the digestive tract, bacteria, bacterial decomposition products and undigested food.

The colon, under physiological conditions, then fulfills a triple function:
The first is to complete the absorption:

- water: which plays an important role in maintaining water balance and solidifying feces. The ileum pours into the cecum between 0.5L and 1.5L of water, 90% of which is reabsorbed in the colon; normal stools contain 100 to 150 mL of water;
- electrolytes: including sodium and chloride, are mostly reabsorbed by the colonic mucosa;
- bile acids;
- some vitaminsnot absorbed in the small intestine to limit hydroelectrolytic losses, at the level of the enterocytes of the right colon (absorption is maximum in the cecum and the ascending colon);
- and toxic substances: which will be transported to the liver to be detoxified there.

The second is to ensure the fermentation of carbohydrate and protein residues, a source of energy for the body and trophic factors for the colonic mucosa. The bacterial flora of the colon constitutes +/- 30 to 40% of the weight of stools; the germs are multiple; Bacterial enzymes attack food residues, leading to a phenomenon of fermentation and putrefaction which releases gases. Some B vitamins and vitamin K are synthesized.

The third is the storage and upper mixing thanks to segmental contraction movements and the propulsion of residual constituents towards the rectum (evacuation of feces) by longitudinal movements (peristaltic movements). It also receives food that has not been digested. Feces are eliminated by contractions of the sigmoid colon and rectum (Mass movements push feces from

the sigmoid colon into the rectum). In infants, the defecation reflex results in automatic evacuation of the rectum, because the external anal sphincter is not yet voluntarily controlled.

Its motor skills are one of the elements of its physiology allowing the colon to fulfill this triple mission. Rectal and anal motor skills, in coordination with colonic movements, play an important role in the controlled evacuation of these residues.

The colon also plays another secretory role, notably mucus from goblet cells which lubricates the colon and protects the mucosa.

5.1. Motor skills problems

Functional intestinal disorders correspond to clinical signs underlying motility disorders of the digestive tract, particularly the colon.

- Pain

Sometimes of intolerable tension, it usually occurs in the right or left iliac fossae or in the hypogastric region. It can also be localized to the hypochondria, tracing the path of the colonic frame. It usually occurs in the post-prandial period but perhaps also in the morning (wake-up-to-morning pain), rarely at night. It progresses for a variable time, from a few hours to a few days, classically relieved by the emission of gas or stools; increased by copious meals, stress, anxiety, physical fatigue, finally improved by relaxation, rest, vacations.

- Intestinal bloating

They are very common during colonopathy, can be generalized throughout the abdomen, or localized at a colonic angle, ranging from simple post-prandial discomfort (and the need to loosen the belt) to very violent painful distension often reinforced by a feeling of anxiety.

5.2. Transit disorders

They vary according to the different clinical forms:

- The constipation :

Constipation is difficulty passing feces or prolonged spacing of defecations. It is due to a decrease in intestinal motility; the feces therefore remain in the colon for a very long time, which has the effect of making them dry and hard, due to too much water absorption.
Constipation is considered chronic when the disorders have existed for at least 6 months.
Insufficient hydration can cause constipation. The color of the urine is an indicator, it should remain clear. In this case, before attacking the body with laxatives, it is advisable to favor natural products on an empty stomach, such as a daily glass of coffee accompanied by a glass of prune juice on demand. Prunes have laxative properties far superior to oranges, lemons or grapes. You should stick to reasonable doses and switch to milder fruit juices when transit returns to normal. Lubricants such as lemon olive oil or paraffin oil which can be added to promote transit at the rate of 2 to 3 tablespoons. Finally, in case of severe constipation, a supplement of laxatives to be administered according to the number of days without stools.

- Diarrhea:

Diarrhea is the frequent passing of liquid or very soft feces, caused by increased motility of the intestines and decreased intestinal absorption.

Like vomiting, diarrhea can lead to dehydration and electrolyte imbalances. Diarrhea can be caused by stress or microbes that irritate the gastrointestinal lining.

Acute diarrhea: less than 2 weeks;
Prolonged diarrhea: 2 to 4 weeks;
Chronic diarrhea: beyond 4 weeks.

The most effective natural treatment for diarrhea, and which is sufficient to quickly obtain good results, is rice cooking water, well loaded with starch. It is also an interesting additional water supply to compensate for dehydration linked to diarrhea which can have serious consequences on the body.

It is always preferable to favor natural products before considering a medicinal treatment such as lemon juice for its soothing properties combined with carrot juice for its pectin contribution. For any treatment with antidiarrheals, antisecretory drugs and transit slowers, a prescription from your doctor and nursing monitoring are strongly recommended so as not to go into excess leading to unfortunate side effects.

- Alternating diarrhea and constipation:

The dominant disorder is constipation in this case (diarrhea is only the consequence of stercoral stasis).

Chapter II.
Digestion and absorption in relation with the different food groups

Digestion and absorption of nutrients takes place in the digestive tract. The small intestine is the main site of these two stages. Its length and absorption surface, amplified by the villi and microvilli forming folds on the surface of the enterocytes, allow prolonged contact with nutrients and gastric, biliary, intestinal and especially pancreatic secretions, which will all contribute to the digestion of nutrients. Digestion and absorption of nutrients differ depending on their nature. Thus, carbohydrates, proteins and lipids are digested and then absorbed following specific mechanisms requiring dedicated enzymes and transport systems. After absorption, which is mainly done by the duodenum-jejunum, with the exception of bile acids and vitamin B12 which are absorbed only in the terminal ileum, the products of digestion or nutrients pass into the systems portal (bones and amino acids) or lymphatic (fatty acids) before being distributed in the body.

1. Hydromineral absorption

More than 8 L of water from food and secretions pass daily into the small intestine where more than 80% of it is reabsorbed by simple diffusion thanks to the high permeability of the epithelium and the creation of concentration gradients during active absorption of solutes.

Absorption takes place mainly in the jejunum (linked to the movement of sugars and amino acids through the epithelium), via extracellular junctions. Sodium is efficiently absorbed in the duodenum intercellularly according to the osmotic gradient and in the jejunum, especially transcellularly (thanks to the glucose-sodium ion [Na^+] and amino acid-Na^+ symports). At the level of the distal small intestine and the colon, absorption takes place by active transport thanks to sodium/proton and chlorine/bicarbonate pumps (entrance of sodium and chlorine with exit of proton and bicarbonate). **Potassium is absorbed passively** in the small intestine. Chlorine is released passively at the proximal intestine and actively at the distal level thanks to the coupled operation of chloride-bicarbonate and sodium-proton pumps. At the bottom of the crypts, there are CFTR *(cystic fibrosis transmembrane conductance regulator)* chloride channels stimulated by cyclic adenosine monophosphate (cAMP); this secretion of chlorine in turn triggers that of Na^+, which causes water movement. The hyperproduction of cAMP, for example under the action of certain bacterial toxins such as that of cholera, can be responsible for massive hydroelectrolytic losses.

2. Carbohydrate foods and sweeteners

the majority of carbohydrates are ingested in the form of starch (bread, pasta) and sucrose (table sugar), associated with a smaller quantity of lactose (dairy products) and fructose (fruit, honey). Cellulose, a constituent of dietary fiber, is also a carbohydrate.

The digestion of carbohydrates is relatively simple, with the exception of starch which requires a first step of intraluminal digestion. The products of this intraluminal digestion are then treated like

natural disaccharides (lactose, sucrose) at the brush border of the enterocytes where they are cleaved into monosaccharides then absorbed.

Cellulose is not digested in the small intestine. They are in fact insensitive to the action of enzymes allowing the digestion of carbohydrates and arrive intact in the colon, explaining their laxative effect.

1.1. Intraluminal digestion of starch:

(salivary α–amylase and pancreatic α–amylase)

Starch digestion begins upon chewing under the influence of salivary α–amylase. The importance of this enzyme is not well known, because its activity is very quickly inhibited by the acidity of gastric juice after swallowing. Starch digestion is therefore essentially carried out by pancreatic α–amylase, a major enzyme in pancreatic juice, which cleaves starch at the β 1-4 glucosidic bonds to produce oligosaccharides and disaccharides. The activity of this enzyme in the duodenal lumen is so important that starch is mainly transformed in the first jejunal loops, allowing the enzymes of the brush border of the enterocytes to continue the digestion of carbohydrates very early.

1.2. Intestinal digestion of carbohydrates:

(enterocyte oligosaccharidases)

The disaccharides and oligosaccharides from the diet and those obtained after the action of α–amylases will then appear in front of the brush border of the enterocytes. This contains numerous enzymes often called ***disaccharidases*** or ***oligosaccharidases*** which will hydrolyze the saccharides. We distinguish two families:

- **α-glucosidases,** including saccharase-isomaltase, glucoamylase and trehalase.

The first two hydrolyze sucrose, maltose and oligosaccharides coming from the action of α-amylase on starch, the last hydrolyzes trehalose (it is a non-reducing disaccharide made up of two glucose units linked by a 1,1-α-glycosidic bond).

The main enzyme in the intestinal brush border for carbohydrate digestion is **sucrose-isomaltase** , which alone carries out all sucrose and isomaltose digestion and 75% of maltose digestion. Its activity is maximal in the first jejunal loops and decreases thereafter.

Glucoamylase accounts for the digestion of oligosaccharides of 4 or more glucose residues from starch digestion, as well as 25% of maltose digestion. Its activity increases throughout the small intestine to be maximal in the ileum.

- **a unique β-galactosidase,lactase,** which hydrolyzes lactose into galactose and glucose.

This last enzyme is the only one not to be inducible. A large, although not clearly defined, percentage of adults no longer have this enzyme. These subjects will develop lactose intolerance, being unable to digest this molecule. This will result in various digestive disorders after ingestion of dairy products (bloating, dyspepsia, intermittent diarrhea), leading to a spontaneous avoidance of lactose from the diet. A simple test allows you to diagnose this lactose intolerance, the hydrogen breath test.

At the end of the action of α-amylases and enterocyte brush border enzymes, carbohydrates are reduced to their simplest form, their three constituent monosaccharides: glucose (80%), galactose and fructose.

It is only in this form that they can be absorbed by the intestine. This digestion of carbohydrates is almost complete from the middle jejunum in a physiological situation.

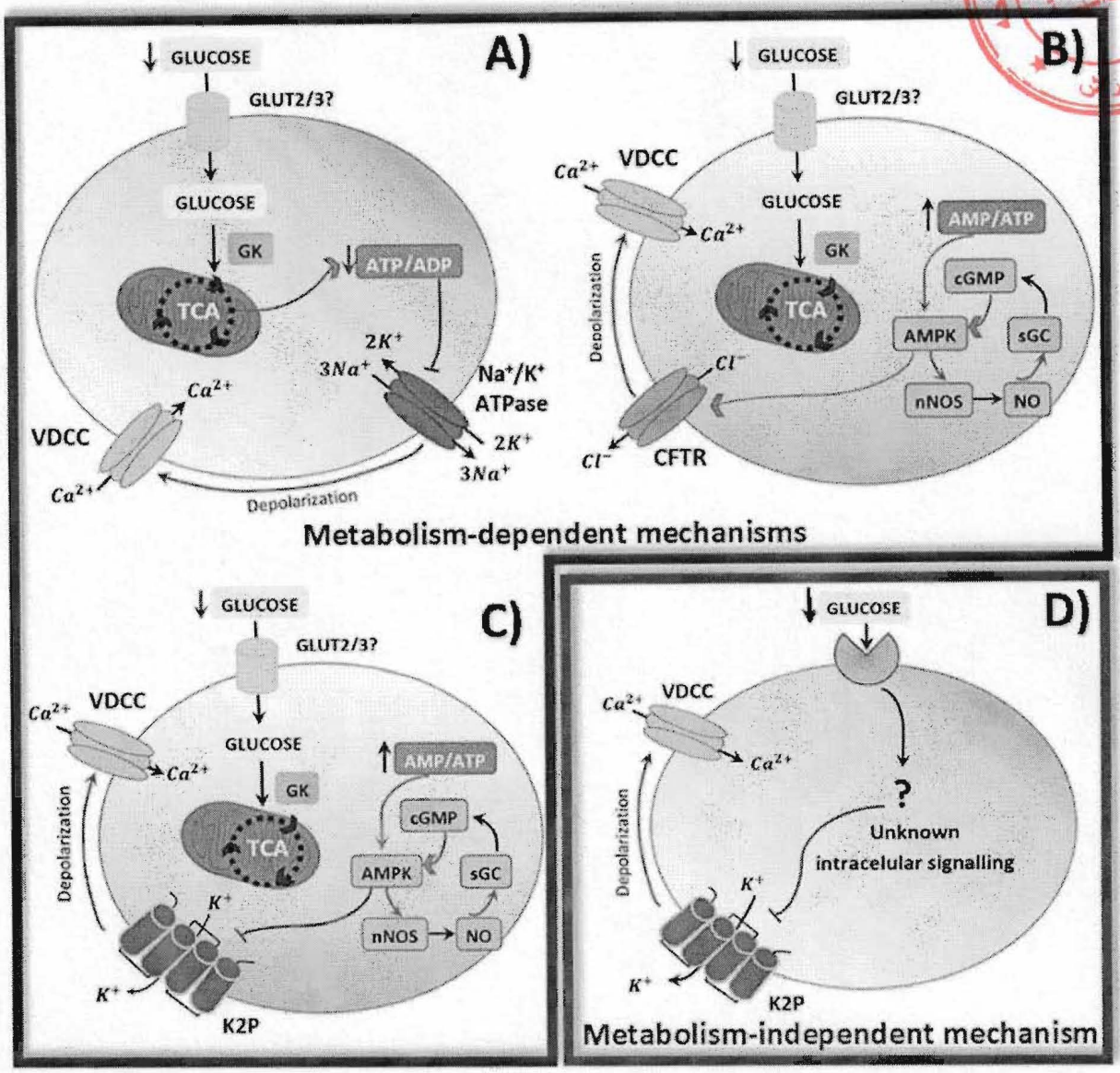
1.3. Absorption of carbohydrates:

Carbohydrates, reduced to monosaccharides by digestion, will be absorbed by enterocytes according to different and specific mechanisms. Being very hydrophilic molecules, monosaccharides cannot cross the lipid phases of cell membranes alone. Their diameter of 0.7 to 1 nm does not allow them to diffuse through the intercellular junctions which allow water molecules and electrolytes whose diameter is less than 0.3 nm to pass.

- **Absorption of glucose and galactose:**

The absorption of glucose and galactose involves the Na+–K+–ATPase pump. It is the predominant mechanism of carbohydrate absorption since it allows the absorption of more than 80% of monosaccharides, only fructose being excluded from this mechanism.

It is an active and saturable process, consuming energy (ATP), which allows the absorption into the enterocyte of a glucose molecule in parallel with two Na+ ions. The Na+–K+–ATPase pump is a homotetramer consisting of four subunits spanning the enterocyte membrane. Glucose and Na+ bind to the apical pole of the enterocyte on a transporter called SGLUT1. The Na+–K+– ATPase pump then maintains a Na+ gradient in the cell by excreting Na+ into the blood circulation through the basolateral pole. The enterocyte is therefore always maintained in a situation of affinity for Na+. It has been shown that in the absence of Na+, glucose does not bind to its transporter and is therefore not absorbed. In the presence of Na+, SGLUT1 deforms to allow glucose and galactose to pass through. The active principle of this glucose transport is the Na+ gradient maintained at the basolateral pole of the enterocyte by the Na+–K+–ATPase pump. The coupled absorption of glucose and sodium explains the benefit of a joint intake of glucose and sodium in rehydration solutions, in order to optimize the reabsorption capacities of the small intestine.



Na+–K+–ATPase pump and glucose

➢ Fructose absorption:

Fructose has a specific transporter on the apical membrane of the enterocyte, called GLUT5. Its affinity for fructose is quite low, and the absorption of fructose is not dependent on a joint mechanism with sodium.

➢ Mechanisms of exit from the enterocyte of glucose andfructose:

Glucose leaves the enterocyte to pass into the blood circulation (portal system) by a facilitated diffusion mechanism, located in the basolateral membrane, independent of sodium, and saturable for a glucose concentration greater than 50 mmol/L $^{-1}$. This diffusion into the circulation is carried out by a specific transporter called GLUT2.

Fructose leaves the enterocyte to enter the bloodstream via the same transporter as glucose, GLUT2, located on the basolateral pole of the enterocyte.

2. Protein foods

The proteins present in the intestinal lumen have a dual origin: on the one hand, dietary proteins, the most numerous, 60-70 to 100 g/day for a varied diet (meat, fish, eggs, milk); and on the other hand, endogenous proteins, represented by digestion enzymes (35 g/day) and by cellular renewal products (30 g/day).

As with carbohydrates, protein digestion begins during an intraluminal phase during which proteins are changed into oligopeptides, then digestion is completed by peptidases present on the enterocyte brush border, allowing their absorption by enterocytes.

2.1. Intragastric digestion:

After chewing, which allows for the dilaceration of proteins, protein digestion begins in the stomach. It is shown that hydrochloric acid secreted by the parietal cells of the stomach allows the gross denaturation of proteins (most proteins first pass through their isoelectric point and precipitate initially). It also makes it possible to reach a pH between 2 and 4, pH at which the pepsinogens secreted by the stomach are transformed into active proteolytic enzymes called pepsins. These pepsins have a known proteolysis activity, but given their elective activity in an acidic environment and the buffering power of meals (measured intragastric pH greater than 5), it is unlikely that they play a large role in protein digestion. They are probably only initiating it.

Indeed, pepsin acts on these proteins brought to pH 4.5 or lower values. The latter splits proteins at the level of aromatic amino acids, transforming them into peptone and peptides whose N-terminal acid is tyrosine and phenylalanine.

The proteolytic effect of pepsin is all the more marked as the polypeptide chain is richer in aromatic amino acids (tryptophan).

Gastric digestion of other proteins (which do not have aromatic amino acids), on the other hand, is very incomplete, delivering polypeptides of still high molecular weight into the duodenum.

Proteins which have not acquired sufficient hydrophilicity (solubility) or which have not been depolymerized in the stomach remain unassailable by intestinal proteases and will be classified as indigestible.

2.2. Intraluminal digestion of proteins:

(pancreatic proteases)

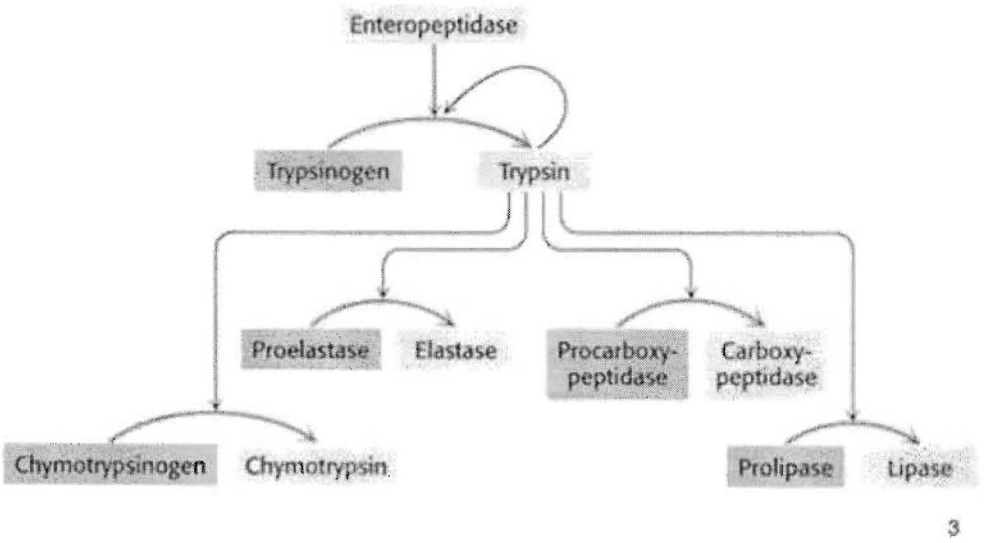
Conversely, pancreatic proteases have a major role in protein digestion. They include endopeptidases (trypsin, chymotrypsin and elastase) and exopeptidases (carboxypeptidases A and B). These enzymes, a major component of pancreatic juice, cleave the proteins present in the intestinal lumen from the proximal duodenum, where the pancreatic juice flows.

Pancreatic proteases are first released into the duodenal lumen in inactive or zymogenic form. Their activation occurs in a cascade, the first step being the activation of trypsinogen to trypsin by enterokinase, a glycoprotein synthesized and released by enterocytes of the duodenum and proximal jejunum.

Endopeptidases and carboxypeptidases have complementary activity. Thus, trypsin cleaves proteins and produces peptides having at their carboxyterminal end an Arg or Lys radical released

in a second step by carboxypeptidase B. Chymotrypsin and elastase cleave proteins into peptides having at their carboxyterminal end respectively aromatic and aliphatic radicals, released secondarily by carboxypeptidase A.
Digestion of proteins by pancreatic proteases is very rapid, resulting in a mixture of amino acids and oligopeptides in less than fifteen minutes during a challenge meal. Protein digestion continues at the brush border of the enterocytes.

Sites of action of proteases:
Pepsin: cuts the chain at the amine function of the aromatic amino acid;
Chymotrypsin: acts at the carboxyl level of the same aromatic amino acids;
Trypsin: cleaves the carboxyl of the basic amino acid;
Elastase: cut neutral amino acids;
Carboxypeptidases: cut the C-terminal amino acids one after the other;
Aminopeptidases (intestinal): cut amino acids at N-terminals close to each other.



Sites of action of pancreatic proteases

The first part of the work is carried out by trypsin, chymotrypsin and elastase (at the same time) which split large molecules into smaller molecules. when these are composed of only a few dozen amino acids (polypeptides), they will be taken up by the carboxypeptidases which reduce them to the state of an oligopeptide composed of 2 to 6 amino acids.

During these hydrolyses, a certain number of amino acids are detached, and the result of the action of pancreatic proteases would be a mixture of 30% free amino acids and 70% oligopeptides (from 2 to 6 amino acids). The free amino acids are mainly arginine, lysine, phenylalanine, tyrosine, and leucine.

The end of protein hydrolysis continues in contact with the intestinal wall thanks to peptidases (aminopeptidases) located in the brush border.

2.3. Digestion by enterocyte peptidases:

Enterocyte peptidases are partly localized in the brush border. However, a large part of them are located intracytoplasmically. Indeed, peptides have the particularity compared to carbohydrates of being able to cross the apical membrane of enterocytes and to be transformed into amino acids, final products of protein digestion, intracytoplasmically.

1.3.1. Brush border peptidases:

Seven brush border peptidases are currently known: ***threeaminopeptidases*** (including ***neutral aminopeptidase*** acting on neutral AAs and ***acidic aminopeptidase*** acting on acidic AAs such as glutamine and asparagine), releasing the N-terminus of peptides, ***two carboxypeptidases*** releasing the C-terminus peptides, ***endopeptidaseand gamma-glutamyl transpeptidase.***

The most active are *neutral aminopeptidase* and *dipeptidyl peptidase IV*. This last enzyme is capable of cutting oligopeptides containing proline located at the NH_2 terminal end of the molecule, it therefore completes the action of aminopeptidase.

Theoretically, the residue should only consist of amino acids. In fact, hydrolysis respects the last dipeptide (affinity) for which it has a low affinity. Likewise, its affinity is lower for groups comprising Glycine, proline and hydroxyproline.

These brush border peptidases will produce from the oligopeptides a mixture of amino acids (60%) ând di- and tripeptides (40%).

Only di- and tripeptides can directly cross the apical membrane of the enterocyte.

1.3.2. Intracytoplasmic peptidases:

Intracytoplasmic peptidases are responsible for 90% of the peptidase activity of the enterocyte. The main ones are Gly-Leu dipeptidase, a prolidase and an aminotripeptidase.

The oligopeptide transfer system is very non-specific. It is an active system, dependent on an H+ gradient on either side of the enterocyte membrane. The di- and tripeptide transporter is called Pept-1. It should be noted that this transporter has no affinity for amino acids. The possibility for di and tripeptides to pass directly through the apical membrane of the enterocytes to be digested intracytoplasmically explains the interest in cases of severe malabsorption of "semi-elemental" enteral nutrition solutes comprising a large number of proteins in the form of di- and tripeptides. and tripeptides.

2.4. Protein absorption:

Protein absorption by the enterocyte occurs either in the form of free amino acids or in the form of di and tripeptides by the Pept-1 transporter. There are around twenty free amino acids absorbed by the enterocyte. We do not specifically know all the absorption pathways of these different amino acids. On the other hand, we know that they involve the sodium gradient, maintained by the Na+–K+–ATPase pump, as for glucose. The absorption of protein breakdown

products is therefore an energy-consuming phenomenon, just like the absorption of sugar breakdown products. The amino acid transfer rate is two Na+ ions for one amino acid.

The transport speed is not the same for all amino acids, it depends on the length and configuration of the side chain of the amino acid. The study by intestinal perfusion in healthy humans of the absorption of a mixture of AAs containing an identical concentration of 18 usual AAs shows interesting effects. Methionine and branched chain AAs (leucine, isoleucine, valine) have the highest absorption rate. Glutamic acid and aspartic acid have the lowest absorption rate.

2.5. Mechanisms of amino acid exit from the enterocyte:

A significant part of the amino acids absorbed by the enterocyte (10%) is used by the intestinal epithelium for its metabolism and its own syntheses. Glutamine, glutamate and aspartate are the amino acids most used by the intestine, covering 80% of the needs of the intestinal epithelium. The passage of amino acids into the bloodstream is independent of sodium. Neutral and basic amino acids leave the enterocyte via the basolateral pole using specific transporter systems called L system and y + system respectively.

3. Lipid foods

Fats or lipids represent almost 50% of the energy provided by food. Lipids are present in food in butter, oil, fats, but also chocolate and many manufactured products. The lipids ingested consist of 98% triglycerides, the remainder being represented by cholesterol, phospholipids and esters of fat-soluble vitamins (A, D, E, K).

The digestion and absorption of lipids are more complex than those of carbohydrates and proteins, particularly due to the hydrophobic nature of lipids.

They require three very distinct steps:

– fragmentation of triglycerides by salivary, gastric and pancreatic lipases;

– the absorption by the small intestine of the products of lipid digestion in the form of micelles formed from bile acids, allowing hydrophobic molecules to be transported across the enterocyte membrane;

– the resynthesis of triglycerides intra-enterocytically before the formation of chylomicrons and the exit not into the portal system but into the lymphatic channels.

3.1. Lipid digestion:

4.1.1. Prepancreatic lipolysis:

Salivary lipase is the first lipid hydrolyzing enzyme. It is active in an acidic environment, and therefore in the stomach. Its role is probably not major. Gastric lipase is also active in an acidic environment (pH around 5) and has specificity for the external position of triglycerides. It appears that its role is quite important in the initiation of pancreatic lipolysis.

4.1.2. Pancreatic lipolysis:

The exocrine pancreas is the major organ involved in lipid digestion. Pancreatic juice contains three different lipolytic enzymes, each with their own specificity:

– *pancreatic lipase* is the main enzyme. It hydrolyzes only triglycerides, which are the vast majority of lipids in the diet;

Pancreatic lipase releases two fatty acids and one monoglyceride molecule from a triglyceride molecule. It acts at the oil-water interface, and therefore requires prior emulsification of triglycerides in order to be effective. Its activity is then multiplied by 1,000. This emulsification is obtained first by antropyloric motility, then in a much finer manner by the action of bile acids which will solubilize the lipids in the diet. In addition to the need for emulsification by bile salts, pancreatic lipase also requires the action of a cofactor also secreted by the pancreas, called colipase. Colipase forms with bile salts and lipase a ternary complex in which colipase anchors lipase in the bile salt-lined interface, allowing lipase access to its substrate, triglycerides. The optimal pH for lipase activity is 6, and 8 in the presence of bile acids. In vivo, it is estimated that pancreatic lipase hydrolyzes 70% of dietary triglycerides.

– *carboxyl ester lipase (CEL)* which hydrolyzes cholesterol esters;

CEL does not act at the oil-water interface but on substrates in solution. It has a preferential action on cholesterol esters and esters of vitamins A and E in the presence of bile acids, but can also hydrolyze long-chain triglycerides.

In the absence of bile acids, it is very active on short-chain phospholipids.

– *phospholipase A2* which hydrolyzes phospholipids.

Phospholipase A2 is secreted as a proenzyme, and is activated in the duodenum by trypsin. Like pancreatic lipase, it requires the oil-water interface to be active, and is therefore dependent on the prior action of bile acids. It specifically catalyzes the hydrolysis of the fatty acid ester bond located at position 2 (internal) on the phosphoglyceride molecule.

Pancreatic lipase is very specific for triglycerides and is very active in vivo. It takes destruction or amputation of more than 80% of the pancreas for steatorrhea to appear due to maldigestion of fats.

4.2. Lipid absorption:

4.2.1. The role of bile acids: micelles

Bile acids play a vital role in the digestion and absorption of lipids. It is under their action that dietary lipids are solubilized into micelles, multimolecular aggregates formed around bile acids due to their very particular property: bile acids are in fact amphipathic molecules, that is to say they are both hydrophobic and hydrophilic. Bile acids will therefore allow the solubilization of dietary lipids by bringing them into contact with their hydrophobic pole. This complex formed of bile acids and dietary lipids located at the heart of the complex constitutes the micelle.

It is in the micelle that pancreatic lipase can digest triglycerides with the help of colipase. Micellar formation begins as soon as the intraluminal concentration of bile acids reaches the critical micellar concentration. The hydrophilic pole of bile acids then allows the products of lipid digestion to be brought to the brush border.

The diffusion of lipolysis products then occurs from the micelle to the intra-enterocyte in a passive manner.

Any disturbance in bile acid metabolism (cholestasis, microbial proliferation, etc.) results in fat malabsorption, highlighting their extreme importance in the digestion and absorption of lipids.

4.2.2. Formation of chylomicrons:

– *Resynthesis of triglycerides:* free fatty acids are taken care of as soon as they enter the enterocyte by two specific fatty acid binding proteins called liver-fatty acid binding protein (L-FABP) and intestine-fatty acid binding protein (I- FABP). I-FABP ensures the intra-entreocyte transport of free fatty acids over 12 C. L-FABP serves as a "reservoir" of free fatty acids while awaiting their transport. Free fatty acids greater than 12 C are re-esterified to triglycerides in the endoplasmic reticulum by acyl-CoA synthetase. Free fatty acids of less than 12 C diffuse directly into the enterocyte to reach the portal system.

– *Formation of chylomicrons and exit from the enterocyte:* the resynthesized triglycerides are joined by phospholipids and apoproteins, the latter being synthesized by the enterocyte. Chylomicrons are clusters of triglycerides covered with 80% phospholipids and 20% apoproteins. They are packaged in vesicles which will fuse with the enterocyte membrane at the basolateral pole, before being excreted into the intercellular space. Their volume prohibits them from crossing the capillary fenestrations, they will penetrate into the intestinal lymphatics through the interstices separating the endothelial cells. They finally join the general circulation through the thoracic duct.

– *Special case of medium-chain triglycerides (MCT):* MCTs differ significantly from long-chain triglycerides (TCL). In fact, they are much more water soluble than TCL. They therefore do not need bile acids to diffuse across the enterocyte membrane, explaining why they can be given in cases of malabsorption due to bile acid deficiency. They are also hydrolyzed much more quickly by pancreatic lipase than TCL. Intra-enterocytically, medium chain fatty acids are not re-esterified into triglycerides, acyl-CoA synthetase having no affinity for fatty acids less than 12 C. They do not enter into the composition chylomicrons and leave the enterocyte through the portal system. This last characteristic explains why MCTs are the only lipids authorized in oral or enteral nutrition in cases of thoracic duct wound (aortic surgery).

5. Vitamins

Lipids and fat-soluble vitamins follow similar pathways during the digestion-absorption phenomenon (extraction from the food matrix, incorporation into micelles, uptake by enterocytes, etc.).

5.1. Hydrolysis of fat-soluble vitamins:

Regarding the hydrolysis of vitamin esters, data obtained in healthy subjects showed that gastric lipase did not significantly hydrolyze retinyl palmitate. Hydrolysis of ***vitamin A esters*** therefore takes place in the duodenum. Pancreatic juice contains several enzymes that could carry out this hydrolysis: cholesterol ester hydrolase and pancreatic lipase. It has been shown that cholesterol ester hydrolase can carry out this hydrolysis in vitro.

Regarding the esterified forms of ***vitamin E***, it has been suggested that they can be hydrolyzed either by pancreatic juice enzymes such as cholesterol ester hydrolase or by enterocyte esterases. Cholesterol ester hydrolase also appears to be the best candidate for the hydrolysis of ***vitamin D esters***.

If the preferred vehicle for bringing lipid-soluble vitamins to the enterocyte appears to be the micelle, it is impossible to exclude the possibility that the vitamins are vectored by liposomes or vesicles, or even proteins. Indeed, it has been shown, for example, that retinoids can bind to a milk protein from the same family as RBP (Retinol Binding Protein): beta-lactoglobulin.

The ***bioaccessibility of a vitamin*** is defined as the proportion of this vitamin which is released from its food matrix during digestion and which is included in the micelles. Bioaccessibility thus represents the fraction of vitamin potentially absorbable by the body. This is a key step in the intestinal absorption of lipophilic micronutrients, which is studied in the laboratory by modeling micelles in vitro (made up of fatty acids, monoglycerides, phospholipids, lysophospholipids, cholesterol and a bile salt).

5.2. Absorption of fat-soluble vitamins

The membrane transport of lipids is a more complex phenomenon than simple passive diffusion, although the latter remains a major phenomenon for the absorption of fatty acids.

Chapter III.
Effects of substances other than nutrients on digestion

1. Food additives

Preservatives, colorings, flavor enhancers, thickeners, emulsifiers... Many food additives are found in our daily diet. Although their presence is authorized in culinary preparations, these substances are not without danger for our health. Their long-term or excessive consumption can be associated with the development of pathologies such as certain cancers. Food additives can also cause digestive problems.
The presence of additives most often indicates that we are dealing with an ultra-processed product. However, overconsumption of ultra-processed products promotes disruptions in our microbiota, with the eventual possibility of triggering digestive disorders.

Another problem raised with these food additives: some are actually FODMAPs, *"carbohydrates that ferment in the colon, leading to the production of painful gas"*.
For all these reasons, food additives should be monitored, particularly in people prone to digestive disorders or who suffer from associated chronic pathologies.

You should particularly be wary of certain emulsifiers. Laboratory studies carried out on mice have shown that these texturants deplete our intestinal flora and increase the risk of developing chronic inflammatory bowel disease.
However, these emulsifiers, which have been singled out, are found in many industrial products, in pastries, biscuits, prepared meals, sauces, etc.:

- E407, Carrageenans
- E435, Polysorbates
- E471, Mono- and diglycerides of fatty acids
- E 472e, Monoacetyl tartaric and diacetyl tartaric esters
- E473, Polyglycerol esters of fatty acids
- E 475, Sucroesters of fatty acids
- E481, Sodium stearoyl-2-lactylate
- E 482, Calcium stearoyl-2-lactylate
- E 491, Sorbitum monsterate
- E492, Sorbitum tristerate
- E493, Sorbitum monolorate
- E494, Sorbitum monooleate
- E495, Sorbitum monopalmitate

Polyols, which are used in the food industry as sweeteners or humectants, can cause different types of discomfort, such as bloating and flatulence.

These additives can promote water retention, and therefore can in certain cases be responsible for diarrhea. The additives in question to watch out for:

- E965, Maltitol
- E421, Mannitol
- E420, Sorbitol
- E96, Xylitol
- E953, Isomalt
- Fructose
- Fructose syrup
- Glucose-fructose syrup
- Corn syrup
- Dextrises/polydextroses (E1200)
- Maltodextrins

2. Medication

Phytosterols, frequently used to reduce the intestinal absorption of cholesterol by reducing, among other things, its bioaccessibility, could act on the micellar incorporation of cholecalciferol (vitamin D_3 has a structure close to that of cholesterol). Indeed, the phytosterols added to the micelles significantly reduce the bioaccessibility of vitamin D (−16 to −36% depending on the sterol species).

Quercetin is a well-studied natural product with multiple pharmacological properties. Quercetin has a dual effect on protein digestion and absorption:

1) suppression of protein digestion by inhibiting trypsin in intestinal fluid;
2) promote intestinal absorption of oligopeptides in intestinal villi cells.

Excessive trypsinogen activation leads to overdigestion, a process that progressively impairs the digestive system and results in pulmonary emphysema. Additionally, if trypsinogen is aberrantly activated in the pancreas, trypsin can damage pancreatic acinar cells resulting in pancreatitis. Thus, the development of trypsin inhibitors has pharmacological importance. Quercetin has been reported as an inhibitor of several serine proteases , including trypsin.

3. Dietary fiber

Gelation of dietary fiber (which is neither digested by endogenous enzymes in the human small intestine nor absorbed) in the intestines may decrease the digestibility and absorption of fats and carbohydrates, but may also affect the absorption of calcium, magnesium and iron.

High consumption of polyphenolic compounds, including ***tannins***, may reduce the bioavailability of iron and copper which may be a causative factor in anemia. Tannins found in green tea or its extracts may harm functions.

Thiocyanates, found in cruciferous vegetables, can decrease the availability of iodine in the thyroid gland and reduce the synthesis of thyroid hormone precursors.

It should be noted that apart from fibers naturally present in foods, all others must demonstrate beneficial physiological effects among the following:

- reduction in transit time;
- increased volume of stools;
- fermentability by colonic flora;
- reduction of total cholesterol or LDL cholesterol;
- reduction in blood sugar or postprandial insulinemia.

These soluble fibers are fermented more or less quickly and completely in the colon. Fermentation, however, generates gas, which can cause gastrointestinal discomfort. Gastrointestinal tolerance is therefore a parameter to take into account in the formulation of foods containing rapidly fermentable soluble fiber.

Technical difficulties generated by fibers:

- at the level of the manufacturing process, products are more difficult to manufacture and production yield decreases;
- at the level of the finished product, the increase in fiber content is often associated with a significant risk of degradation of organoleptic qualities;
- In addition, fermentable fibers can cause undesirable effects such as bloating or gas production;

Products rich in fiber tend to be more difficult to produce, less sensory appreciated by the consumer while being more expensive to purchase.

Chapter IV.
Bacterial ecosystems

1. Implantation of bacteria in the digestive tract of the newborn

The intestinal microbiota is "an ecosystem composed of microorganisms established in a specific environment called a microbiome". it is an extremely complex ecosystem, comprising approximately 10^{14} microorganisms covering nearly 400 bacterial species. It is an active element of intestinal physiology, with metabolic functions, barrier flora and stimulation of the intestinal immune system. The formation of this ecosystem begins very quickly after birth. The newborn, sterile at birth, becomes colonized with flora resulting from contact with its mother and its environment. Although the factors for the establishment of the flora are little known, many factors will influence the establishment of this microbiota: mode of delivery, environment, feeding method, gestational age and antibiotic therapy. Recent data shows changes in the establishment of this flora, with a delay in the establishment of enteric bacteria of maternal origin, due among other things to the strict hygienic conditions surrounding childbirth. The clinical consequences of these modifications are poorly understood but could be responsible for an absence of barrier flora or poor stimulation of the intestinal immune system.

1.1. Microbiota and birth route:

The genera *Bifidobacterium* and *Bacteroides* are significantly more frequently found in infants born vaginally compared to those born by cesarean section. The latter are significantly more colonized by the genera Clostridium and *Lactobacillus* during the first 3 months of life, differences which persist up to 6 months of life but become non-significant.

In addition, the bacteria found in the stools of children born by cesarean section are, as stated above, usually skin bacteria. This means that the implantation of the microbiota in these newborns occurs mainly through skin-to-skin contact.

1.2. Microbiota and antibiotics:

The involvement of antibiotics in the alteration of the microbiota raises not only the question of those administered to the newborn but here, even more, those administered to pregnant women. A study, carried out on a Brazilian population, demonstrated a dominance of *Lactobacillus* in healthy pregnant women and a microbial composition of low diversity at the vaginal level unlike women carrying group B *streptococcus* who received antibiotic prophylaxis.

Monitoring of the antenatal period until the child was 7 years old showed that children exposed to antibiotics during their antenatal life (2nd and 3rd trimester of pregnancy) had a significant increase in the risk of obesity of 84% compared to unexposed children. This exposure is also associated with significant increases in body mass index (BMI), waist circumference, and body fat percentage.

1.3. Microbiota and breastfeeding:

The newborn's breastfeeding method logically has an impact on the establishment of the newborn's intestinal microbiota and has been the subject of numerous studies. A study showed the existence of a significant association between the composition of the newborn's intestinal microbiota and the feeding method. The objective of this study, carried out in Boston, was to determine the composition of the intestinal microbiota of 30 premature newborns, born at less than 32 weeks of amenorrhea (AS) during a period of approximately 6 weeks after birth, and having been exposed to 3 different nutritional regimes: exclusive breastfeeding (AM), exclusive artificial breastfeeding (AA) and breastfeeding from pasteurized human donor milk (LD). The authors found significantly greater initial bacterial diversity and a more progressive acquisition of diversity in the AM group compared to the AA group. Furthermore, the composition of the microbiota of the LD group was closer to that of the AM group than of the AA group. Another study involving 12 very low birth weight newborns (pilot study) found that oral administration of colostrum every 2 hours for 46 hours leads to significant changes in the oral microbiota (analysis by sequencing at 48 hours and 96 hours) in comparison with a comparable control group. The authors found significantly more *Planococcacea* in the colostrum group and *Staphylococcae* and *Moraxella* in the control group.

Furthermore, the results of another study demonstrate that exclusive breastfeeding makes it possible to minimize modifications of the microbiota secondary to exposure to antibiotics in the perinatal period at 3 months and 1 year compared to a group of newborns having been exposed to antibiotics but not exclusively breastfed.

Breast milk thus allows, among other functions, the establishment of a stable and rich microbiota, through the presence of numerous identified components.

The oligosaccharides contained in breast milk (and colostrum) have prebiotic and anti-inflammatory properties. They are not digestible by the newborn due to their complex structure, which led the authors to investigate the reasons for their presence in breast milk since they could not be metabolized by the newborn. They have thus demonstrated that these oligosaccharides allow the selection of the *Bacteroidetes* and *Lactobacilli families* (beneficial to the acquisition of a balanced microbiota) by serving as a substrate and inhibit the growth and adhesion of opportunistic pathogenic bacteria through the higher presence of Bacteroidetes and Lactobacilli. The initial inoculation, during vaginal birth, seems to be the first step in a succession of events: the first bacteria reaching the digestive tract do not constitute, on their own, a stable microbiota. Breast milk, by its composition, therefore allows the selection of symbiotic bacteria (by providing them with metabolites allowing their multiplication and growth) and protects against opportunistic pathogens.

2. Distribution of bacteria in the digestive tract

The "Human microbiome project" has identified 30 phyla (Division), 51 classes, 125 orders, 493 families, 929 genera and 1500 bacterial species.

Generally speaking, the human microbiota is dominated by the following 4 phyla: *Firmicutes*, *Actinobacteria*, *Proteobacteria* and *Bacteroidetes*.

Stools have the greatest species diversity, followed by samples of oral, skin, and vaginal origin. Each individual appears unique in terms of bacterial species diversity although there are signatures for a given host.

For example, for the digestive microbiota of the human species, 3 enterotypes, that is to say major types of microbial communities, could be defined according to the predominant taxon, ***Bacteroidetes,****Prevotella* or *Ruminococcus*. *Bacteroides* species represent approximately 25% (between 20 and 30%) of the bacteria present in the human colon. Most of the remaining 70-80% of colonic isolates consist of poorly characterized Gram-positive anaerobes. Well-studied facultative species, such as *E. coli* and enterococci, are numerically minor, constituting less than 1% of colonic isolates.

Several international projects relating to the study of the microbiota and its implication in health and disease are underway. The composition and variations of healthy microbiota as well as the dynamics of community establishment during childhood and physiological modifications throughout life are essential knowledge to understand the role of the microbiota in disease.

2.1. Oral microbiota:

The oral microbiota is all the microorganisms present in the oral cavity. These microorganisms are mainly bacteria, around 700 species. Viruses, fungi, protozoa and archaea are also present.

Long called oral flora, the oral microbiota is acquired at birth from maternal and environmental microbiota. These microbiotas colonize the child's oral cavity. The eruption of primary teeth drastically modifies the existing ecosystem. New surfaces with different physicochemical characteristics must be colonized. Overall, bacterial diversity and richness increase and diverge from the maternal microbiota during the development of the oral cavity and from the age of 2 years would be close to those observed in adults.

The oral microbiota forms biofilm or plaque on tooth surfaces depending on the environment and host response. In a healthy state, with good dental hygiene, the composition of the microbiota remains stable in balance with its environment and the host. The balance of the microbiota, however, remains fragile and under the influence of various factors such as excess sugars, acid, lack of toothbrushing, etc. An imbalance in the microbiota called dysbiosis occurs and can locally lead to caries (cavities) or periodontal disease. Analyzes by new generations of sequencing (NGS) of pathological microbiota such as dental plaque collected within a carious lesion or a periodontal pocket show that certain bacterial species are common but their proportion has been modified, that certain species appeared while others disappeared compared to a microbiota collected from healthy surfaces. Local infectious diseases due to dysbiosis lead to inflammation, a host response. The concept of a dysbiotic oral cavity as a remote source of infection is now accepted. Thus, periodontal diseases, with their significant bacterial load associated with a failure of the immune system, are comorbidity factors of different organ pathologies such as cardiovascular, pulmonary and renal pathologies. Alongside them, patients with systemic diseases such as diabetes, rheumatoid arthritis, and systemic lupus erythematosus are more susceptible to destructive periodontal disease. The expression of local mediators would modify the composition of the oral microbiota and cause dysbiosis.

The oral microbiota contains a diverse set of microorganisms. A part is common to the different microbiota of the body, for example the fungus *candida albicans* present in the intestinal microbiota and the vaginal microbiota , the bacterium *Helicobacter pylori* which is also found in the stomach or the anaerobic bacteria *Porphyromonas gingivalis* which It is found in periodontal pockets and then "migrates" into the body via the vascular system.

But another part of these bacteria is entirely specific to the mouth. We will thus find a number of aerobic bacteria due to the air we breathe, as well as anaerobic bacteria which hide in pockets that are difficult to access and will therefore be more difficult to eliminate.

The more different families of pathogenic bacteria you harbor, the more difficult it is to eradicate them.

2.2. Gastric microbiota:

The gastric microbiota, often ignored, is nevertheless underestimated even though there is an interaction with the bacterium Helicobacter pylori (Hp). If HP is now well known, the gastric microbiota is to date little explored and often unknown.

The acidic environment suggested the poverty of such a microbiota in favor of the intestinal microbiota which had to date polarized research. Even if it is true that the gastric microbiota (10 to 1000 bacteria/ml) is less quantitatively dense than the intestinal microbiota (10 billion to 10,000 billion bacteria/ml), a disturbance in the balance of the gastric microbiota can have consequences all along the intestinal tube. The stomach is indeed the first digestive step due to acid secretion, but also a first line of defense against external pathogenic strains. This balance can be disrupted during dyspepsia, but also during gastritis, ulcers or gastric cancers often linked to the presence of HP. Long-term use of antibiotics or proton pump inhibitors (PPIs) can also be a source of dysbiosis of the gastric microbiota. A healthy stomach would therefore be the gateway to a healthy host, which amounts to saying that dysbiosis of this specific microbiota must be corrected and rebalanced.

The combination of two probiotic strains, presenting significant gastric tropism, has clinically demonstrated significant benefit in the management of the gastric microbiota: Lactobacillus *reuteri* DSM 17938 and *Lactobacillus reuteri* ATCC PTA 6475 (forming Lactobacillus reuteri Gastrus®). Isolated from breast milk, these two strains resist gastric acidity (pH less than 3) and offer complementary actions:

- Lactobacillus reuteri DSM 17 938 produces a powerful anti-pathogenic agent: reuterin, with an action demonstrated in vitro on Hp. It would also improve digestive motility and motor skills, thus facilitating gastric emptying;
- Lactobacillus reuteri ATCC PTA 6475 has powerful adhesion to the walls of the stomach, reinforcing the gastric epithelial barrier, as well as a unique anti-inflammatory action. This strain also regulates gastric acid secretion.

In clinical studies carried out in patients treated with triple or quadruple therapy to eradicate HP, supplementation with *Lactobacillus reuteri Gastrus®* increases the HP eradication rate by 9% and reduces the side effects of treatment compared to to the placebo. Compliance with treatment and patient comfort are improved.

2.3. Intestinal microbiota:

Around 100,000 billion bacteria are counted in the human intestine, 10 times more than human cells. Following the human genome description projects, intensive research is focused on determining the role of resident bacteria in human health and disease, that is, characterizing the "second human genome".

The intestinal microbiota (from the Greek *mikros*: small and *bios*: life) is a complex ecological community of its collective activities and its interactions with humans. In this niche, balance is ensured by control feedbacks, but external factors or even certain resident bacteria can destabilize and promote an acute or chronic pathology.

The first weeks of life are decisive in the establishment of the intestinal microbiota but also in the development of these interactions. Prematurity promotes initial dysbiosis (an imbalance within the intestinal flora. This may be a reduction in the number of good bacteria and confined or supplanted species increasing to fill the void) and the dynamics of microbiota implantation different intestinal function of full-term newborns. Dysbiosis of the intestinal microbiota of premature infants can lead to early infectious diseases. Its impact on the rest of life remains to be determined.

The gut microbiota influences the development of the immune system, susceptibility to pathogens and inflammation.

Indeed, the microbiota protects against the installation of exogenous microorganisms through competition for space and substrates. However, the stability of the microbiota should not be considered as a simple inert barrier but rather a dynamic balance.

During child development, the digestive microbiota presents complex dynamics with successive waves of replacement of bacterial species until reaching adult stability.

Certain bacteria are described for their destabilizing or, on the contrary, stabilizing power of the microbiota. For example, *Bacteroides thetaiotaomicron* is described as a stabilizer of the intestinal microbiota, because it competes with exogenous opportunistic pathogenic bacteria (*Vibrio cholerae*,*Shigella* spp. and *Salmonella* spp.), it is a source of nutrients when dietary carbohydrates are scarce and finally it inhibits inflammation.

Clostridium difficile is a pathobiont, the number of autochthonous bacteria can increase very quickly following antibiotic therapy, then lead to colitis. Resilience of the microbiota will lead to a decrease in C. *difficile inoculum* during recovery. The pathogenic bacteria will then resume its status as a commensal bacteria, a member of the normal human microbiota (change in commensal/pathogenic status).

In inflammatory bowel diseases such as Crohn's disease, in the remission phase, a decrease in the ratio of *Firmicutes* to *Bacteroidetes* is observed as a specific signature of the disease.

Metabolic diseases such as diabetes mellitus and obesity are also widely studied today from the perspective of intestinal dysbiosis. In an obese individual, a microbiota imbalance is observed with a *Firmicutes / Bacteroidetes ratio* of around 100/1 associated with a *Bacteroidetes deficiency*.

3. Effect of foods on the bacterial ecosystem

The human population is exposed to numerous environmental and food chemical contaminants (heavy metals, pesticides, nanoparticles, plastics, persistent organic pollutants, food additives, newly formed toxicants). These exposures could disrupt the intestinal microbiota, a key player in human health, and thus participate directly or indirectly in the establishment of various chronic diseases such as obesity, type 2 diabetes, metabolic disorders, cancers, diseases inflammatory, reproductive, immune but also neurological.

The key role of the intestinal microbiota on health and its link with diet has now been demonstrated. We know that its needs are specific: fibers and certain long-chain fatty acids (omega-3) have a favorable effect on its diversity and its functioning, but their deficit, as well as certain pesticide residues, emulsifiers and sweeteners, lead to intestinal dysbiosis. Or over the last fifty years, changes in the feeding of farm animals, in crop protection (pesticides), as well as the growing supply of ready-to-eat products and the resulting evolution in the preferences of consumers, have been sources of disruption of the microbiota (ultra-processed products represent 35% of calories consumed). Health based on a healthy microbiota requires a paradigm shift in the way we eat. To do this, we must act at all links in the food system, through a review of certain agricultural practices and the agri-food industry in order to improve the supply of quality products, but also through a vast education and training effort. to help with food choices and menu composition.

4. Bacteria and food in the colon

The microbiota has significant metabolic activity, notably allowing the fermentation of substrates available in the colon. Every day, 10 to 60 g of undigested carbohydrates enter the colon and undergo more or less complete fermentation. Fibrolytic bacteria express different hydrolases (polysaccharidase, glycosidase) not produced by humans, which release small carbohydrates transformed by glycolytic bacteria into pyruvate, then into short-chain fatty acids (acetate, propionate or butyrate), final products of fermentation. This process is accompanied by the production of gas (methane, carbon dioxide, hydrogen, even hydrogen sulfide). Acetate, propionate and butyrate are rapidly absorbed by the colonic epithelium to be eventually metabolized away from the digestive system. This results in a supply of energy and stimulation of colonic sodium absorption. Butyrate is the main nutrient for colonocytes. It also has local immunomodulation properties. The volume and nature of the gases produced can be responsible for digestive symptoms, a consequence of stretching of the colonic wall (bloating, flatulence, pain).

Proteins can arrive in the colon and are the main source of nitrogen for the microbiota. The protease activity of certain bacteria allows them to hydrolyze proteins into amino acids that can undergo a fermentation process after reductive deamination. It results in the formation of short-

chain fatty acids, dicarboxylic acids, branched fatty acids and ammonia, but also phenolic and indolic compounds detoxified by colonic cells.

The microbiota makes it possible to metabolize the fraction of bile acids that have escaped the enterohepatic cycle of bile acids. Associated with deconjugation, this process leads to the production of metabolites, mainly excreted in the stools in the form of lithocholic acid and bile acid esters.

The microbiota also makes it possible to synthesize vitamin K, which covers around 60% of needs. Antibiotic therapy can disrupt vitamin K status by deterioration of the colonic flora.

Chapter V.
Excretion of main constituents

1. Fecal excretion (defecation)

This is the end of the digestion process. It is the voluntary evacuation of undigested (unabsorbed) substances through the anus via the rectum (faeces - feces) by slow but powerful peristalsis. Dietary fiber increases the strength of contractions.

Digestion waste remains for 12 to 24 hours in the colon, which it travels slowly under the effect of slow contractions of colonic peristalsis (one wave approximately every 30 minutes). There they undergo concentration with reabsorption of water and mineral salts (sodium, potassium).

Little by little, more compact, more or less pasty or solid stools are formed. Long and powerful contractions, which only occur three or four times a day, then propel the stools towards the rectal bulb where they are stored for a few hours.

The need to have a bowel movement is felt when the pressure of the stool becomes too strong on the rectal wall.

- Defecation combines reflex actions (opening of the internal sphincter, activity of the levator ani muscles) and voluntary actions (opening of the external sphincter, thrusting of the abdominal muscles).
- A prolonged blockage of the external sphincter temporarily suspends the entire process.

Defecation occurs between 2 times a day and 3 times a week depending on lifestyle, habits and diet more or less rich in plant fibers.

Feces are composed of water, proteins, undigested fats, polysaccharides, bacterial biomass, ash and undigested food residues.

The average water content of feces is 75%, the variation can be attributed to differences in fiber intake, as non-degradable fiber absorbs more water in the colon; a vegetarian diet allows for a higher water content of 78.9% while a diet that contains less fiber and more protein will have lower humidity (72.6%). Fiber intake also affects transit time, which was positively correlated with % dry matter. The variation in moisture content is influenced by age; Older people were found to excrete the greatest amount of water in feces of all age groups. Other deviations from the median value may be caused by disease. The average water content of feces is 0.1 L/day. The average pH values for fecal water were recorded at pH 6.9 with a range of pH 5.0-8.0.

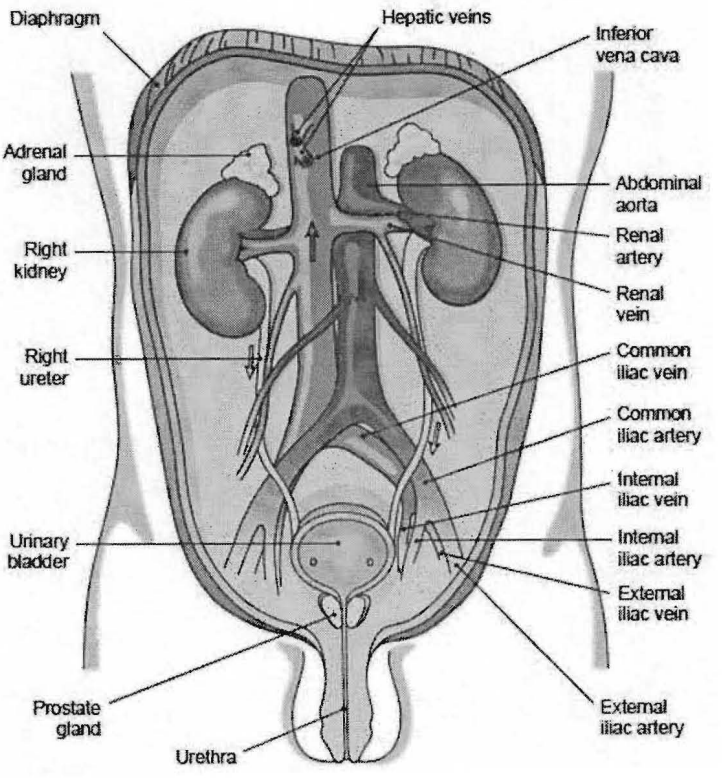
The remaining 25% of fecal matter is therefore composed of solid matter, of which organic matter represents between 84 and 93%. The organic solids fraction can be broken down into fractions of 25 to 54%

bacterial biomass, 2-25% proteins or nitrogenous material (in addition 50% of the bacterial biomass is made up of proteins), 25% carbohydrates or any other undigested non-nitrogenous plant material and 2 to 15% undigested lipids. These fractions are strongly dependent on food intake and its availability.

A significant proportion of the fecal mass is made up of bacteria with an estimate of between 25 and 54% of dry solids. The large variation observed is due to differences in methodology used between microscopic counting techniques and separation of bacterial biomass. The high nitrogen content of feces is partly due to undigested proteins shed in the feces but is also due to the high protein content of the bacterial biomass in the feces,

2. Urinary excretion

The most important organ of the excretory system is undoubtedly the kidney. Each person has two kidneys and these **filter the** blood. They are located under the last ribs, rather at the back of the body, on each side of the spine and resemble very dark red beans. Each kidney is made up of millions of small filtration units called **nephrons**. Blood therefore arrives at each kidney through a **renal artery** which brings blood into the **network of** blood capillaries which surround each of the nephrons. This circulation makes it possible to remove nitrogenous waste (urea and others) and excess substances such as water and mineral salts. The substances collected will form **urine (water**, mineral salts (chlorides, sulfates, phosphates, etc.), urea, uric acid, hippuric acid and ammonia).
The blood thus "cleaned" leaves the urinary system via the **renal vein**.
The nephron consists of a renal corpuscle and a renal tubule. These are highly vascularized, therefore surrounded by blood vessels, so that a good part of the blood is filtered. The non-cellular elements constituting the blood, such as electrolytes, water, urea and other small molecules, will pass from the blood capillaries into the lumen (interior) of the renal corpuscle and renal tubules. One of the main functions of the renal tubules is the reabsorption of water and NaCl (salt). The liquid then contained in these tubes is called **the filtrate.** The latter will be transformed into urine after processes of dilution or concentration of urea and small molecules. The urine thus formed will be excreted by the kidney through the renal collecting tubule towards the ureter and then the bladder:
The ureters are simply tubes connecting the kidneys to the bladder. Their sole function is to carry urine from the kidneys to the bladder.



Urinary excretory system

The bladder: This is an expandable reservoir that collects urine before it is evacuated. At the base of the bladder there is a sphincter (circular muscle) which, when it contracts, provides "holding" (which prevents the involuntary flow of urine through the urethra).

The urethra: The urethra is the tube that connects the bladder to the outside of the body. When the bladder is full, what we call **urination** occurs. This action consists of expelling urine through the urethra, to the outside of the body. In women, the urethra is between 3 cm and 4 cm long and opens near the vaginal opening. In humans, this same duct is approximately 20 cm long and urine must pass through it before being evacuated outside the human body.

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