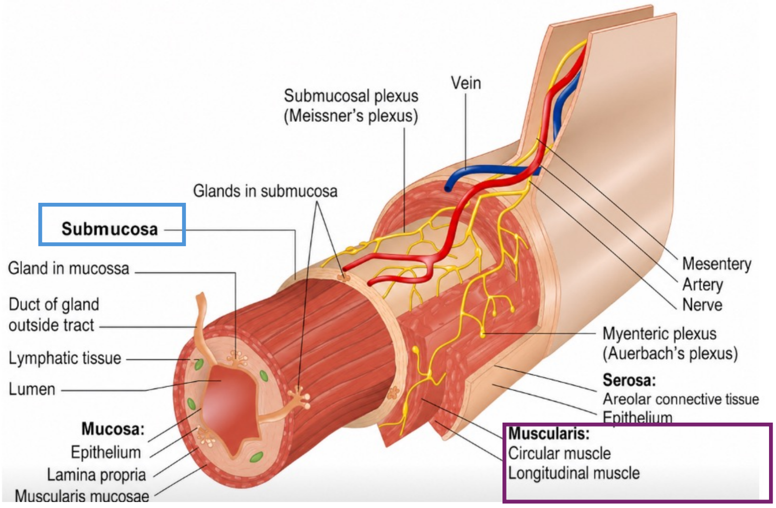
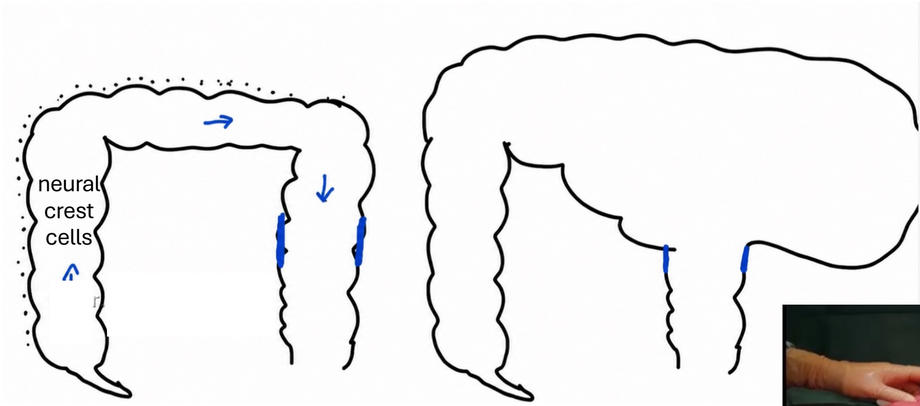
Gastro-Intestinal System

Layers of GI Wall



The wall of the gastrointestinal tract is made of four main layers.
The innermost layer is the **mucosa**. It is the layer in contact with the lumen, which is the internal space where food passes.
Around the mucosa we find the **submucosa**.
After the submucosa there is the muscular layer, called the **muscularis**.
Finally, the outermost layer is the **serosa**, a connective tissue layer that covers the gastrointestinal wall externally.
So, from the inside to the outside, we have:
mucosa;
submucosa;
muscularis;
serosa.
The mucosa is further divided into:
epithelium;
lamina propria;
muscularis mucosae.
It is important not to confuse the muscularis mucosae with the muscularis proper.
The muscularis is the main muscular layer and participates in peristalsis and gastrointestinal motility.
The muscularis mucosae, instead, is part of the mucosa and does not play an important role in gastrointestinal motility.
In the submucosa and muscularis there are nerve plexuses, which are local networks of neurons.
The plexus located in the submucosa is called the **submucosal plexus** or **Meissner's plexus**. This plexus mainly innervates the glands of the submucosa and regulates gastrointestinal secretions.
The plexus that innervates the muscular layer is called the **myenteric plexus** or **Auerbach's plexus**. This plexus regulates gastrointestinal motility and peristalsis.
Therefore, the two key concepts are:
Meissner's plexus mainly controls gastrointestinal secretions;
Auerbach's plexus mainly controls gastrointestinal motility.

Neural Crest Cell Migration in the GI Tract



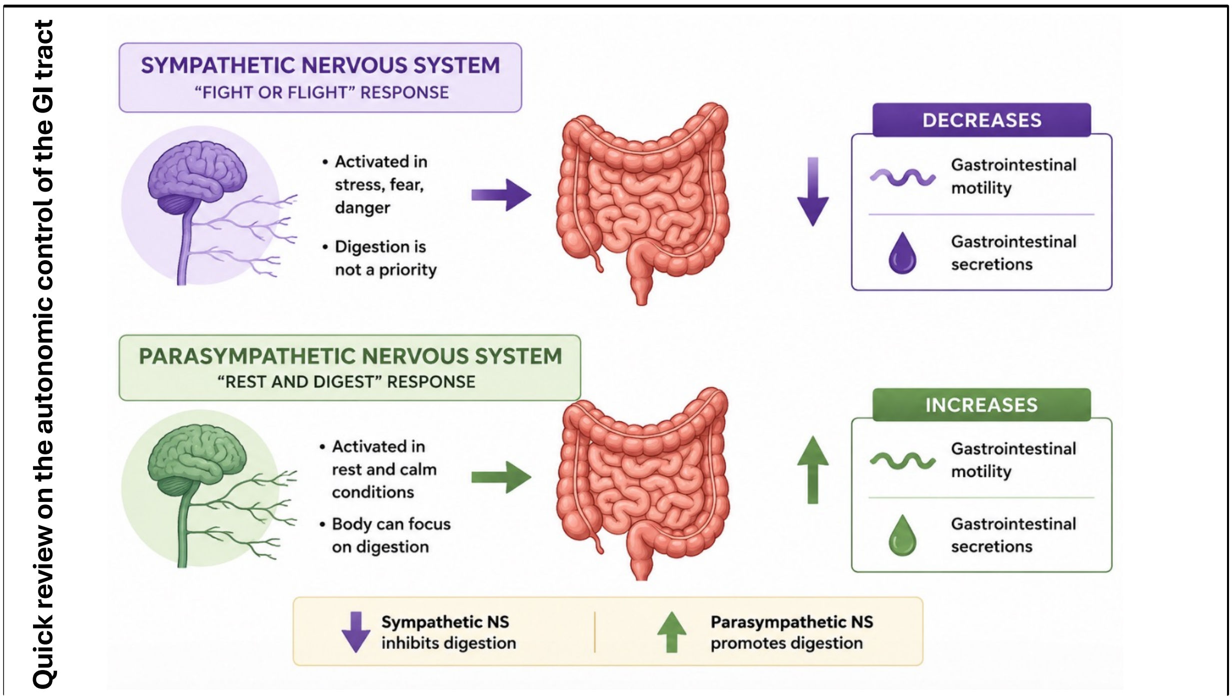

Hirschsprung disease

Meissner's plexus and Auerbach's plexus form the enteric nervous system. Meissner's plexus and Auerbach's plexus form the enteric nervous system. It is represented by autonomic enteric ganglia located within the digestive tract. It is partly independent form the central nervous system (CNS).

In this location we found about 100 milions odf neurons. For this reason it is coalled as little brain.

Where do these ganglia come from?

During embryonic development, some cells called **neural crest cells** migrate from the central nervous system to the gastrointestinal tract. Here, they settle and form the enteric nervous system.
The enteric nervous system is essential for peristalsis and gastrointestinal motility.
If there is a defect in the migration of neural crest cells during development, some parts of the gastrointestinal tract may remain without ganglion cells.
An area without ganglion cells is called an aganglionic segment.
If a segment of the colon lacks enteric innervation, normal peristalsis cannot occur in that area. As a result, intestinal contents cannot move forward properly.
The material accumulates in the proximal part, that is, before the aganglionic segment. To push the contents forward, the proximal segments contract more strongly and may become hypertrophic and dilated.
This condition is called Hirschsprung disease.
Therefore, Hirschsprung disease is caused by a defect in the migration of neural crest cells into the gastrointestinal tract, resulting in the absence of the enteric nervous system in a portion of the intestine.



The enteric nervous system works autonomously, but it is also modulated by the autonomic nervous system, which includes the sympathetic and parasympathetic nervous systems.

When the sympathetic nervous system is activated, for example during fear, stress, or danger, the body prepares for the "fight or flight" response.

In these conditions, digestion is not a priority. For this reason, the sympathetic nervous system reduces:

gastrointestinal motility;

gastrointestinal secretions.

In contrast, the parasympathetic nervous system is mainly active during resting conditions. This is the moment when the body can focus on digestion.

The parasympathetic nervous system increases:

gastrointestinal motility;

gastrointestinal secretions.

Therefore:

the sympathetic nervous system inhibits digestion;

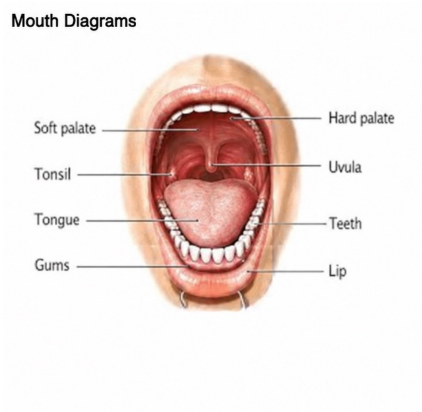
the parasympathetic nervous system promotes digestion.

Digestion

Many secretions are produced in the gastrointestinal tract.
To better understand them, we can follow the journey of food through the GI tract and therefore discuss the digestive process.

Digestion can be divided into two mechanisms:
mechanical digestion, which includes all the movements that break down, mix, and transport food;
chemical digestion, which includes chemical processes and reactions carried out by molecules called enzymes, which transform nutrients into substances that the body can absorb and use.

The First Digestion in the Mouth



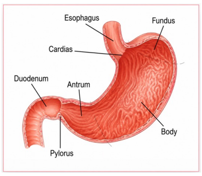
Mechanical digestion ⇨ **Teeth**

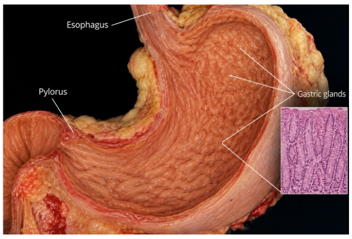
Chemical digestion ⇨ **Saliva containing**
Ptyalin or salivary amylase
begins the digestion of carbohydrates

The first step of digestion takes place in the mouth.

Digestion begins as a form of mechanical digestion carried out by the teeth. Breaking food into smaller pieces and chewing properly allows enzymes to attack the food more easily and therefore improves digestion.
A first chemical digestion also begins in the mouth. For this reason, it is important to keep food in the mouth for some time and chew it thoroughly.
Saliva contains several substances. Some help disinfect the food introduced into the mouth, while others participate in digestion. Among these substances there is an enzyme called **ptyalin** or **salivary amylase**, which begins the digestion of carbohydrates, especially starch.
Once chewing is completed, the food bolus passes through the esophagus, is swallowed, and reaches the stomach.

Gastric Digestion in the Stomach





Mechanical digestion ⇨ **Peristaltic movements**

Chemical digestion ⇨ **Gastric juice containing digestive enzymes and hydrochloric acid**

Produced by gastric glands

Enzymes:
pepsin
Chymosin
gastric lipase

This acidic pH has two main functions:

making the stomach environment hostile to pathogens;
activating digestive enzymes

Inside the stomach we also find both types of digestion: mechanical and chemical.

Mechanical digestion occurs through peristaltic movements. We have already seen these movements in the esophagus, and they continue in the stomach. These contractions, produced by the stomach muscles, move and mix the food so that it can be attacked by the enzymes present in gastric juice.

Chemcal digestion is due to the production of the gastric juice secreted by the gastric glands located in the stomach wall.
Among the most important enzymes we find:
Pepsin (protease), which begins protein digestion;
Chymosin (idrolase), involved in milk digestion;
gastric lipase (idrolase), which starts fat digestion.
All these substances are mixed with **hydrochloric acid**.
Hydrochloric acid is produced by the gastric glands and creates the acidic pH of the stomach.

This acidic pH has two main functions:
making the stomach environment hostile to pathogens;
activating digestive enzymes.
Like all acids, hydrochloric acid is corrosive. However, the stomach wall is protected by a layer of mucus.
If the cardia or pylorus, the valves that close the stomach above and below, do not function properly, hydrochloric acid may escape and damage nearby tissues, especially the esophagus.
The so-called “heartburn” is caused by the reflux of acidic substances into the esophagus.

PEPSIN

Target: Proteins
Action: Breaks proteins into smaller peptides
Activation: Pepsinogen → activated by HCl
Main role: Protein digestion

CHYMOSIN

Target: Milk proteins (casein)
Action: Coagulates milk in the stomach
Main role: Slows gastric emptying and helps milk digestion
Important in: Infants and newborns

GASTRIC LIPASE

Target: Lipids (triglycerides)
Action: Begins fat digestion by producing fatty acids
Main role: Initial digestion of fats in the stomach

HCl

Action:
- Creates a very acidic environment (pH ~1.5–2)
- Activates pepsin from pepsinogen
- Denatures proteins, making digestion easier
- Helps destroy pathogens and microorganisms introduced with food

Note:
The stomach wall is protected from HCl by a mucus layer

All Produced by: Gastric glands of the stomach

1. Pepsin
Pepsin is the main enzyme involved in gastric digestion.
It is secreted as **pepsinogen** (inactive form);
hydrochloric acid (HCl) activates it by converting pepsinogen into pepsin;
pepsin breaks proteins into smaller chains called peptides.
Therefore:
Proteins → peptides

2. Chymosin
Chymosin (or gastric rennin) is particularly important in infants.
It acts on milk proteins, especially casein;
it causes milk coagulation in the stomach;
this slows gastric emptying and facilitates milk digestion.

3. Gastric Lipase
Gastric lipase begins fat digestion.
It acts on triglycerides;
it breaks them down into:
- fatty acids;
- diglycerides or monoglycerides.

However, fat digestion in the stomach is still limited and continues mainly in the duodenum thanks to pancreatic lipase and bile.

Role of Hydrochloric Acid (HCl)
HCl:

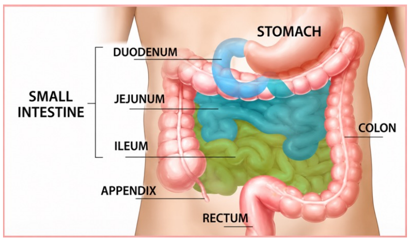
creates a very acidic environment (pH ~1.5–2);
activates pepsin;
denatures proteins, making them easier to digest;
helps destroy microorganisms introduced with food.

Note:
Pepsinogen is the inactive form of pepsin.
It is produced by the chief cells of the gastric glands to prevent the enzyme from digesting the stomach cells.
When pepsinogen enters the gastric lumen, it encounters hydrochloric acid (HCl), which lowers the pH to about 1.5–2.
The highly acidic environment causes a change in the structure of pepsinogen and leads to the removal of a small inhibitory fragment of the protein.
In this way, pepsinogen is converted into its active form:

$$Pepsinogen \underset{low\ pH}{\overset{HCl}{\rightarrow}} Pepsin$$

Once formed, pepsin itself can activate additional pepsinogen molecules. This process is called autocatalysis.

Enteric Digestion in the Duodenum

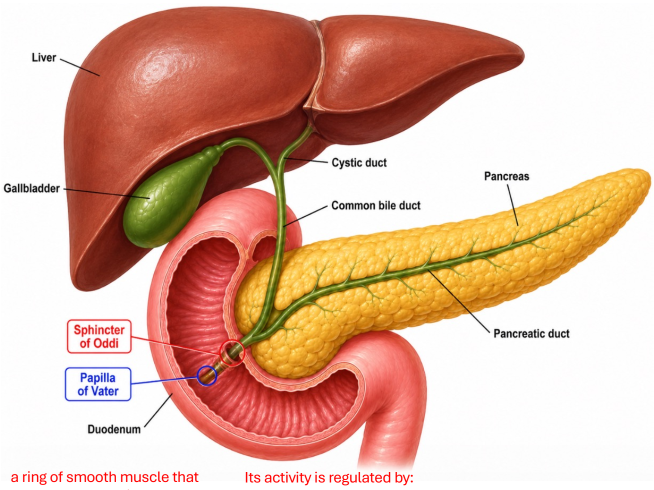


Mechanical digestion ⇨ **Peristaltic movements**

Chemical digestion ⇨
- **pancreatic juice**
- **intestinal juice**
- **bile**

Once digestion in the stomach is completed, nutrients pass into the duodenum.
The duodenum is the first part of the small intestine and begins at the pylorus, the exit of the stomach.
Peristaltic movements continue here and allow the movement of nutrients through the intestine.
In the duodenum, food is attacked by new digestive juices containing additional enzymes:
pancreatic juice, produced by the pancreas;
intestinal juice, produced in the duodenum;
bile, produced by the liver and released into the duodenum for fat digestion.

Pancreatic juice production



a ring of smooth muscle that controls the opening of the ducts

Its activity is regulated by:
- SNA and GI hormones form duodenum

Acinar cells produce the panceratic juice which contains:

- **Digestive enzymes**
- **Bicarbonate**
(to neutralize HCl from the stomach)

Pancreatic juices are produced by the exocrine portion of the pancreas, particularly by the acinar cells.

These juices contain:
digestive enzymes;
bicarbonate, which helps neutralize the acidity coming from the stomach.
Once produced, pancreatic juices enter small ducts inside the pancreas, which merge into the main pancreatic duct.
The pancreatic duct reaches the duodenum and, in most cases, joins the common bile duct coming from the liver and gallbladder.

Together, they entry into the duodenum through a small opening called the:
major duodenal papilla (papilla of Vater)
The entry of pancreatic juices into the duodenum is controlled by the:
sphincter of Oddi (a ring of smooth muscle that controls the opening of the ducts).
Its activity is regulated by the autonomic nervous system (ANS) and by gastrointestinal (GI) hormones, including CCK.
Specifically, when food reaches the duodenum, hormones such as secretin and CCK (cholecystokinin) stimulate the pancreas to release pancreatic juice into the intestine.

Hormones released by duodenum

Secretin

Secretin is produced by the **S cells** of the duodenum.

It is released when highly acidic content coming from the stomach enters the duodenum.
Its main functions are:
•stimulating the pancreas to produce bicarbonate;
•neutralizing gastric acidity.

CCK (Cholecystokinin)

CCK is produced by the **I cells** of the duodenum and jejunum.
It is mainly released when:
•fats;
•proteins
reach the intestine.

Its main functions are:
•stimulating the pancreas to release digestive enzymes;
•causing contraction of the gallbladder;
•relaxing the sphincter of Oddi;
•slowing gastric emptying.

Digestive enzymes of the pancreatic juice

1. Enzymes for carbohydrates
Pancreatic amylase
digests starch and glycogen;
produces smaller sugars (maltose and dextrins).

2. Enzymes for proteins
They are secreted as inactive zymogens to prevent self-digestion of the pancreas.
Trypsin
derived from trypsinogen;
breaks proteins into peptides.
Chymotrypsin
derived from chymotrypsinogen.
Carboxypeptidase
removes amino acids from the ends of peptides.
Elastase
digests elastic proteins.

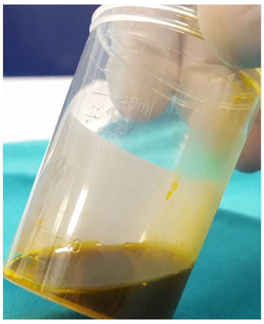
3. Enzymes for lipids
Pancreatic lipase
the main enzyme for triglyceride digestion;
produces fatty acids and monoglycerides.
Phospholipase A2
digests phospholipids.
Cholesterol esterase
hydrolyzes cholesterol esters.

4. Enzymes for nucleic acids
Ribonuclease
digests RNA.
Deoxyribonuclease
digests DNA.

Bile

Produced by: liver
Stored in: gallbladder

released by gallbladder contraction into duodenum upon fats and lipds arrival into duodenum



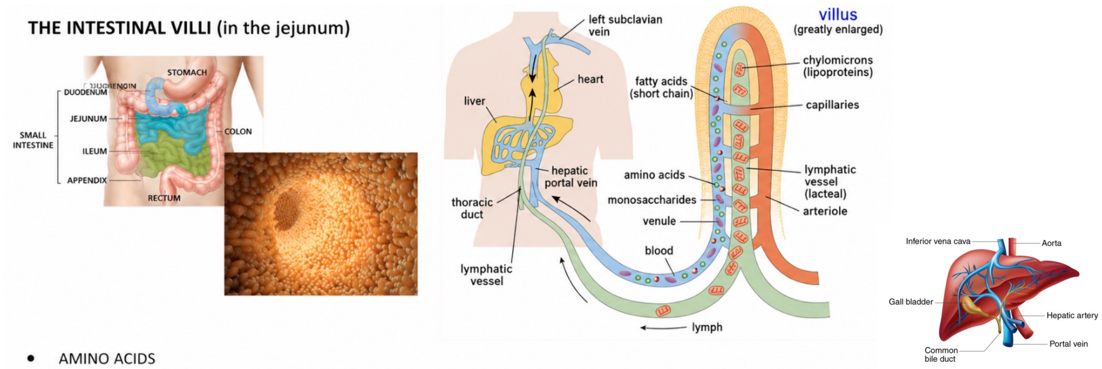
Contains:
- bile salts
- Phospholipids
- Cholesterol
- Bicarbonate

Bile salts function:
emulsification of fats to favour the action of the pancreatic lipases

Bile is produced by the liver and stored in the gallbladder.
When fats and lipids reach the duodenum, the gallbladder contracts and releases bile into the intestine.
Bile does not contain digestive enzymes, but it contains:
bile salts;
phospholipids;
cholesterol;
bicarbonate.
The main function of bile salts is the emulsification of fats.
In practice:
large lipid droplets are broken down into smaller droplets;
this greatly increases the surface area available for the action of pancreatic lipase.
Therefore, bile facilitates the digestion and absorption of fats and fat-soluble vitamins (A, D, E, K).

Absorption

First Phase: Intestinal Villi in the Jejunum



NUTRIENTS

- AMINO ACIDS
- GLUCOSE
- GLYCEROL
- WATER
- MINERAL SALTS

⟹ HEPATIC PORTAL VEIN ⟹ LIVER ⟹ INFERIOR VENA CAVA ⟹ GENERAL CIRCULATION

- FATTY ACIDS ⟹ LYMPHATIC VESSEL ⟹ THORACIC DUCT / LEFT SUBCLAVIAN VEIN ⟹ SUPERIOR VENA CAVA ⟹ GENERAL CIRCULATION

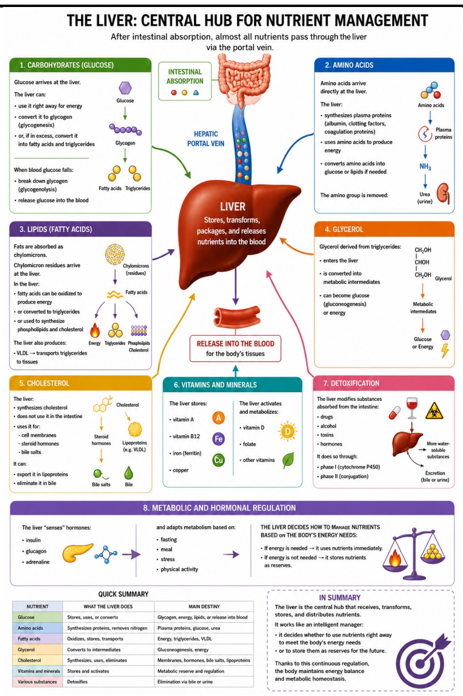
After digestion is completed, absorption begins.
Nutrients have been broken down into smaller molecules:
carbohydrates become glucose;
proteins become amino acids;
fats become fatty acids.
These substances must now leave the intestine and be transported to the cells of the body.

In the second part of the small intestine, the jejunum, there are structures called intestinal villi, which greatly increase the absorption surface.
Inside each villus we find two transport systems:
blood capillaries;
a central lymphatic vessel called the lacteal.

Blood capillaries absorb mainly water-soluble substances, such as:
amino acids;
glucose;
water;
mineral salts;
glycerol;
water-soluble vitamins.
These substances enter the bloodstream and travel through the hepatic portal vein to the liver, where they are further processed and purified. Then, through the inferior vena cava, they reach the heart and are distributed throughout the body.

Fats are different because they are poorly soluble in water and cannot easily enter blood capillaries.
Inside intestinal cells (enterocytes), fatty acids and monoglycerides are reassembled into particles called chylomicrons.
These chylomicrons enter the lymphatic capillary of the villus, the lacteal.
They then follow the lymphatic circulation:

lacteal → lymphatic vessels → thoracic duct → subclavian vein → heart
Therefore, lipids mainly enter the lymphatic system and reach the heart without first passing through the liver.
So, inside the intestinal villi:
the blood system mainly transports water-soluble nutrients;
the lymphatic system mainly transports fats.



The Liver: The Body's Nutrient Distribution Center

After intestinal absorption, almost all nutrients absorbed in the small intestine first reach the liver through the hepatic portal vein.

For this reason, the liver can be considered a true metabolic distribution center: it controls, transforms, stores, and distributes nutrients according to the body's needs.

The liver therefore plays an essential role in maintaining metabolic homeostasis, that is, the body's internal balance.

1. Carbohydrate Metabolism

Glucose absorbed from the intestine rapidly reaches the liver.

Here, the liver determines the fate of this nutrient according to the body's energy requirements.

If the body needs immediate energy, glucose is directly used in cellular metabolic reactions.

When glucose is present in excess, the liver converts it into glycogen through the process of glycogenesis. Glycogen represents a rapidly available energy reserve.

If glycogen stores are already sufficient, excess glucose can be converted into fatty acids and triglycerides, which are then stored in adipose tissue.

When blood glucose levels decrease, for example during fasting, the liver breaks down glycogen through glycogenolysis and releases glucose back into the bloodstream, helping maintain stable blood glucose concentrations.

2. Amino Acid Metabolism

Amino acids derived from protein digestion also reach the liver through the portal vein.

The liver uses these amino acids to:

synthesize plasma proteins, such as albumin and clotting factors;

produce apolipoproteins;

provide energy when necessary;

convert amino acids into glucose during fasting or energy deficiency.

During amino acid metabolism, the amino group containing nitrogen is removed.

This process produces ammonia, a toxic substance that the liver converts into urea through the urea cycle.

Urea is then eliminated by the kidneys through urine.

3. Lipid Metabolism

Fats follow a different pathway compared with other nutrients.

After intestinal absorption, they are transported in the form of chylomicrons through the lymphatic system and later reach the bloodstream.
Chylomicron remnants subsequently arrive at the liver, where lipids can:
be oxidized to produce energy;
be converted into triglycerides;
be used to synthesize phospholipids and cholesterol.
The liver also produces lipoproteins, such as VLDLs, which transport triglycerides to peripheral tissues.
Hepatic lipid metabolism is therefore essential both for energy production and for fat transport throughout the body.
4. Glycerol Metabolism
Glycerol mainly derives from triglyceride breakdown.
In the liver, it is converted into metabolic intermediates that can:
enter glycolysis to produce energy;
participate in gluconeogenesis to generate new glucose.
In this way, the liver can also use products of lipid metabolism to support overall energy metabolism.
5. Cholesterol Metabolism
The liver plays a central role in cholesterol regulation.
It can:
synthesize cholesterol;
recover it from the intestine;
use it to produce cell membranes, steroid hormones, and bile salts.
Bile salts are essential for fat emulsification during digestion.
The liver can also:
export cholesterol through lipoproteins;
eliminate it through bile.
6. Vitamins and Minerals
The liver represents an important storage organ.
It can store:
vitamin A;
vitamin B12;
iron in the form of ferritin;
copper.
In addition, the liver participates in the metabolic activation of several vitamins, such as vitamin D and folates.
This function is essential for ensuring a constant availability of micronutrients even when dietary intake varies.
7. Detoxification
One of the liver's most important functions is detoxification.
The liver modifies potentially harmful substances absorbed from the intestine or present in the bloodstream, such as:
drugs;
alcohol;
toxins;
hormones.
Detoxification occurs in two phases:
Phase I, mainly mediated by cytochrome P450 enzymes;
Phase II, called conjugation.
These processes make substances more water-soluble, facilitating their elimination through bile or urine.
8. Metabolic and Hormonal Regulation
The liver continuously responds to hormonal signals coming from the body.
The main hormones involved include:
insulin;
glucagon;
adrenaline.
Thanks to these signals, the liver adapts metabolism to different physiological conditions:
after a meal, it promotes storage and synthesis;
during fasting, it mobilizes energy reserves;
during stress or physical exercise, it increases glucose and energy availability.
Conclusion
The liver is not only a digestive organ, but also a true metabolic control center.
It receives nutrients from the intestine, analyzes them, transforms them, stores them, or distributes them to tissues according to the body's needs.
Through these activities, the liver maintains the body's energetic, metabolic, and chemical balance, contributing essentially to the survival of the organism.

Chylomicrons

Fatty acids e i monoglycerides enter into enterocytes.

1.I fatty acids e i monoglycerides are transported into the **smooth endoplasmic reticulum**.

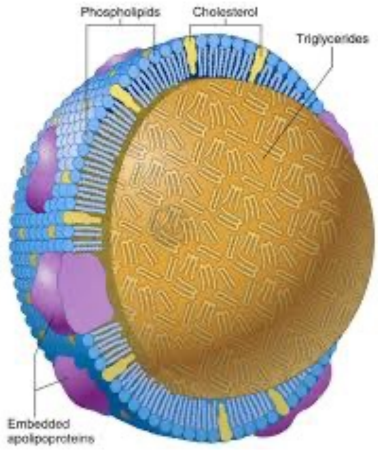
2. Here, they are reassembled to form triglycerides

$$\text{Fatty } acids + Monoglycerides \rightarrow Triglycerides$$

3. Triglycerides are then combined with:

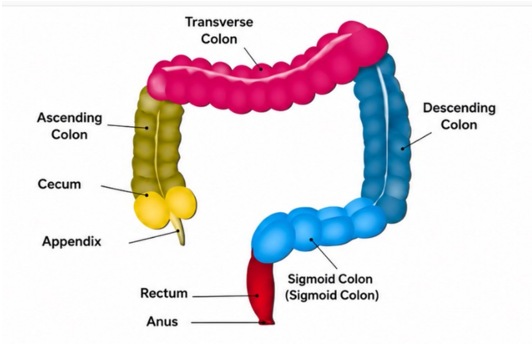
- Phospholipids
- Cholesterol
- special proteins called apolipoproteins

The final result is a large lipid particle called **Chylomicron**



Absorption

Second Phase: Large intestine



- WATER
- MINERAL SALTS
- VITAMINS

- INTESTINAL FLORA

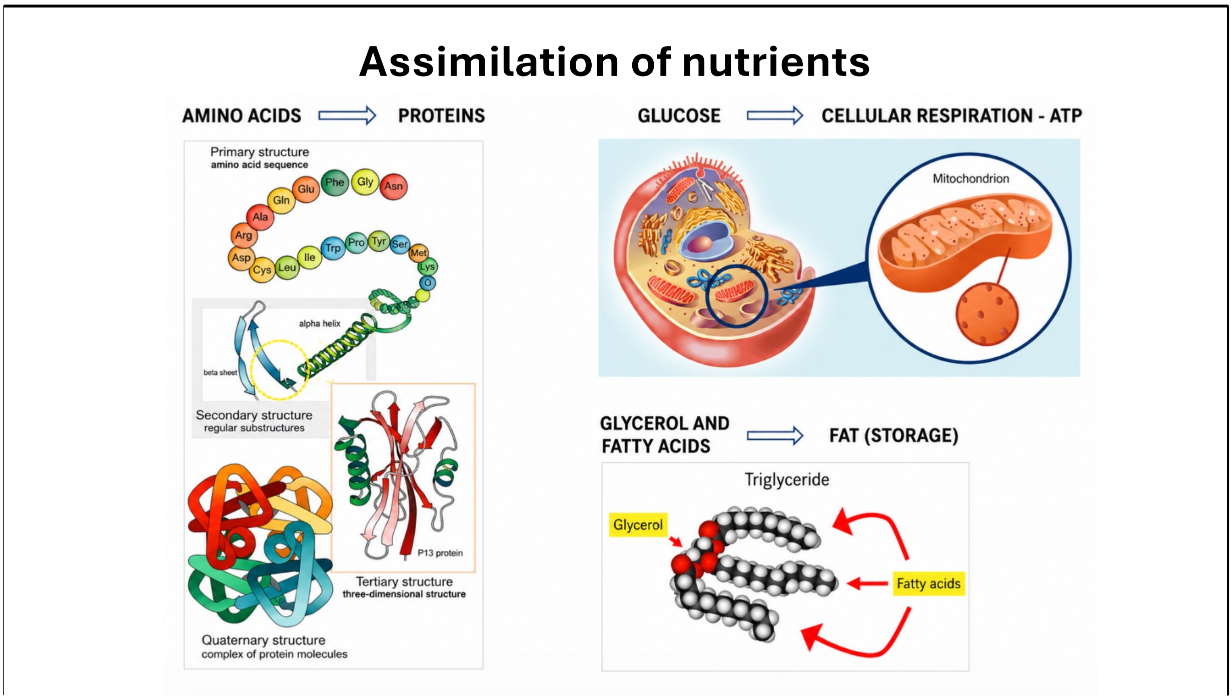
1. help complete digestion

2. produce vitamins that our body cannot synthesize on its own

Absorption – Second Phase
The substances that remain in the intestine continue the absorption process in the large intestine.
The large intestine comprises:
•**cecum colon** ascending colon
•transverse colon
•descending colon
•sigmoid colon
rectum anal canal

Here, the following are reabsorbed:
water;
mineral salts;
vitamins.

The intestinal flora, or microbiota, also plays an important role. It is made of bacteria living in symbiosis with our body.
These bacteria:
feed on digestive residues;
help complete digestion;
produce vitamins that our body cannot synthesize on its own.



At this point, nutrients have entered the circulation and reached all the cells of the body.
Amino acids are used to build proteins.
Glucose enters the cells and is used in the mitochondria during cellular respiration to produce ATP, which is chemical energy.
Glycerol and fatty acids are used to build fat reserves.
The cellular use of substances obtained from food is called **assimilation**.