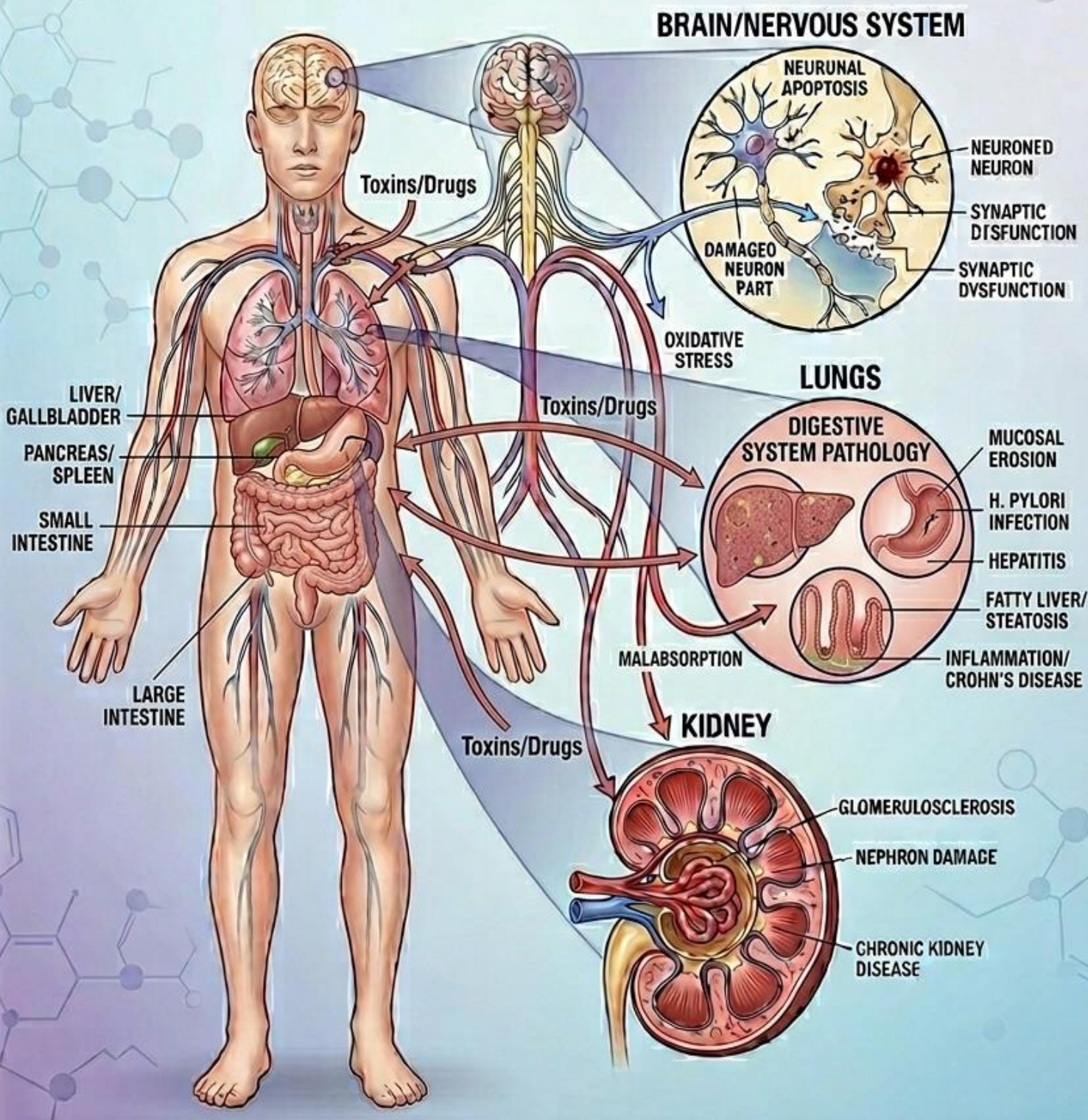
# PHYSIOPATHOLOGY OF MAJOR FUNCTIONS

## MASTER I PHARMACOTOXICOLOGY

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# Physiopathology of Major Functions

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MASTER I PAHRAMACOTOXICOLOGY

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# Canevas du module

Intitulé du Master: Pharmacotoxicologie

Semestre : 1

Intitulé de l'UE : Découverte

Intitulé de la matière 1 : Physiopathologie des grandes fonctions

Crédits : 2

Coefficients : 2

Objectifs de l'enseignement :

Cette matière donne aux étudiants les notions : les organes et leurs physiologie aussi les anomalies et les maladies de ces organes (dysfonctionnement)…etc.

Connaissances préalables recommandées :

Pour permettre aux étudiants de suivre cette matière il est recommandé de connaitre les notions en biologie cellulaire, biologie animale et physiologie.

Contenu de la matière :

I- Physiopathologie du Tube Digestif

II- Physiopathologie du Foie

III- Physiopathologie du Rein

IV- Physiopathologie du Poumon

V- Hématotoxicité et physiopathologie de système lymphatique

VI- Neurotoxicité

VII- Toxicité Embryonnaire

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Chapter VII: Embryotoxicity

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# Physiopathology of Gastrointestinal Tract

# I.1. Generalities on the gastrointestinal system

The gastrointestinal (GI) tract comprises essential digestive organs and accessory structures (Figure 1). Key GI structures include the mouth, pharynx, oesophagus, stomach, small intestine, large intestine, and anus. Accessory organs supporting GI function are the salivary glands, liver, gallbladder, and pancreas.

The GI tract is divided into upper and lower segments. Digestion begins in the upper GI tract's mouth (oral cavity). The mouth contains various structures, including teeth that facilitate chewing and tearing food. Permanent teeth replace primary teeth around age six. Adults have 32 permanent teeth: 16 in the upper maxilla and 16 in the lower mandible. The muscular lips and cheeks are connective tissue structures lined with mucus-secreting stratified squamous epithelial cells, offering protection against abrasion caused by wear and tear.

Lips and cheeks facilitate the movement and retention of food within the mouth, while the teeth tear and grind it. This process, known as mastication or chewing, is a mechanical action. Lips and cheeks also contribute to speech and facial expression.

The tongue, a muscular organ, is covered in moist, pink mucosa. It is characterized by numerous papillae, small bumps that provide a rough texture and house thousands of taste buds, which are responsible for the sensation of taste.

The tongue, a muscular organ covered in moist, pink mucosa (lining tissue), plays a critical role in taste perception. Tiny bumps called papillae dot its surface, each housing taste buds that transmit taste sensations to the brain. The tongue also aids in chewing, swallowing, and speech.

The roof of the mouth, or palate, consists of two distinct regions: the hard, bony portion in the front and the soft, muscular portion in the back. The soft palate, along with the uvula (a small, teardrop-shaped projection), assists with swallowing. Located on the sides of the palate are the palatine tonsils, composed of lymphoid tissue.

Salivary glands, responsible for saliva production, are scattered throughout the mouth. These glands release a fluid containing water, electrolytes, mucus, and enzymes to moisten food, initiate digestion, and lubricate the passage through the digestive tract.

Upon thorough chewing (mastication) and mixing with saliva, food transforms into a soft mass called a bolus. This bolus then travels down the oesophagus, a muscular tube connecting the mouth to the stomach. The oesophagus secretes mucus to ease the bolus's passage and protect its lining. Two sphincter muscles regulate the flow of materials: the upper oesophagal sphincter controls entry, while the lower oesophagal sphincter (also known as the cardiac sphincter) governs the passage from the oesophagus to the stomach.

The oesophagus exhibits a unique muscular composition. The upper portion comprises voluntary skeletal muscle, allowing for conscious control during swallowing. In contrast, the lower portion comprises involuntary smooth muscle, enabling a more automated process.

The stomach, a muscular sac-like organ located in the upper left abdomen, receives food from the oesophagus. A muscular valve, the lower oesophagal sphincter, regulates food entry into the stomach (see Figure 3). The stomach's blood supply and nerve connections are vital for its functions. Arterial blood comes from the celiac artery, and venous blood drains through the hepatic vein. The vagus nerve provides parasympathetic stimulation, enhancing stomach movement (motility) and juice secretion. Conversely, the sympathetic nervous system plays a role in regulating stomach activity during stress responses.

The lower gastrointestinal tract, following the stomach, is the small intestine, where most digestion and absorption occur. It consists of three sections: the duodenum, jejunum, and ileum. The small intestine receives blood supply from the superior mesenteric artery and is innervated by both sympathetic and parasympathetic nerves.

The duodenum, measuring 25 cm, connects to the stomach and is primarily responsible for food breakdown using enzymes. Its inner wall's large surface area, lined with villi, facilitates efficient absorption. The duodenum controls stomach emptying through hormones secretin and cholecystokinin.

The jejunum, larger and more vascular than the duodenum, has longer villi and circular folds for increased nutrient absorption.

The ileum, the final and longest segment, absorbs vitamin B12 and bile salts. It measures around 4 meters and connects to the large intestine at the ileocecal valve. The mesentery suspends the ileum from the abdominal wall, and its peristaltic contractions are slower than other intestinal parts.

The large intestine, also known as the colon, is wider and shorter than the small intestine. It consists of four regions: the caecum, colon, rectum, and anus. Enzymes from the small intestine complete digestion in the upper half of the large intestine, while bacteria produce B vitamins. The large intestine's mucosa secretes mucus to facilitate faecal passage and protect the colon walls. The anus also secretes mucus to protect the anal canal.

The ileum's food residue enters the caecum as a fluid with minimal nutrients. While the small intestine absorbs some water, the primary function of the large intestine is water absorption, transforming food residue into semi-solid faeces. Additionally, the large intestine absorbs certain vitamins, minerals, electrolytes, and drugs.

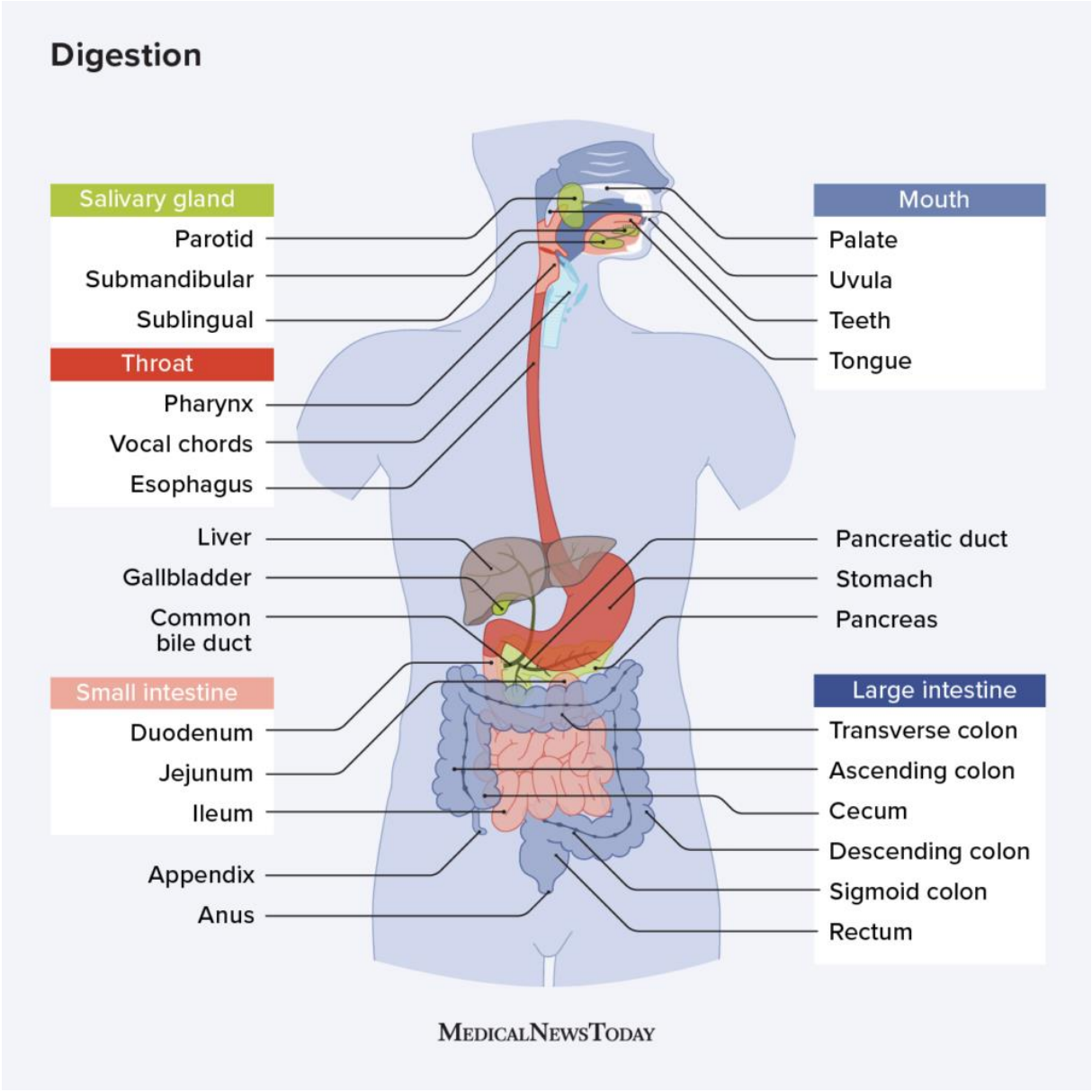



**Figure 1. The gastrointestinal tract.**

## I.2. Tongue

The tongue plays a crucial role in both internal and external sensory perception. Despite its visibility, it remains relatively understudied, with contradictory or incomplete information in existing literature. The tongue functions as both a motor organ, involved in speech and chewing, and a sensory organ, transmitting information about the oral cavity's contents to the central nervous system. Moreover, the tongue and its taste apparatus serve as part of the innate immune system. A prime example is the alteration or loss of taste perception, often an early indicator of infection, as observed during the SARS-CoV-2 pandemic.

The tongue is divided into two main sections: the root (radix lingue) at the back and the body (corpus lingue) at the front. The root is covered in mucous glands and lymphatic tissue, forming the lingual tonsil, and lacks papillae. The body of the tongue houses the three types of taste papillae. Circumvallate papillae are arranged in a V-shape at the tongue's back. Foliate papillae are ridges and slits located along the tongue's sides. Fungiform papillae, the most numerous, are scattered across the tongue's front surface, interspersed with filiform papillae. Both types are less common along the tongue's edges and more abundant in the central regions (Figure 2).

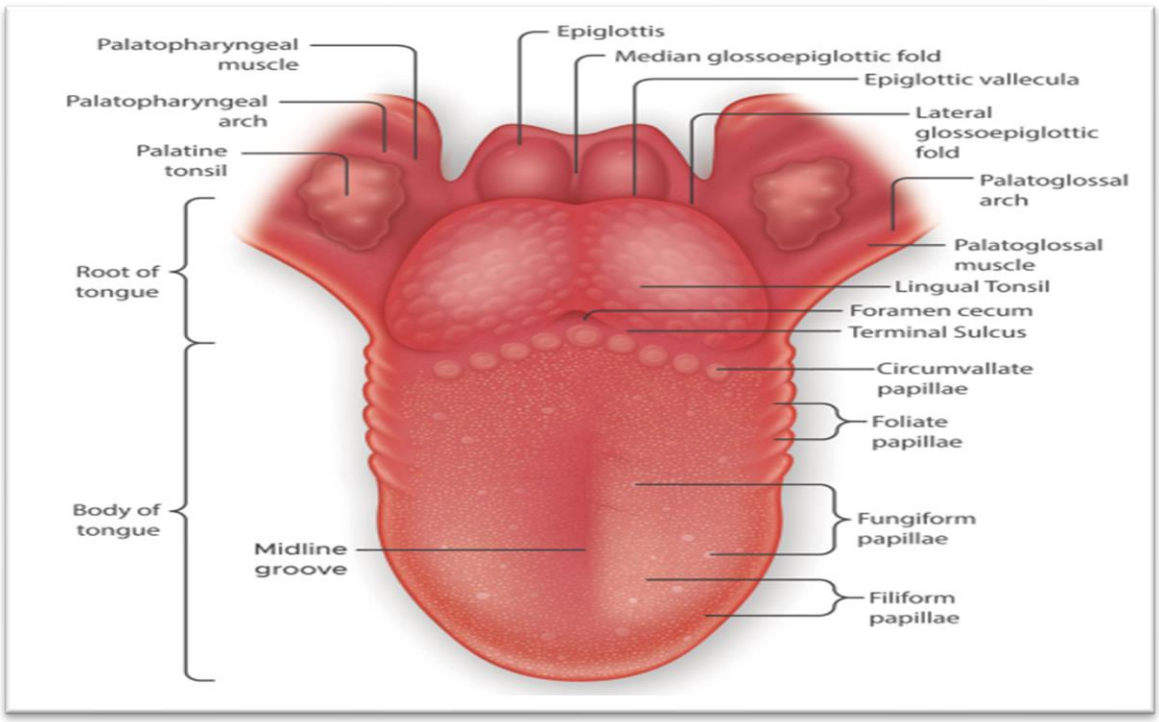



**Figure 2. Gross anatomy of the human tongue**

The distribution of taste buds on the tongue has been a subject of debate for centuries, with the popular belief that certain areas of the tongue are more sensitive to specific tastes (sweet, sour, salty, bitter, and umami). However, recent research has shown that all five basic tastes can be detected by taste buds all over the tongue.

While there may be slight variations in sensitivity to certain tastes in different regions of the tongue, these differences are not as pronounced as previously thought. Taste perception is influenced by a variety of factors, including the concentration of the taste stimulus, the presence of other tastes, and individual differences in taste sensitivity.

**The taste buds**, which are specialized receptors for the sense of taste, are widely distributed throughout the oral cavity. While the majority of our 10,000 taste buds are located on the tongue, they can also be found in other areas of the mouth.

**Papillae**, small peg-like projections, cover the dorsal surface of the tongue. Circumvallate and fungiform papillae are two types of papillae that contain taste buds. The circumvallate papillae are larger, round structures located at the back of the tongue, while the fungiform papillae are smaller and more numerous, found on the top of the tongue.

**Gustatory cells**, epithelial cells in the taste buds, are responsible for responding to chemicals dissolved in saliva. These cells have long microvilli, called gustatory hairs, that protrude through the taste pore. When stimulated, these hairs depolarize and transmit impulses to the brain.

**The facial nerve (VII)** innervates the anterior part of the tongue, while the glossopharyngeal and vagus nerves innervate the other taste bud-containing areas.

Taste bud cells are among the most dynamic cells in the body, undergoing rapid turnover. They are replaced every seven to ten days by basal cells located in the deeper regions of the taste buds (Figure 3).

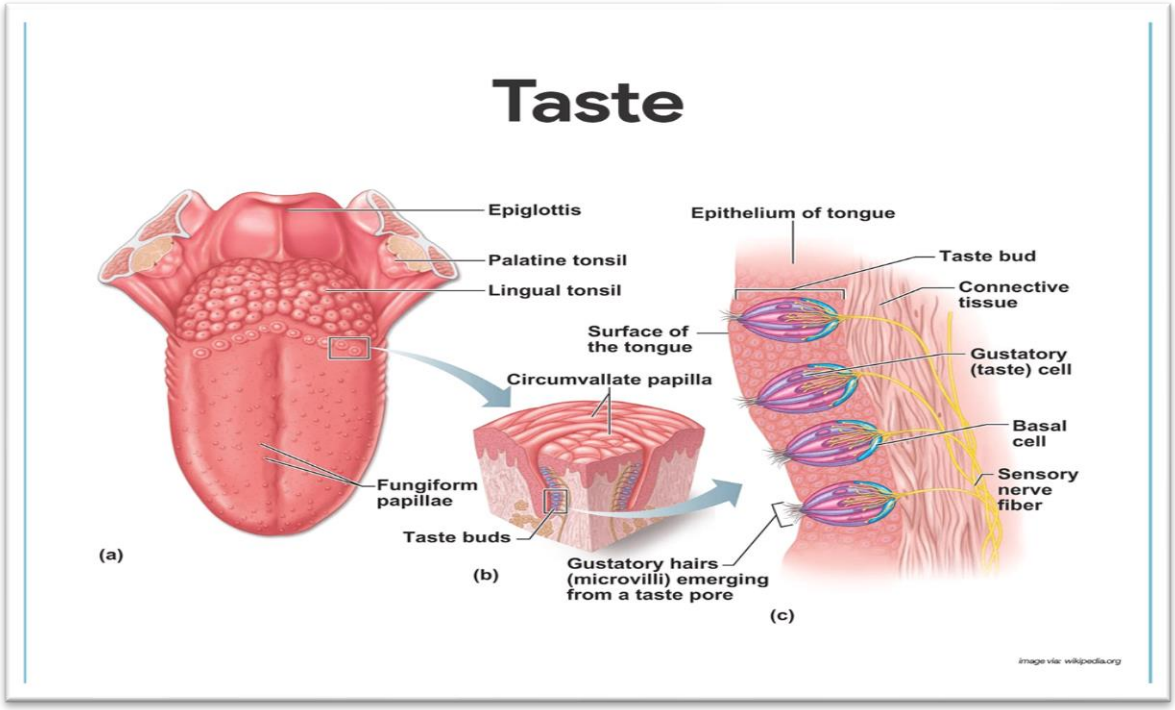



**Figure 3. Taste buds' location**

## I.2.1. Taste sensation mechanism

The low-sodium-sensing cell is depolarized by the influx of sodium ions (Na+) through amiloride-sensitive epithelial sodium channels (ENaC). Additional sodium influx through voltage-gated sodium channels (VGNaC) generates an action potential that ultimately leads to the release of ATP through CALHM1/3 channels, independent of intracellular calcium (Ca2+).

In the perception of sweet, bitter, and umami tastes, tastants bind to cell surface G protein-coupled receptors (GPCRs), initiating a signaling cascade involving phospholipase Cβ2 (PLCβ2) and inositol 1,4,5-trisphosphate (IP3). IP3 mobilizes Ca2+ from the endoplasmic reticulum (ER) by activating the IP3 receptor type 3 (IP3R3), increasing intracellular Ca2+ concentration. The rise in intracellular calcium activates transient receptor potential cation channel subfamily M member 5 (TRPM5) channels, which depolarize the plasma membrane and create action potentials through voltage-gated sodium channels (VGNaC). These changes in membrane potential and increased intracellular Ca2+ trigger the release of ATP into the channel synapse through CALHM1/3 channels, stimulating the gustatory neuron and completing the signal transduction from the taste cell to the afferent nerve (Figure 4).

The perception of sour taste involves a series of events initiated by the OTOP1 receptor, which detects protons (H+ ions) from acidic substances. The influx of protons into the taste bud cell depolarizes the membrane, blocking potassium channels and triggering action potentials. These electrical signals lead to the release of the neurotransmitter serotonin, which activates afferent nerve fibres, ultimately transmitting the sour taste sensation to the brain.

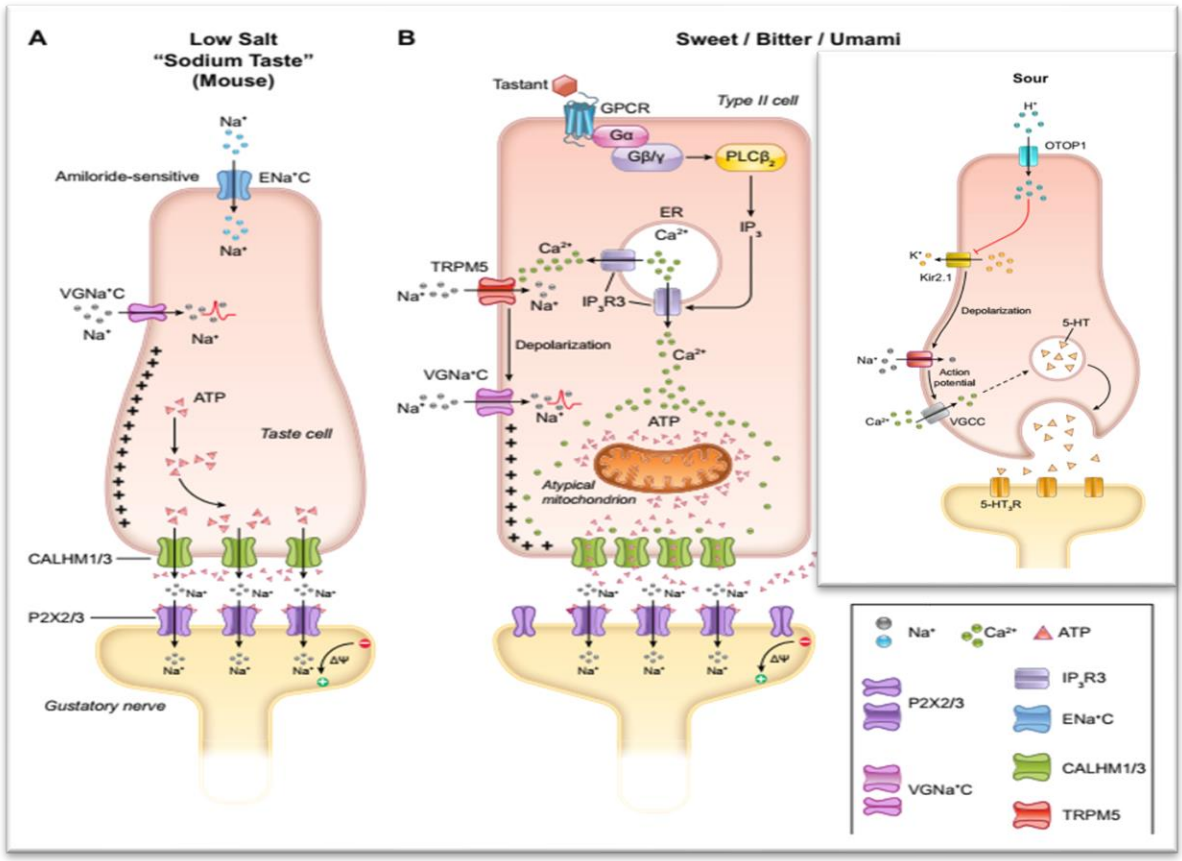



**Figure 4. Taste mechanism and signalling.**

# I.3. Salivary Glands

Three pairs of large salivary glands contribute to saliva formation, in addition to the numerous small glands in the oral mucosa. They are located outside the mouth and release their secretions into the oral cavity through ducts (Figure 5). There are two groups of salivary glands: accessory glands, consisting of a few clusters of secretory elements located in the chorion of the oral cavity and in the connective tissue septa separating the muscles of the tongue, and the main glands, composed of numerous secretory elements and excretory ducts, represented by the parotid glands, submandibular glands, and sublingual glands.

The parotid gland is located in front of and below the ear, between the skin and the masseter muscle. Its excretory duct (parotid duct or Stensen's duct) ends in the vestibule of the mouth at the level of the second upper molar. They possess only serous secretory elements in the form of acini composed of pyramidal cells delimiting a very small lumen. Each cell is polarized with an apical pole where the secretory granules (enzymatic proteins: amylase, maltase, ribonuclease) are located and a basal pole rich in organelles necessary for protein synthesis where the nucleus is located. The acini are surrounded by myoepithelial cells. The excretory ducts end in a single duct that opens into the oral cavity.

The submandibular gland is located below the muscles of the floor of the mouth on the inner surface of the lower jaw. The excretory duct opens under the tongue at a small elevation near the frenulum. They have a predominance of serous elements, identical to those of the parotid gland, and mucous elements which are generally associated with a layer of serous cells: thus, the mucous tubules end in a serous crescent (Giannuzzi's crescent). The mucous tubules are elongated formations with a larger lumen than that of the acini. The glandular cells are prismatic and the apical pole is filled with mucus which pushes the nucleus and organelles towards the basal membrane. In routine staining, the cytoplasm of mucous cells appears clear.

The sublingual gland is located directly on the musculature of the floor of the mouth. It has several short excretory ducts that open on both sides of the tongue and a larger duct that ends at the level of the frenulum of the tongue with that of the submandibular gland. They are composed only of mucous tubules; the excretory elements are identical to those of the parotid and submandibular glands.

Salivary secretion is primarily controlled by neural influences, with the parasympathetic nervous system playing a dominant role. While sympathetic input slightly modifies saliva composition, particularly by increasing protein content, it has minimal effect on volume. Chewing triggers reflexes that stimulate saliva secretion, but the anticipation of a meal can also initiate

secretion through central triggers. This conditioned response, as demonstrated by Pavlov's experiments, links a neutral stimulus (e.g., a bell) to a physiological response (salivation). Salivary secretion is also stimulated by nausea but inhibited by fear or during sleep. Sensory stimuli such as smell, taste, sound, sight, and pressure in the mouth activate the salivatory nuclei in the brainstem. Parasympathetic fibers then travel to the otic and submandibular ganglia, where they release acetylcholine. This neurotransmitter stimulates salivary gland activity, leading to increased saliva production and vasodilation. Factors like sleep, fatigue, and fear can influence salivary secretion (Figure 5).

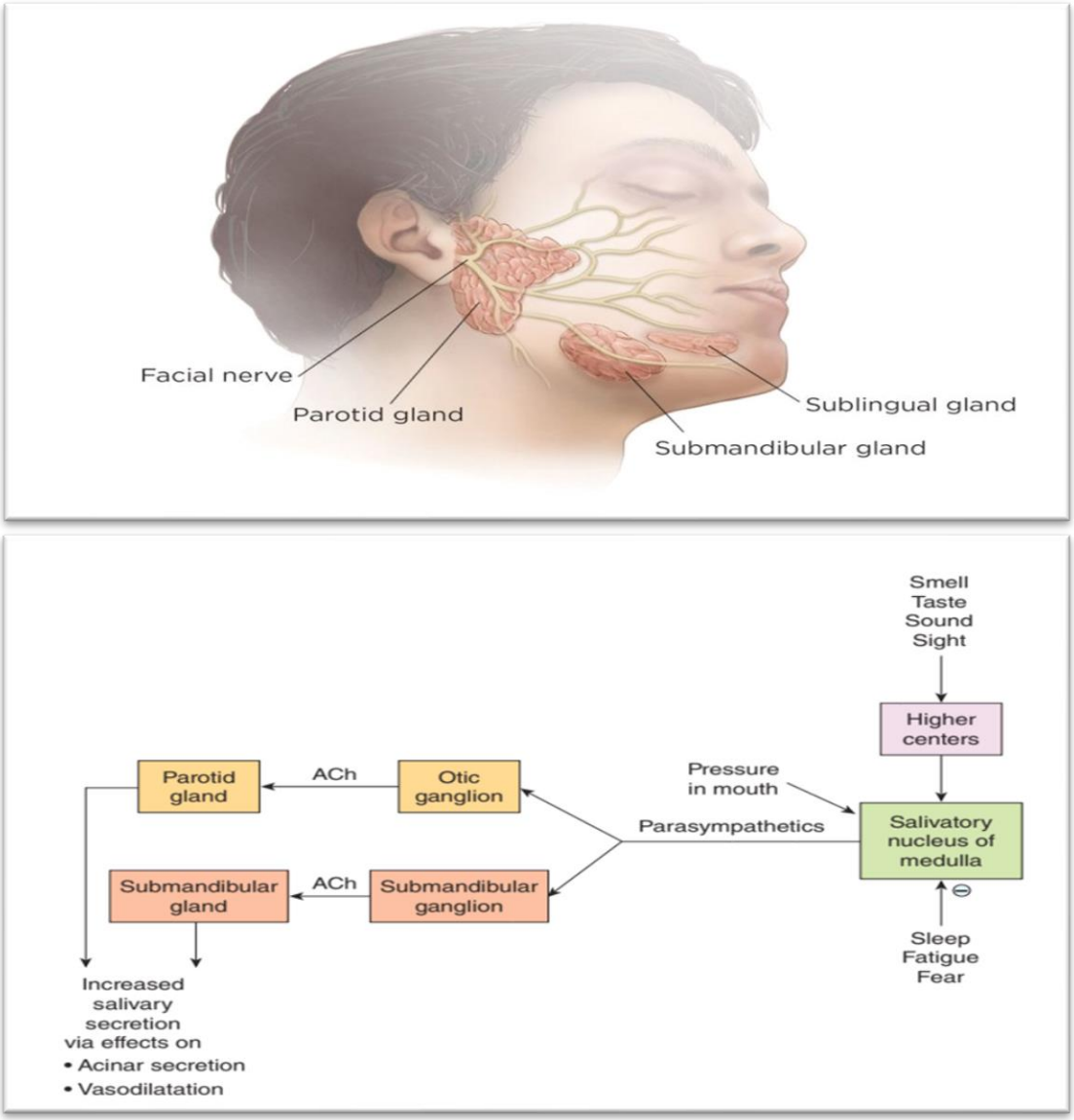



**Figure 5. Salivary Glands anatomy and the parasympathetic nervous system's regulation of salivary secretion**

## I.4. Oesophagus

The oesophagus is a muscular tube connecting the mouth to the stomach. The oesophagus is divided into cervical, upper thoracic, middle thoracic, and lower thoracic portions, extending approximately 40 cm in length. Key landmarks include the sternal notch, azygous vein, and inferior pulmonary vein. The upper oesophageal sphincter controls entry into the oesophagus, while the lower oesophageal sphincter, or gastroesophageal junction, regulates passage into the stomach. The oesophagus's muscular wall propels food through peristaltic contractions (Figure 6).

Peristalsis, a wave-like muscular contraction, propels food through the digestive tract. The food bolus moves through areas of contraction while relaxing adjacent areas. This coordinated movement occurs in the oesophagus, stomach, small intestine, and large intestine, facilitating digestion and nutrient absorption.

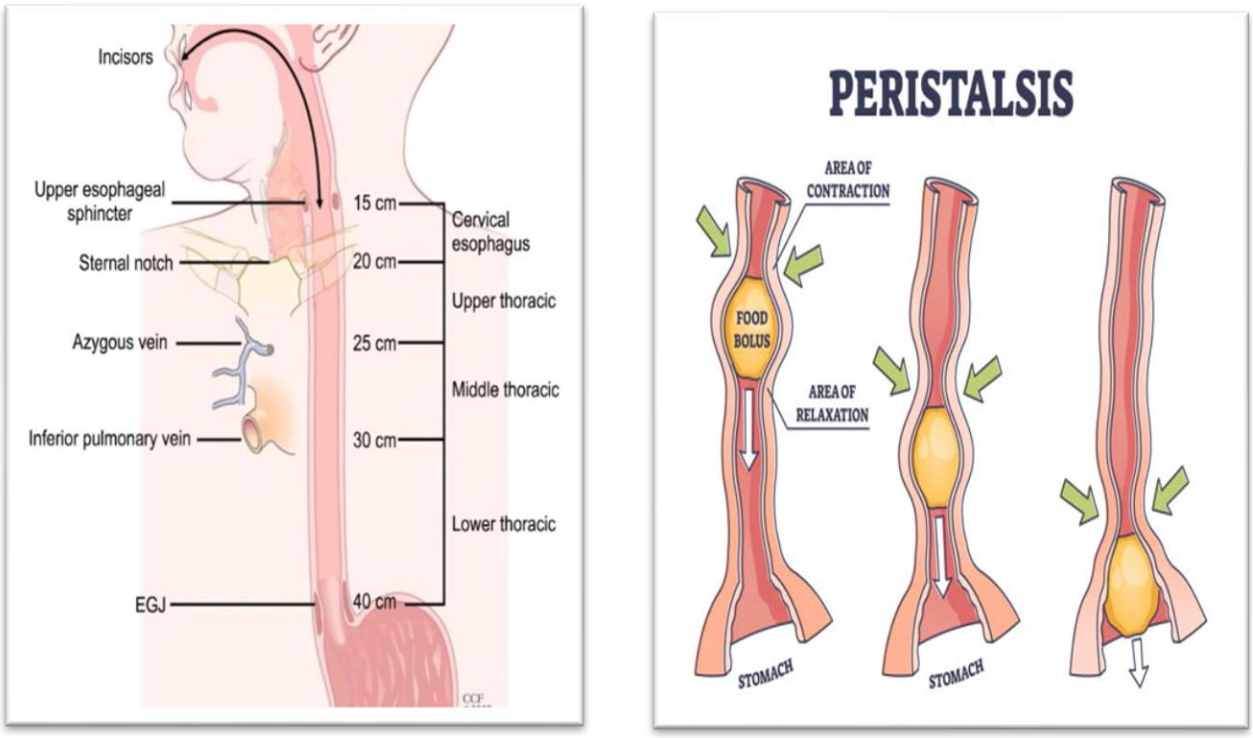



**Figure 6. Anatomy of the esophagus and Peristalsis**

## I.5. Innervation of the Gastrointestinal Tract

The innervation of the gastrointestinal (GI) tract, which involves a complex network of nerves. The central nervous system, specifically the brain and spinal cord, coordinates this innervation. Extrinsic nerves, such as the vagal and splanchnic nerves, connect the central nervous system to

the GI tract. The enteric nervous system, located within the GI tract walls, plays a key role in regulating its functions. The parasympathetic nervous system, originating in the brainstem, and the sympathetic nervous system, originating in the spinal cord, both send fibers to the enteric nervous system. This intricate network ensures coordinated control of GI motility, secretion, and blood flow (Figure 7).

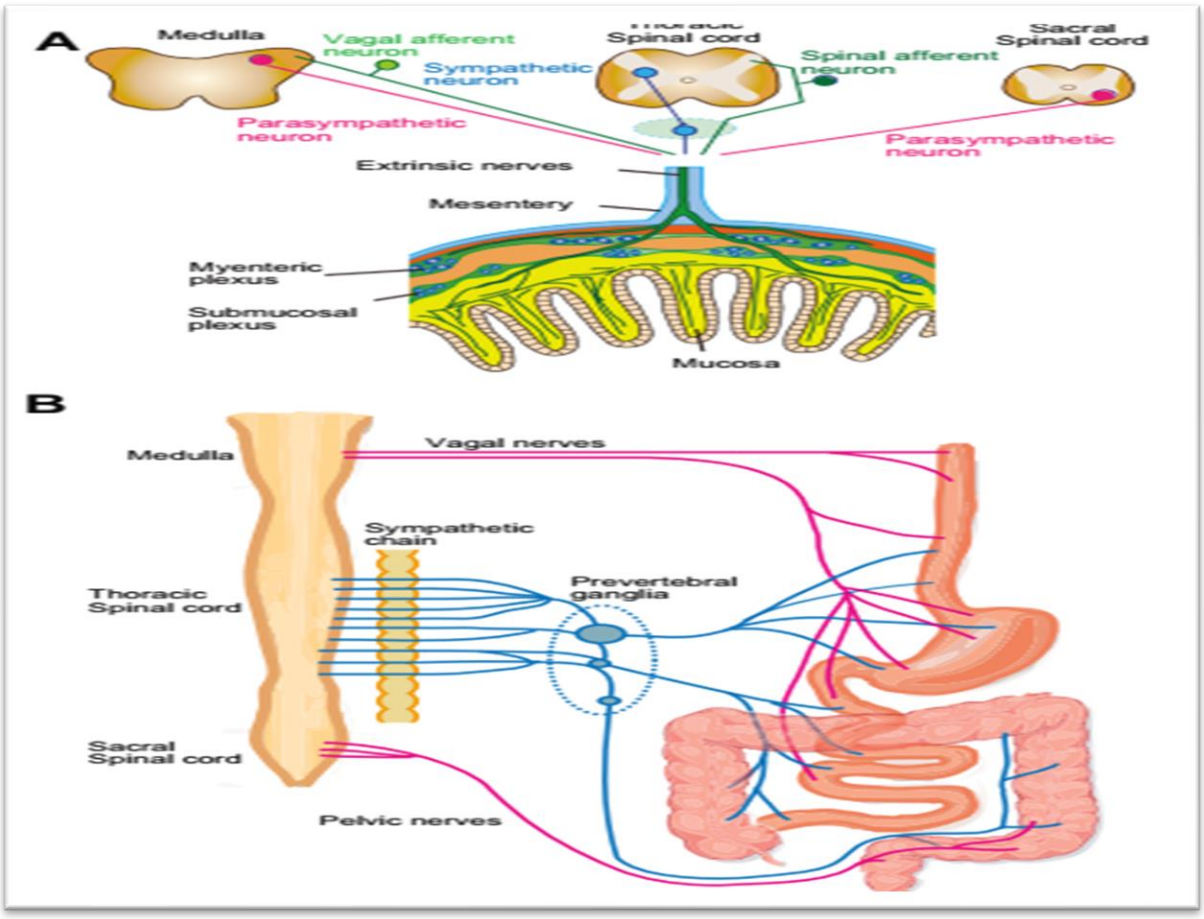



**Figure 7. Innervation of gastrointestinal tract.**

## Innervation of intestine

The intestine is a long, muscular tube that is divided into three sections: the duodenum, the jejunum, and the ileum. It is part of the gastrointestinal (GI) tract and is responsible for most of the digestion and absorption of nutrients (Figure 8).

* **Mucosa**: This is the innermost layer of the small intestine. It is lined with a mucous epithelium that helps to protect the intestine from damage. The mucosa also contains villi, which are tiny finger-like projections that increase the surface area for absorption.

* **Submucosa**: This is the middle layer of the small intestine. It contains blood vessels, nerves, and lymphatic vessels. It also contains glands that secrete mucus and digestive enzymes.
* **Muscularis**: This is the outermost layer of the small intestine. It is composed of two layers of smooth muscle: a circular muscle layer and a longitudinal muscle layer. These muscles contract to propel food through the small intestine.
* **Serosa**: This is the outermost layer of the small intestine. It is a thin membrane that covers and protects the intestine.

The intestine is also innervated by the enteric nervous system, which is a network of nerves that controls the movement of food through the intestine and the secretion of digestive enzymes. The enteric nervous system is regulated by the autonomic nervous system, which is part of the peripheral nervous system.

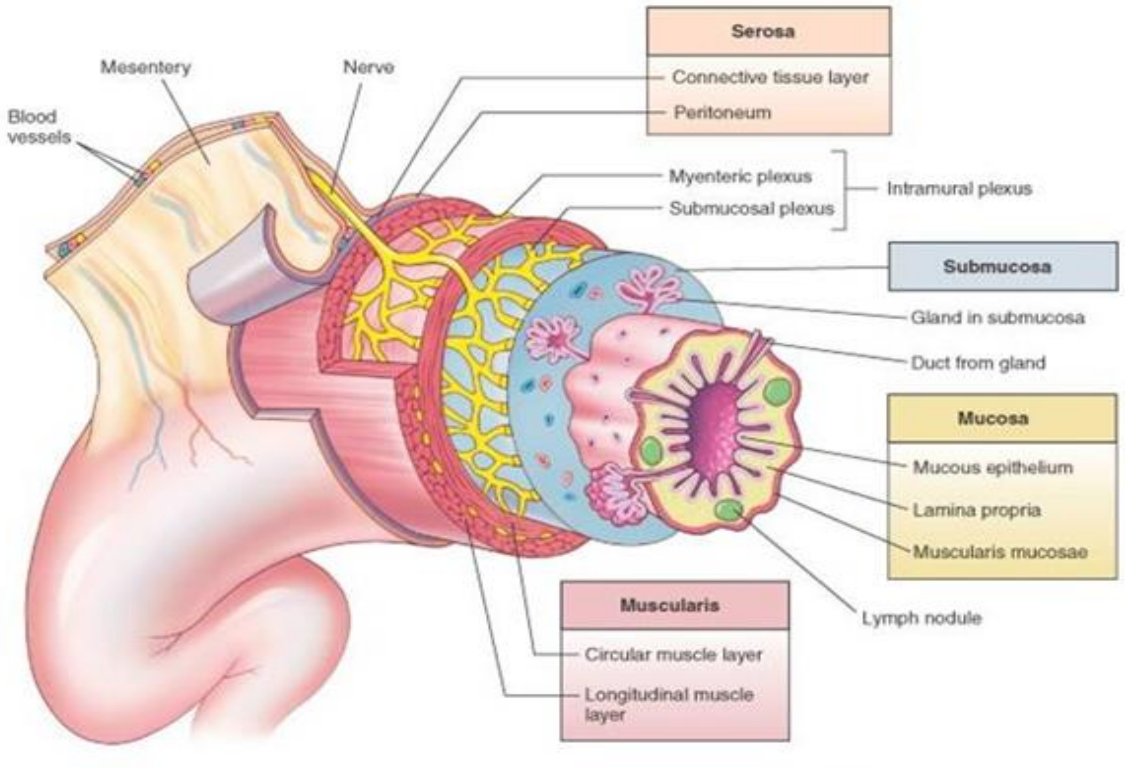



**Figure 8. Anatomy and innervation of the intestine**

The enteric nervous system (ENS, Figure 9) is a complex network of neurons and glial cells located within the walls of the gastrointestinal (GI) tract. It is often referred to as the "second brain" because of its extensive network and ability to function independently of the central nervous system (CNS). The ENS plays a crucial role in regulating various GI functions, including:

Motility: The ENS controls the movement of food through the GI tract through peristalsis, which are rhythmic contractions of the muscular walls.

Secretion: The ENS regulates the secretion of digestive enzymes, mucus, and hormones.

Blood flow: The ENS controls blood flow to the GI tract, ensuring adequate oxygen and nutrient supply.

Sensation: The ENS is responsible for sensing changes in the GI tract, such as the presence of food, changes in pH, and distension.

The ENS is composed of two major plexuses: Myenteric plexus: This plexus is located between the circular and longitudinal muscle layers of the GI tract. It is responsible for controlling GI motility. Submucosal plexus: This plexus is located in the submucosa, beneath the muscularis externa. It is responsible for controlling secretion and blood flow. The ENS receives input from the CNS via the vagus nerve and the splanchnic nerves. However, the ENS can also function independently, integrating sensory information from the GI tract and generating appropriate responses.

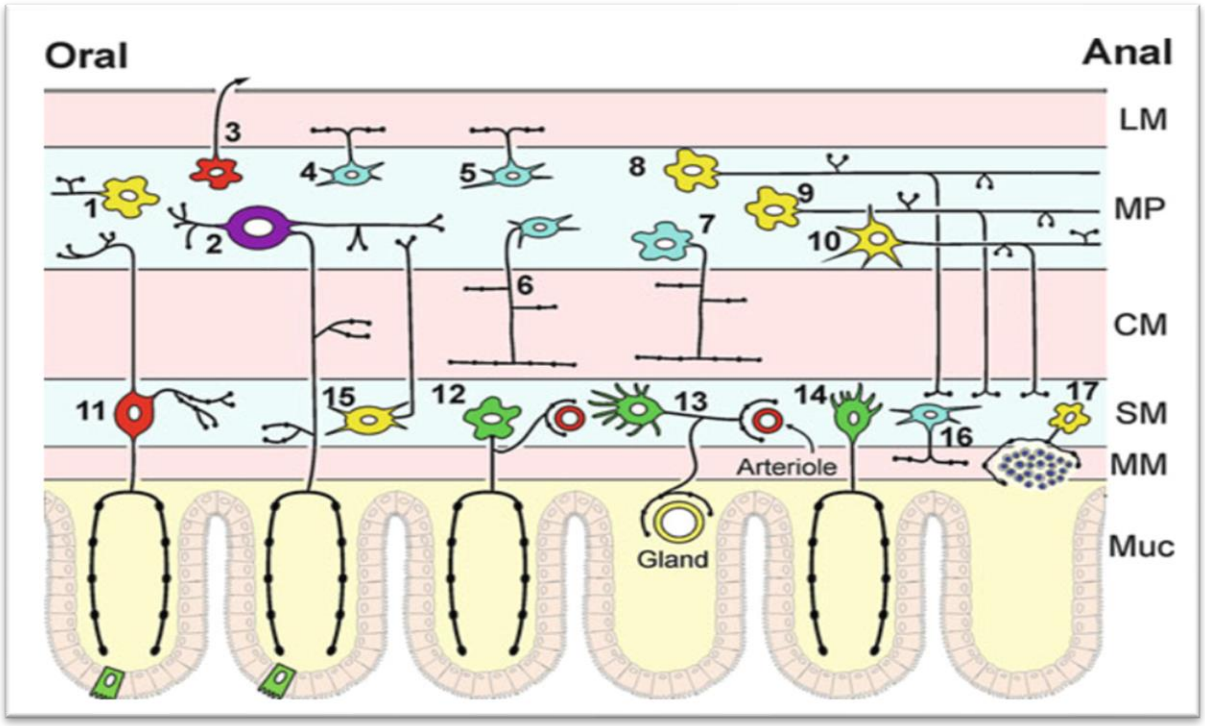



**Figure 9. Neuron types in the ENS.**

The types of neurons in the small intestine, that have been defined by their functions, cell body morphologies, chemistries, key transmitters and projections to targets. LM longitudinal muscle, MP myenteric plexus, CM circular muscle, SM submucosal plexus, Muc mucosa. Neuron Types: Ascending interneurons (1); Myenteric intrinsic primary afferent neurons (IPANs) (2); Intestinofugal neurons (3); Excitatory longitudinal muscle motor neurons (4); Inhibitory longitudinal muscle motor neurons (5); Excitatory circular muscle motor neurons (6); Inhibitory circular muscle motor neurons (7); Descending interneurons (local reflex) (8); Descending interneurons (secretomotor and motility reflex) (9); Descending interneurons (migrating myoelectric complex) (10); Submucosal IPANs (11); Non-cholinergic secretomotor/vasodilator neurons (12); Cholinergic secretomotor/vasodilator neuron

(13); Cholinergic secretomotor (non-vasodilator) neurons (14); Uni-axonal neurons projecting to the myenteric plexus (15); motor neuron to the muscularis mucosa (16); innervation of Peyer's patches (17).

## I.6. Smooth muscles contraction

As vascular smooth muscles, the intestinal smooth muscle cells contract via a signaling pathways involving calcium rising inside the cell. Contractile neuro-transmitters bind to receptors on the cell membrane, activating G proteins and triggering the phospholipase C (PLC) pathway. PLC catalyzes the breakdown of phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). DAG activates protein kinase C (PKC), while IP3 releases calcium from intracellular stores. Increased calcium levels can also result from calcium influx through L-type calcium channels. Calcium binds to calmodulin, activating myosin light chain kinase (MLCK). MLCK phosphorylates myosin light chain (MLC20), leading to its interaction with actin filaments and muscle contraction. Relaxation occurs through the removal of calcium from the cell and the dephosphorylation of MLC20. This intricate process involves a complex interplay of signaling molecules and cellular mechanisms, ensuring precise regulation of vascular tone and blood flow (Figure 10).

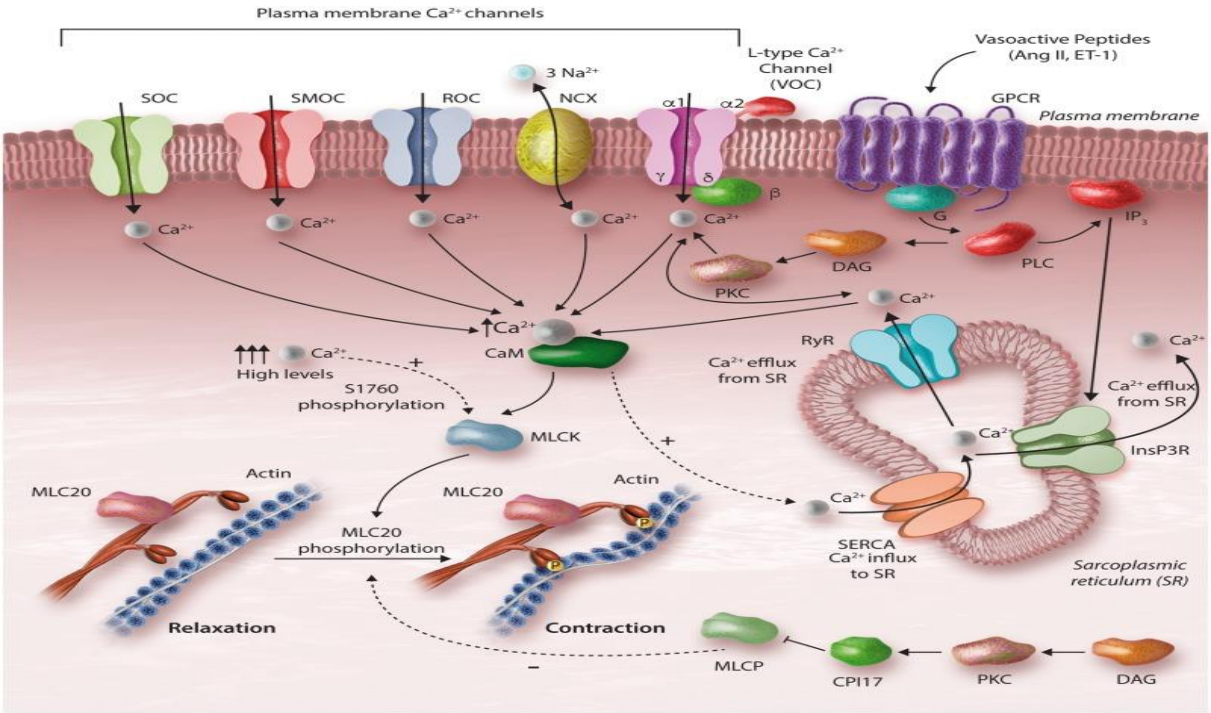



**Figure 10. Contractile signaling pathway of smooth muscle.**

# I.7. Stomach

The stomach is a sac-like organ that stores food and aids in digestion (Figure 11). It receives food from the esophagus and releases it into the small intestine. The stomach's shape varies depending on its fullness and body position.

The stomach has three main functions: 1) storing food until it can be properly digested and absorbed, 2) secreting hydrochloric acid and enzymes to initiate protein digestion, and 3) mixing food with gastric juice to create chyme, a thick mixture that can pass into the duodenum.

The entrance to the stomach is called the cardia, and the dome-shaped upper portion is called the fundus. The main body of the stomach is followed by the antrum, and the exit point to the small intestine is called the pylorus.

The muscular layer of the stomach has three layers of muscle fibers (longitudinal, circular, and transverse), allowing it to contract in various ways. These contractions help to mix food, break it down, and move it towards the pylorus.

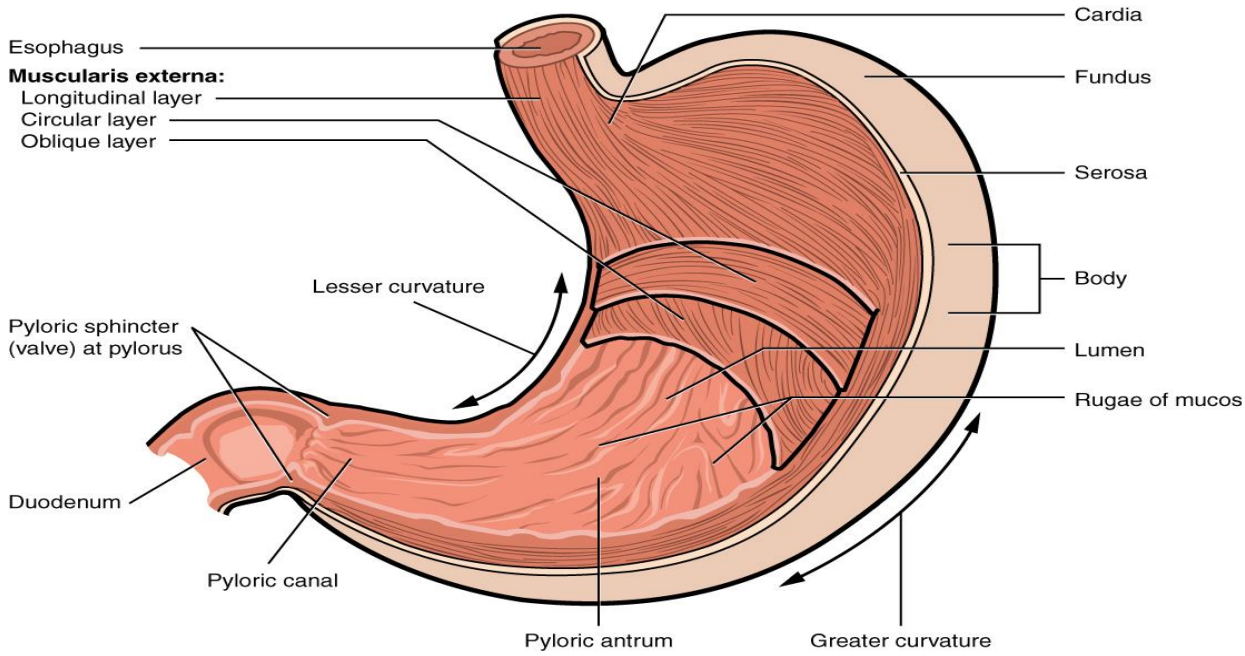



**Figure 11. Anatomy of the stomach**

## I.7.1. Gastric secretion

Two primary pathways that stimulate gastric acid secretion by parietal cells. In the direct pathway, acetylcholine, gastrin, and histamine directly bind to their respective receptors on the parietal cell membrane. This binding triggers a signaling cascade that ultimately activates the proton pump, an enzyme responsible for pumping hydrogen ions (H+) into the stomach lumen. In

the indirect pathway, acetylcholine and gastrin stimulate enterochromaffin-like (ECL) cells, which release histamine. Histamine then binds to H2 receptors on parietal cells, also activating the proton pump and leading to HCl secretion. These two pathways, both directly and indirectly, contribute to the overall stimulation of gastric acid secretion.

The gastric HCl secretion is ensured by Parietal cells in the gastric mucosa secrete hydrochloric acid (HCl) through a complex mechanism involving multiple ion channels and enzymes (Figure 12). Upon stimulation, the proton pump, an ATP-dependent enzyme, actively pumps hydrogen ions (H+) out of the cell and potassium ions (K+) into the cell. To maintain electrical neutrality, chloride ions (Cl-) follow the hydrogen ions through the CFTR channel. Potassium ions are recycled back into the extracellular space via the KvLQT1 channel. The intracellular generation of bicarbonate ions (HCO3-) occurs through the action of carbonic anhydrase, which catalyzes the conversion of carbon dioxide (CO2) and water (H2O) into carbonic acid. Bicarbonate is then transported into the bloodstream, neutralizing the secreted HCl. This intricate process ensures the delivery of hydrochloric acid into the stomach lumen, facilitating digestion. Stimuli such as acetylcholine, gastrin, and histamine bind to their respective receptors on the parietal cell membrane, initiating a cascade of intracellular events. G proteins, activated by ligand binding, trigger the phospholipase C (PLC) and adenylyl cyclase (AC) pathways. PLC activation leads to the production of inositol 1,4,5-trisphosphate (IP3), which mobilizes calcium from intracellular stores. Elevated calcium levels activate protein kinase C (PKC) and other downstream signaling molecules. Simultaneously, AC activation generates cyclic AMP (cAMP), which activates protein kinase A (PKA). Both PKC and PKA ultimately converge on the proton pump, a transmembrane protein responsible for pumping hydrogen ions (H+) into the stomach lumen. Additionally, enterochromaffin-like (ECL) cells release histamine, further stimulating parietal cells through H2 receptors. The hormone somatostatin, released by D cells, inhibits gastric acid secretion by blocking the proton pump. These interconnected pathways precisely regulate gastric acid secretion in response to various physiological and environmental factors, ensuring optimal digestion and maintaining the stomach's acidic environment.

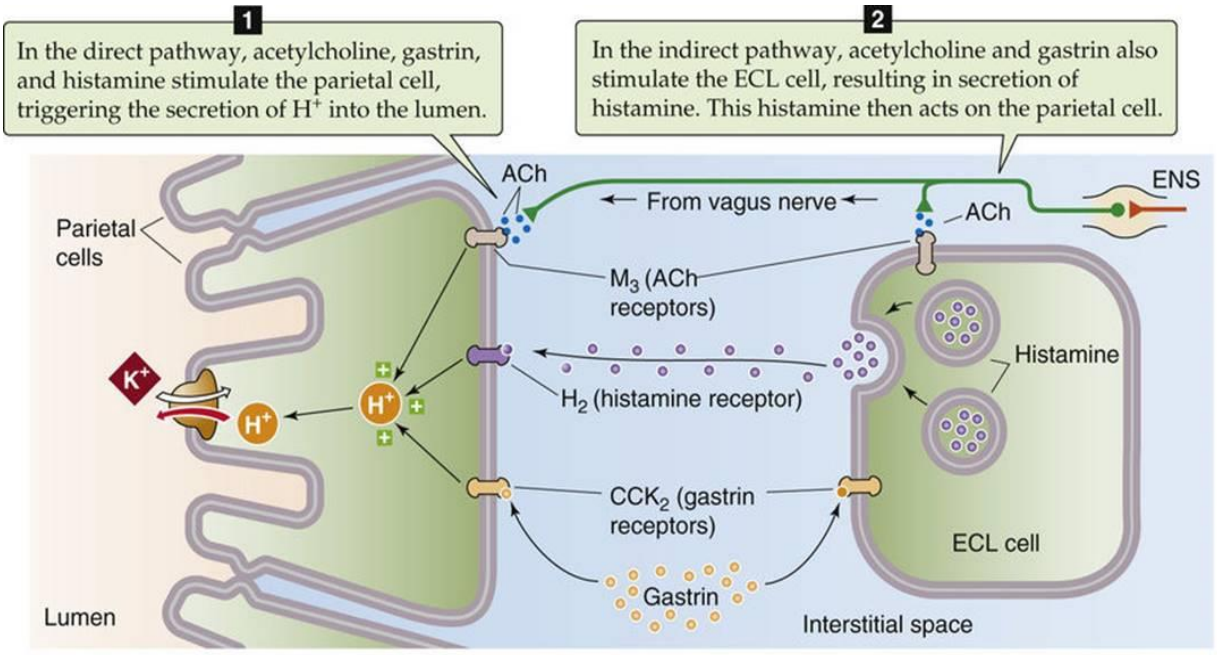
# I.8. Some digestive diseases

## I.8.1. Peptic ulcer

Peptic ulcers, commonly affecting the stomach or upper small intestine, are caused by an imbalance between mucosal protective mechanisms and aggressive factors. Gastric ulcers manifest as a loss of gastric mucosal tissue extending into the muscularis, forming a sclerotic inflammatory base (Fig. 4), and presenting as more superficial tissue loss ulcers (ulcers, erosions, abrasions).

Mucosal defense mechanisms include mucus, blood flow, prostaglandins, nitric oxide, antioxidants, and bicarbonate. Aggressive factors include stomach acid, pepsin, *Helicobacter pylori* (*H. pylori*) bacteria, and nonsteroidal anti-inflammatory drugs (NSAIDs). *H. pylori* infection is a major cause of peptic ulcers. It colonizes the stomach mucosa, leading to inflammation, epithelial damage, and gastritis. This can disrupt antral somatostatin release and increase gastrin secretion, further contributing to ulcer formation. NSAIDs can also cause peptic ulcers by damaging the stomach mucosa directly and reducing prostaglandin production. Prostaglandins help protect the stomach lining by increasing mucus secretion, blood flow, and epithelial cell repair. Other risk factors for peptic ulcers include excessive alcohol consumption, smoking, stress, and irregular eating habits. These factors can weaken the stomach's mucosal defenses and increase the risk of ulceration.

Symptoms of peptic ulcers include abdominal pain, nausea, vomiting, and weight loss. In severe cases, bleeding can occur. Treatment for peptic ulcers often involves medications to reduce stomach acid, eradicate *H. pylori* infection, and protect the stomach lining. Lifestyle changes, such as avoiding irritants like alcohol and spicy foods, can also help prevent or manage ulcers.



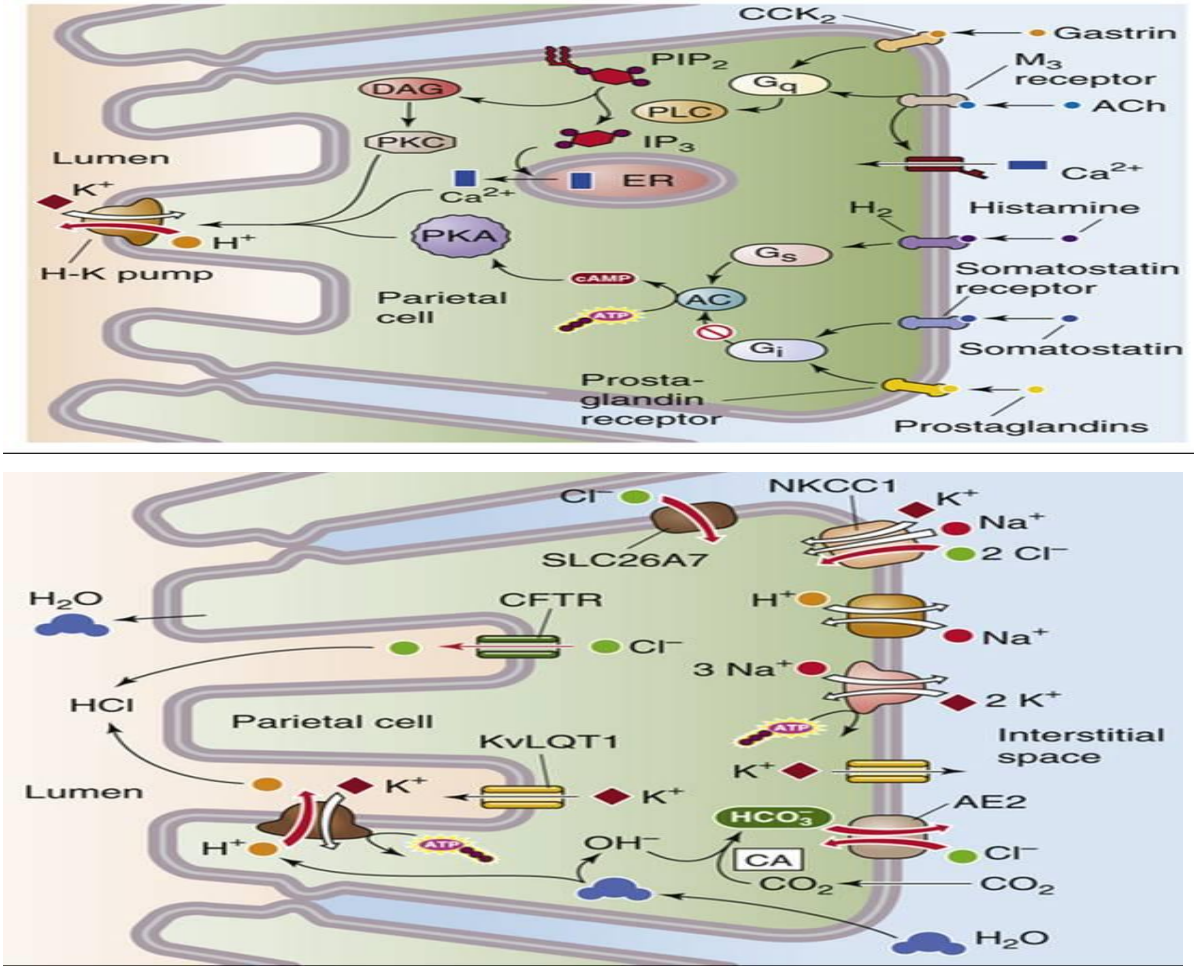
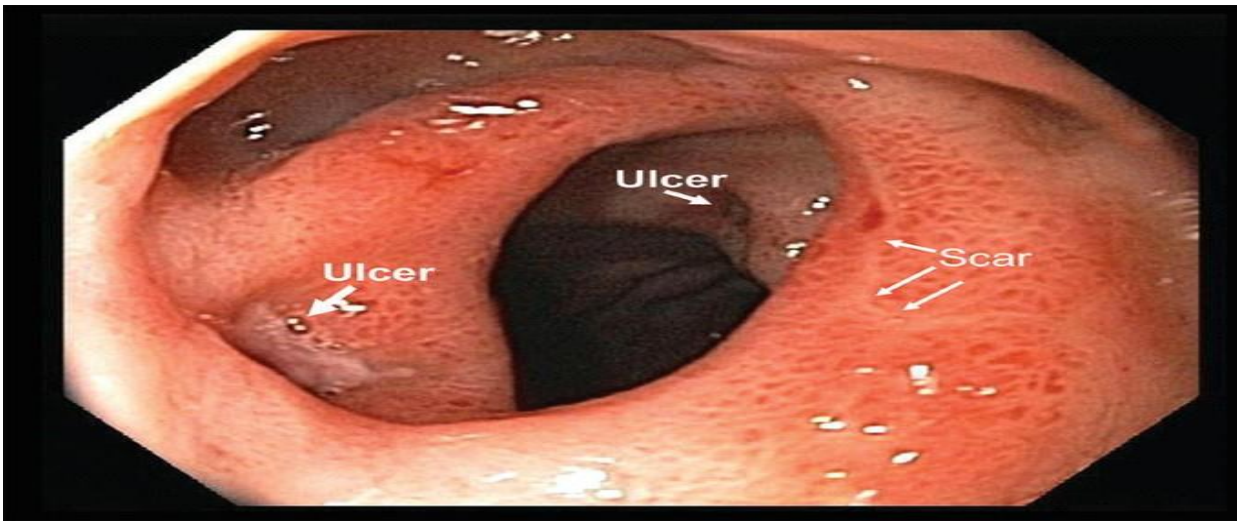



**Figure 12. intricate signaling pathways that regulate gastric acid secretion by parietal cells**



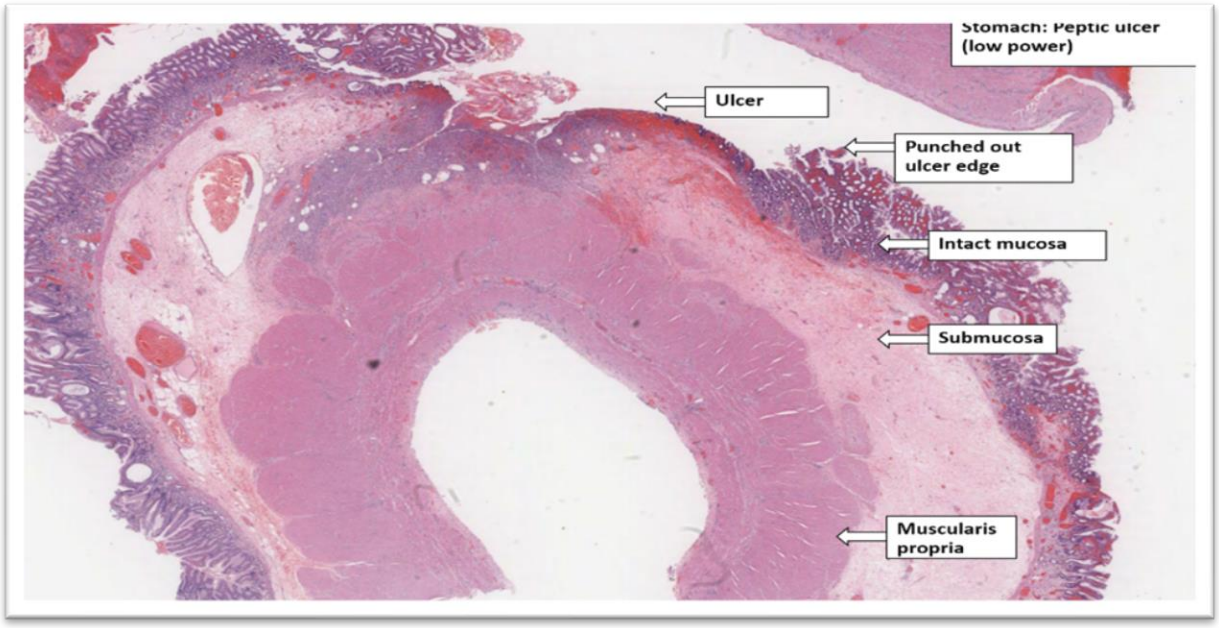



**Figure 13. Peptic ulcer**

Awarded the Nobel Prize in Physiology or Medicine by Marshall and Warren in 2005 for the surprising and unexpected discovery that stomach inflammation (gastritis) and gastric and duodenal ulcers are caused by the bacterium *H. pylori*, which infects the stomach.

*H. pylori* infection is more common in childhood and depends on hygienic conditions. This gram-negative bacillus is resistant to gastric acid due to its strong urease activity. Bacterial urease hydrolyzes gastric urea and produces ammonia, which neutralizes HCl and thus creates a microenvironment conducive to bacterial survival. It penetrates the mucus layer and colonizes the surface of superficial gastric cells, primarily in the antrum. Such exposure will induce the activation of innate and acquired immune responses in the host. Several chemokines, cytokines, and antimicrobial peptides are involved in the modulation of these responses.

### I.8.2. Crohn disease

Crohn's disease is a chronic inflammatory bowel disease that can affect any part of the gastrointestinal tract, from the mouth to the anus. This condition causes inflammation and swelling in the lining of the digestive tract, leading to a variety of symptoms.

Common symptoms of Crohn's disease include abdominal pain and cramping, persistent diarrhea, rectal bleeding, fatigue, weight loss, malnutrition, fever, and mouth sores. In some cases, the inflammation can extend beyond the digestive tract and affect other organs, such as the eyes, skin, and joints. Crohn's disease, as depicted in the image, is a type of inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract, from the mouth to the anus. Unlike

ulcerative colitis, which primarily affects the large intestine, Crohn's disease can cause inflammation in discontinuous patches throughout the digestive tract.

The intestinal epithelium plays a crucial role in maintaining homeostasis by acting as a physical barrier and regulating immune responses. Specialized epithelial cells, such as Paneth cells and microfold cells, contribute to this process by producing antimicrobial peptides and sampling luminal antigens, respectively.

In a healthy gut, antigen-presenting cells (APCs) like dendritic cells present antigens to T cells and B cells, triggering a controlled inflammatory response. However, in inflammatory conditions like Crohn's disease, epithelial barrier dysfunction, often linked to genetic factors like NOD2 and NF-κB polymorphisms, allows luminal contents to enter the lamina propria. This triggers an excessive immune response, with dendritic cells activating various T cell subsets, including TH1, TH17, and TH2 cells. These activated T cells, along with macrophages, produce pro-inflammatory cytokines like IFN-γ, TNF-α, IL-12, and IL-23, perpetuating the inflammatory cycle.

Additionally, luminal contents, including dietary components and the gut microbiota, can influence the immune response. T cells can also produce IL-4, IL-6, IL-21, and IL-22 in response to dendritic cell activation, further modulating the immune response.

various extraintestinal manifestations that can be associated with inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis. These extraintestinal manifestations can affect multiple organ systems, often occurring simultaneously with or preceding the development of gastrointestinal symptoms. Some of the common extraintestinal manifestations associated with Crohn's disease

**Dermatological**: Aphthous stomatitis, Erythema nodosum, Psoriasis and Pyoderma gangrenosum

**Ocular**: Uveitis, Scleritis and Episcleritis

**Vascular**: Portal hypertension, Thromboembolism, Thrombosis and Pulmonary embolism

**Arthropathy**: Arthritis, Ankylosing spondylitis and Sacroiliitis

**Respiratory**: Obstructive sleep apnea and Chest infections

**Hepatobiliary**: Primary sclerosing cholangitis, Cirrhosis, Colorectal cancer and Small-bowel cancer

**Inflammatory**: Asthma, Bronchitis, Pericarditis, Rheumatoid arthritis and Multiple sclerosis

**Other**: Metabolic bone disease.

**Diagnostic**

Some tests can be used to confirm the disease' injury like:

**Laboratory Tests:**

**Serological Tests:**

- C-Reactive Protein (CRP): While not specific to IBD, elevated CRP levels can indicate inflammation and are useful for monitoring disease activity.
- Antineutrophil Cytoplasmic Antibody (ANCA): pANCA is associated with ulcerative colitis (UC) and can help differentiate it from Crohn's disease (CD).
- Anti-Saccharomyces cerevisiae Antibody (ASCA): ASCA is more specific for CD and can be a useful diagnostic marker.
- Other Antibodies: IgG anti-laminaribioside carbohydrate antibody (ALCA), IgA anti-chitobioside carbohydrate antibody (ACCA), IgG anti-mannobioside carbohydrate antibody (AMCA), and anti-outer-membrane porin C (OmpC) antibody can also provide valuable information for diagnosis and disease characterization.
- MicroRNAs: Emerging as potential biomarkers for IBD diagnosis and monitoring disease activity.

**Stool Tests**:

- Fecal Calprotectin: A non-invasive marker of intestinal inflammation, useful for monitoring disease activity and differentiating IBD from irritable bowel syndrome (IBS).
- Fecal Lactoferrin: Another marker of intestinal inflammation, but less widely used than fecal calprotectin.

**MicroRNA**: Can be used as a non-invasive biomarker for IBD diagnosis and monitoring.

Endoscopic and Pathological Tests:

**Lower Endoscopy (Colonoscopy):** A crucial tool for diagnosing IBD, allowing for visual inspection of the colon and rectum, as well as tissue biopsy for histological examination.

By combining these diagnostic tools, clinicians can accurately diagnose IBD, monitor disease activity, and guide treatment decisions.

## I.8.3. Irritant bowl syndrome

The gut-brain axis represents a dynamic, bidirectional communication network linking the central nervous system (CNS), enteric nervous system (ENS), autonomic nervous system, immune system, and gut microbiota. As illustrated in the figure, the CNS—comprising the brain and spinal cord—regulates mood, cognition, stress, and visceral perception, and communicates with the ENS via the vagus nerve and with the immune system through the HPA-axis and glucocorticoids. The autonomic nervous system serves as a conduit between the brain and gut, influencing gastrointestinal functions such as secretion, motility, and permeability. Meanwhile, the immune system interacts with both the CNS and ENS, playing a crucial role in maintaining homeostasis and responding to microbial signals. At the foundation of this network lies the enteric microbiota,

which modulates immune responses and neural activity, thereby influencing brain function and emotional states. This intricate interplay underscores the profound impact of gut health on mental and neurological well-being (Fig. 14). The stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of stress hormones from the adrenal glands, while pain engages the nervous and gastrointestinal systems, influencing pain perception. Both stress and pain contribute to mood disorders, sleep disturbances, cognitive dysfunction, and menstrual irregularities. The middle section highlights immune activation, where altered gut microbiota and proinflammatory cytokines mediate communication between the brain and gut. At the base, the gut microbiota interacts directly with immune cells, shaping immune responses and influencing systemic inflammation. This conceptual framework underscores the importance of holistic approaches to health, recognizing that emotional stress and physical pain can trigger biological cascades that affect immunity, digestion, and mental well-being.

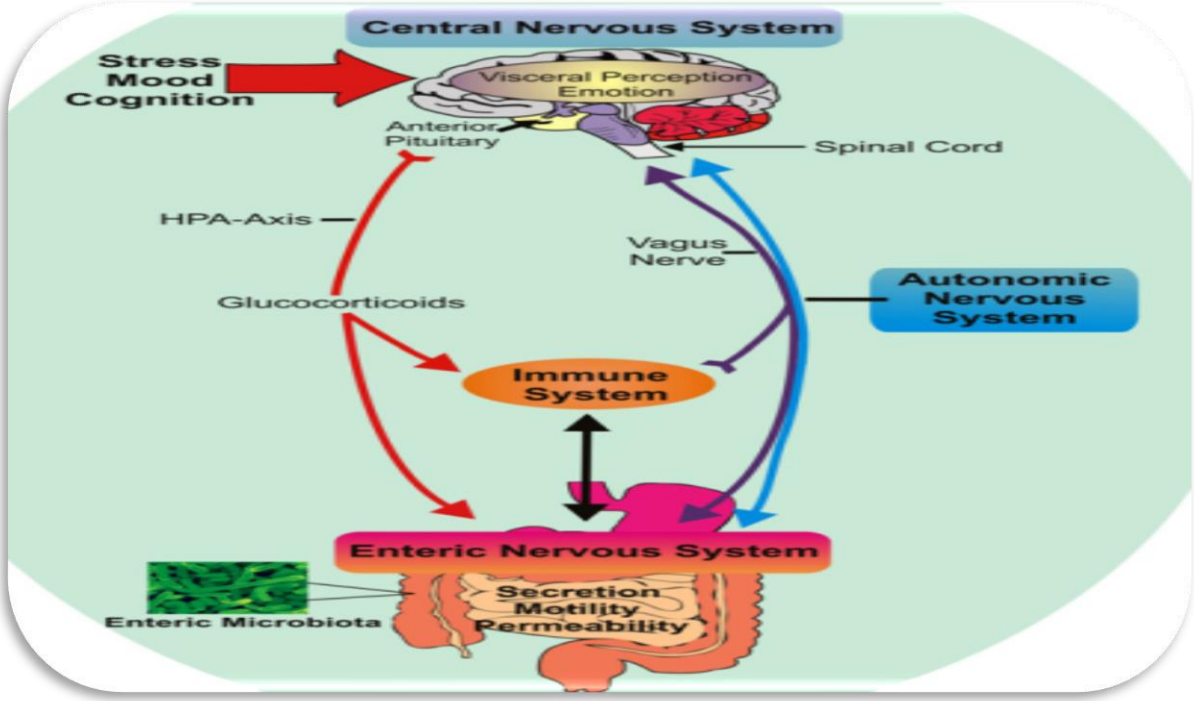



**Figure 14. The control of the gastrointestinal system the central nervous system**

## I. 8.4. Enteric Nervous System Degeneration

Degeneration of the enteric nervous system (ENS) involves the loss or dysfunction of its neurons and glia, which critically impairs peristaltic reflexes essential for normal gut propulsion. In congenital cases like Hirschsprung's disease, a failure of neural crest cell migration during embryogenesis results in aganglionosis of the distal colon, where the absence of inhibitory neurons—responsible for nitric oxide and VIP-mediated relaxation—leads to persistent tonic contraction, functional obstruction, increased risk of enterocolitis, and the classic failure to pass meconium in newborns. Acquired neurodegeneration manifests differently, as seen in Parkinson's disease, where α-synuclein aggregates form Lewy bodies within myenteric neurons, disrupting dopamine-mediated inhibition and yielding gastroparesis (delayed gastric emptying) alongside severe constipation that affects up to 80% of patients; similarly, Chagas disease caused by Trypanosoma cruzi infection provokes autoimmune destruction of ENS neurons, culminating in megaesophagus and megacolon due to uncoordinated peristalsis. Enteric glia play a pivotal supportive role by maintaining epithelial barrier integrity and providing neurotrophic factors to neurons; their depletion exacerbates oxidative stress, promotes neuroinflammation, and further destabilizes gut homeostasis.

## I.8.4. Autonomic Neuropathy

Extrinsic nerve damage disrupts the coordinated propulsion and accommodation essential for effective gastrointestinal motility. In diabetic autonomic neuropathy, chronic hyperglycemia generates oxidative stress and advanced glycation end-products that preferentially damage vagal preganglionic fibers, reducing acetylcholine (ACh) release and thereby impairing the gastric pacemaker activity of interstitial cells of Cajal, which manifests as gastroparesis with symptoms including nausea, vomiting, and bezoar formation; this creates a vicious feedback loop where delayed emptying exacerbates postprandial hyperglycemia and further accelerates neuropathy. Other etiologies, such as amyloidosis, involve protein deposits in postganglionic neurons that result in unopposed parasympathetic activity, leading to nocturnal diarrhea, while alcoholism or paraneoplastic syndromes similarly target these fibers, producing erratic bowel patterns. Sympathetic dominance, often seen in advanced neuropathy, inhibits gastrointestinal secretion and motility through noradrenergic pathways, promoting chronic constipation and, in severe cases, overflow fecal incontinence.

## I.8.5. Visceral Hypersensitivity

Altered sensory processing in visceral hypersensitivity amplifies innocuous stimuli, such as normal gut distension, into debilitating pain. In irritable bowel syndrome (IBS), peripheral sensitization occurs through upregulation of transient receptor potential vanilloid 1 (TRPV1) channels and 5-HT receptors on visceral afferents, which lowers their activation thresholds and heightens responsiveness to mechanical or chemical stimuli; mast cell-derived mediators like histamine and proteases further exacerbate this by directly sensitizing nociceptors. Central amplification compounds the issue, with spinal cord wind-up phenomena—repetitive C-fiber activation leading to temporal summation—and hyperactivity in brainstem nuclei such as the locus coeruleus enhancing nociceptive signal transmission, while prefrontal cortex dysregulation integrates psychological stress to perpetuate the cycle. The gut-brain axis plays a key role, as corticotropin-releasing factor (CRF) released from the hypothalamus in response to stress heightens both motility and pain perception via vagal afferent pathways.

# References


- OpenStax. (2024). 27.1 Gastrointestinal tract structures and functions. In Fundamentals of Nursing. https://openstax.org/books/fundamentals-nursing/pages/27-1-gastrointestinal-tract-structures-and-functions
- Histology Guide. (n.d.). Gastrointestinal tract. https://histologyguide.com/slidebox/14-gastrointestinal-tract.html
- Chaudhari, N., & Roper, S. D. (2010). The cell biology of taste. Journal of Cell Biology, 190(3), 285–296.
- Roper, S. D., & Chaudhari, N. (2017). Taste buds: Cells, signals and synapses. Nature Reviews Neuroscience, 18(8), 485–497.
- Kenhub. (2021). Taste buds: Anatomy and function. Kenhub GmbH. https://www.kenhub.com/en/library/anatomy/taste-buds
- Kessler, A. T., & Bhatt, A. A. (2018). Review of the major and minor salivary glands, part 1: Anatomy, infectious, and inflammatory processes. Journal of Clinical Imaging Science, 8, 47.
- Kenhub. (2014). Salivary glands: Overview, anatomy, clinical aspects. Kenhub GmbH. https://www.kenhub.com/en/library/anatomy/the-salivary-glands
- TeachMeAnatomy. (2025). GI tract anatomy – oesophagus to anal canal. https://teachmeanatomy.info/abdomen/gi-tract/
- Furness, J. B. (2012). The enteric nervous system and neurogastroenterology. Nature Reviews Gastroenterology & Hepatology, 9(5), 286–294.
- Costa, M., Brookes, S. J. H., & Hennig, G. W. (2000). Anatomy and physiology of the enteric nervous system. Gut, 47(Suppl IV), iv15–iv19.
- Guyton, A. C., & Hall, J. E. (2021). Textbook of medical physiology (14th ed.). Elsevier.
- Sachs, G., Shin, J. M., & Hunt, R. (2010). Novel approaches to inhibition of gastric acid secretion. Current Gastroenterology Reports, 12(6), 437–447.
- Venerito, M., Vasapolli, R., Rokkas, T., & Malfertheiner, P. (2018). Gastric cancer: Epidemiology, prevention, and therapy. Helicobacter, 23(Suppl 1), e12518.
- Baumgart, D. C., & Sandborn, W. J. (2012). Crohn’s disease. The Lancet, 380(9853), 1590–1605.
- Wójcik, B., et al. (2016). Extraintestinal manifestations of Crohn’s disease. Przegląd Gastroenterologiczny, 11(4), 241–246.

- Moloney, R. D., O'Mahony, S. M., Dinan, T. G., & Cryan, J. F. (2015). Stress and the microbiota–gut–brain axis in visceral pain: Relevance to irritable bowel syndrome. CNS Neuroscience & Therapeutics, 21(3), 193–209.
- Mayer, E. A. (2011). Gut feelings: The emerging biology of gut–brain communication. Nature Reviews Neuroscience, 12(8), 453–466.
- Simrén, M., Törnblom, H., & Palsson, O. S. (2017). Management of the multiple symptoms of irritable bowel syndrome. The Lancet Gastroenterology & Hepatology, 2(2), 112–122.
- Goldstein, A. M., & Hofstra, R. M. W. (2015). Genetic basis of Hirschsprung disease. Current Opinion in Pediatrics, 27(6), 689–694.
- Furness, J. B. (2012). The enteric nervous system and neurogastroenterology. Nature Reviews Gastroenterology & Hepatology, 9(5), 286–294.
- Klingelhoefer, L., & Reichmann, H. (2015). Pathogenesis of Parkinson disease—the gut–brain axis and environmental factors. Nature Reviews Neurology, 11(11), 625–636.
- Adad, S. J., et al. (2001). Megacolon secondary to Chagas disease: A review. Revista do Instituto de Medicina Tropical de São Paulo, 43(4), 203–210.
- Camilleri, M. (2007). Diabetic gastroparesis. New England Journal of Medicine, 356(8), 820–829.
- Werth, B. A., et al. (1992). Non-invasive assessment of gastrointestinal motility disorders in diabetic patients with and without cardiovascular signs of autonomic neuropathy. Gut, 33(9), 1199–1203.

# Chapter II Physiopathology of Liver

# II.1. Generalities on pancreas and liver

The pancreas is a vital organ with dual exocrine and endocrine functions, as illustrated by its anatomical and histological organization. Anatomically, it is situated between the spleen and the duodenum of the small intestine, with the pancreatic duct converging with the common bile duct to facilitate the release of digestive secretions into the duodenum. The exocrine component consists of acinar cells, which synthesize and secrete digestive enzymes essential for nutrient breakdown. Histologically, the endocrine function is localized within the pancreatic islets, which contain distinct cell populations: alpha cells that produce glucagon and beta cells that secrete insulin. These hormones play a central role in glucose homeostasis. The integration of exocrine and endocrine activities within the pancreas underscores its critical role in both digestive physiology and metabolic regulation (Fig. 15). Anatomically, the pancreas is divided into distinct regions including the head, tail, and lobular structures, with the pancreatic duct and common bile duct facilitating the transport of digestive secretions into the duodenum. Histologically, the exocrine portion is composed of acinar cells that synthesize and release digestive enzymes into the pancreatic duct, forming pancreatic juice essential for nutrient breakdown. The endocrine component is represented by pancreatic islet cells, which secrete hormones such as insulin and glucagon directly into the bloodstream, playing a pivotal role in glucose homeostasis. This structural and functional integration underscores the pancreas's central role in both digestive physiology and metabolic regulation (Fig. 16).

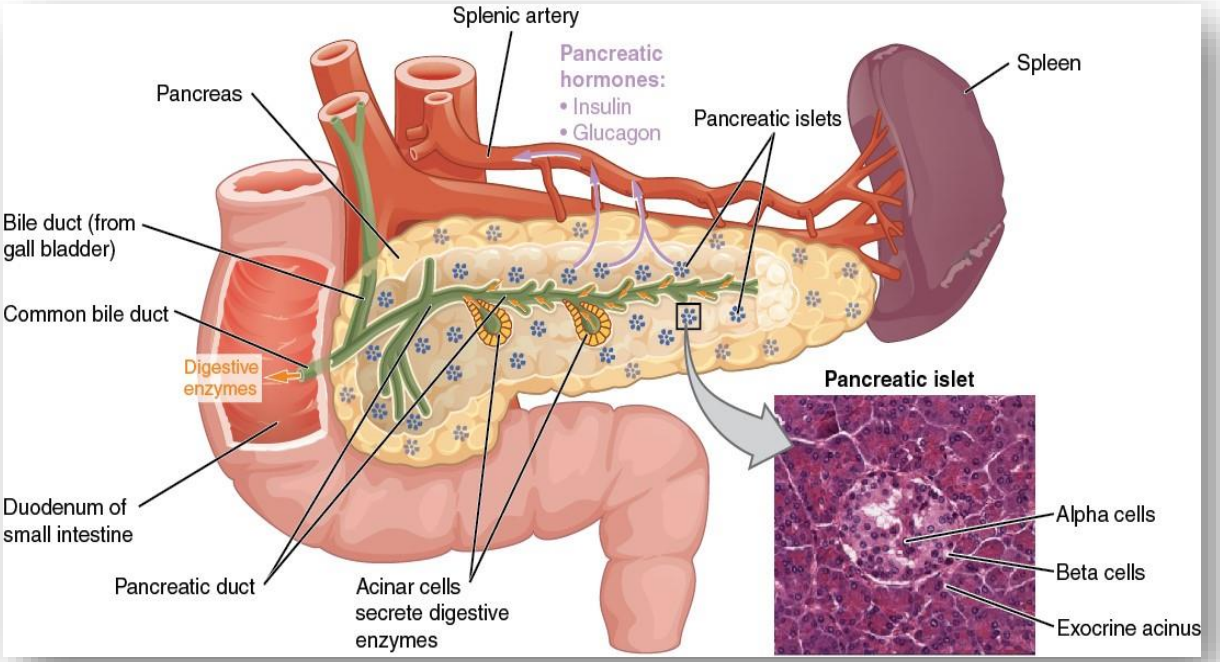



**Figure 15. Pancreas' position in the human body.**

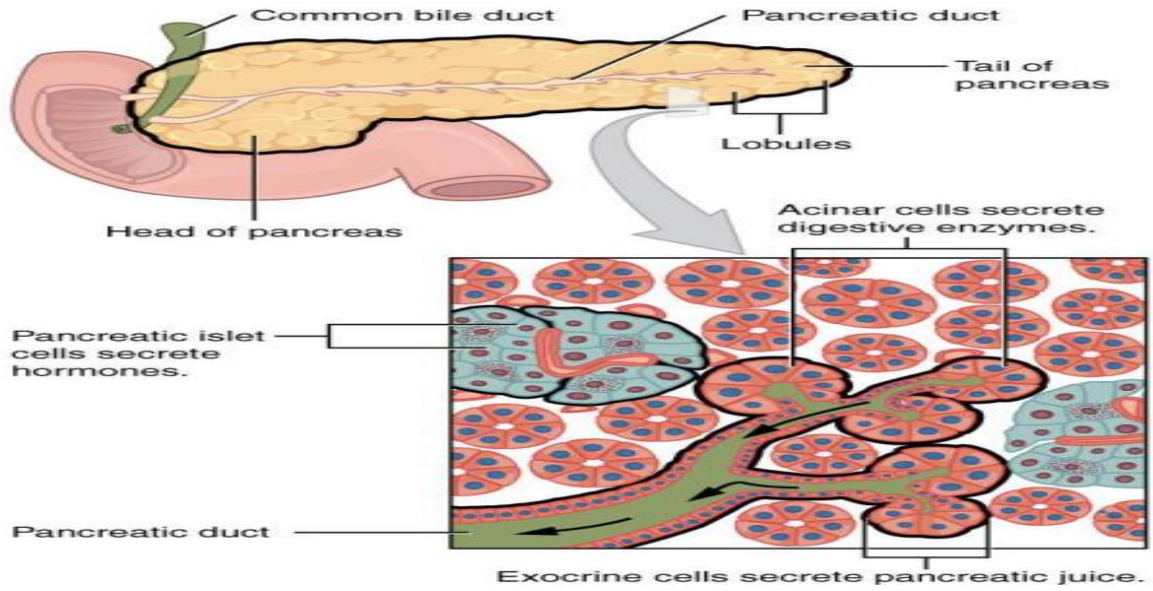



**Figure 16. macroscopic anatomy and microscopic histology of the pancreas and its dual exocrine and endocrine functions**

The liver is a highly vascularized organ responsible for critical metabolic, detoxification, and synthetic functions. Macroscopically, it is anchored by the falciform ligament and receives dual blood supply from the hepatic artery and portal vein, while venous drainage occurs via the vena cava. Microscopically, the liver is organized into hexagonal lobules, each centered around a central vein and bordered by portal tracts containing branches of the bile duct, hepatic artery, and portal

vein. Blood from the portal vein and hepatic artery flows through sinusoids toward the central vein, facilitating exchange with hepatocytes. Concurrently, bile produced by hepatocytes is secreted into canaliculi, which drain into bile canals and ultimately into the bile duct. This countercurrent flow of blood and bile within the lobule reflects the liver's dual role in processing bloodborne substances and producing bile for digestion. The structural integration of vascular and biliary pathways within the lobular architecture is essential for maintaining hepatic function and systemic homeostasis (Fig.17).

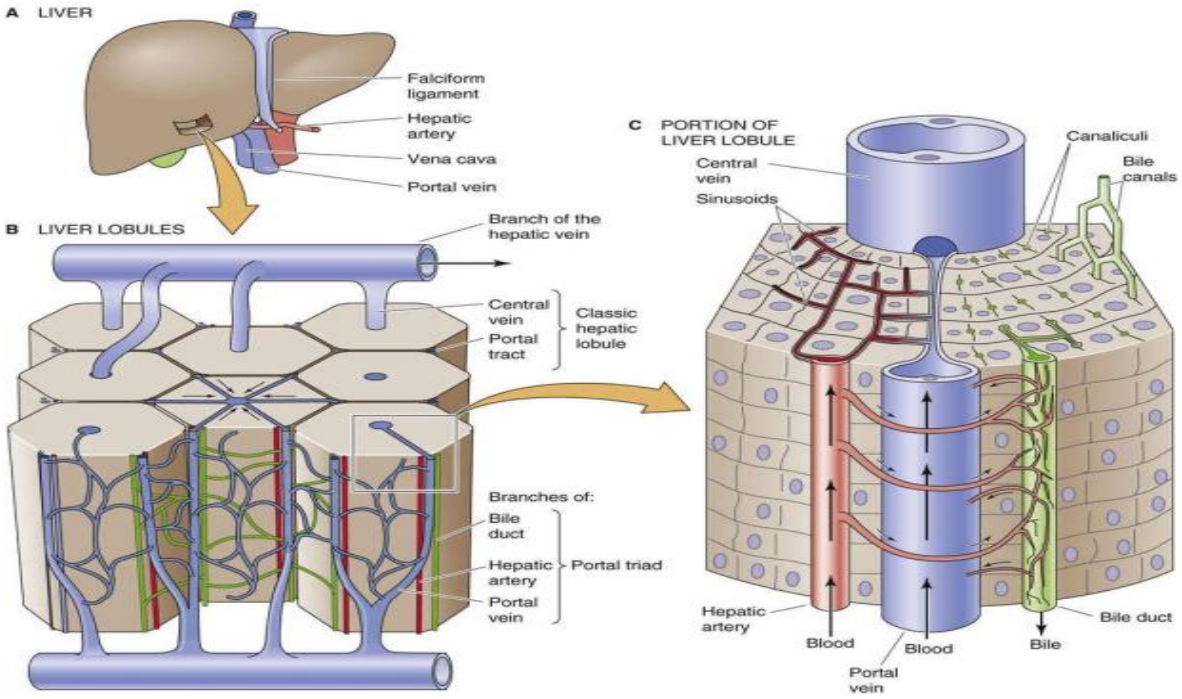



**Figure 17. Comprehensive overview of the liver's anatomical and microanatomical organisation, emphasising its vascular and biliary architecture.**

# II.2. Liver diseases

## II.2.1. Hepatitis

A global health challenge, signifies an inflammatory cascade within the liver, often culminating in the death of its primary functional cells, the hepatocytes. This hepatocyte demise, termed necrosis, is not a singular event but a complex interplay of molecular pathways, triggered by a variety of insults ranging from viral infections and alcohol abuse to autoimmune dysregulation and drug-induced injury. Understanding the intricate physiopathology of hepatitis and necrosis is paramount for developing effective therapeutic strategies to combat liver disease. Recent research has illuminated the diverse and overlapping mechanisms of regulated cell death, the nuances of

the immune response, and the critical role of the gut-liver axis in the progression of this complex disease.

The liver, a vital organ with a remarkable regenerative capacity, is constantly exposed to a barrage of aggressions. When these aggressions overwhelm its protective mechanisms, a cascade of events is initiated, leading to hepatocyte injury and death. While historically, cell death was broadly categorized into apoptosis (programmed cell death) and necrosis (uncontrolled cell death), recent discoveries have unveiled a more nuanced spectrum of regulated cell death (RCD) pathways. These include necroptosis, a programmed form of necrosis; pyroptosis, a highly inflammatory form of cell death; and ferroptosis, an iron-dependent form of cell death driven by lipid peroxidation. In the context of hepatitis, multiple of these pathways can be activated simultaneously or sequentially, contributing to the overall liver damage.

Viral hepatitis, caused by a group of hepatotropic viruses (A, B, C, D, and E), represents a major cause of liver inflammation and necrosis worldwide. The liver injury in viral hepatitis is not solely a direct consequence of viral replication but is largely immune-mediated. The host's immune response, while attempting to clear the virus, inadvertently causes collateral damage to hepatocytes. For instance, in chronic Hepatitis B (HBV) and Hepatitis C (HCV) infections, the persistent presence of viral antigens leads to a state of chronic inflammation. This is characterized by the infiltration of immune cells, such as T cells and natural killer (NK) cells, which recognize and eliminate infected hepatocytes. However, this continuous immune-mediated killing, coupled with the virus's ability to evade the immune system, results in a smoldering fire of inflammation and a gradual loss of liver function, often progressing to fibrosis, cirrhosis, and hepatocellular carcinoma. Alcoholic hepatitis (AH) is a severe and life-threatening form of alcohol-associated liver disease. Its physiopathology is multifactorial, involving direct hepatotoxicity from alcohol metabolism, oxidative stress, and a robust inflammatory response. The metabolism of ethanol generates reactive oxygen species (ROS) and toxic byproducts that directly damage hepatocytes, leading to both apoptosis and necrosis. Furthermore, chronic alcohol consumption disrupts the integrity of the gut barrier, allowing bacterial products, such as lipopolysaccharide (LPS), to translocate into the bloodstream and reach the liver. This "leaky gut" phenomenon activates Kupffer cells, the resident macrophages of the liver, which in turn release a torrent of pro-inflammatory cytokines, such as TNF-α and IL-1β, exacerbating liver injury and promoting the recruitment of other immune cells. Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by the loss of immune tolerance to the body's own liver antigens. The pathogenesis of AIH is thought to involve a complex interplay of genetic predisposition, environmental triggers, and a dysregulated immune response. In genetically susceptible

individuals, environmental factors, such as viral infections or certain drugs, may trigger an autoimmune cascade. This results in the activation of autoreactive T cells that recognize and attack hepatocytes, leading to a form of hepatitis characterized by interface hepatitis, or "piecemeal necrosis," where lymphocytes are seen attacking hepatocytes at the portal-parenchymal interface. A key feature of AIH is a defect in regulatory T cells (Tregs), which are responsible for maintaining immune homeostasis and preventing autoimmunity. This failure of immune regulation allows the unchecked proliferation of autoreactive lymphocytes and the perpetuation of liver damage. The final common pathway of chronic liver injury, regardless of the etiology, is the development of fibrosis, an excessive accumulation of extracellular matrix proteins, which can progress to cirrhosis and end-stage liver disease. Hepatocyte death, particularly necrosis, is a potent trigger for fibrosis. The release of damage-associated molecular patterns (DAMPs) from necrotic cells activates hepatic stellate cells, the primary fibrogenic cells in the liver. These activated stellate cells then transform into myofibroblast-like cells, producing large amounts of collagen and other matrix proteins that distort the normal liver architecture and impair its function. In conclusion, the physiopathology of hepatitis and necrosis is a complex and multifaceted process involving a diverse array of etiologies and molecular mechanisms. The traditional view of necrosis as a passive, uncontrolled form of cell death has been replaced by a more sophisticated understanding of regulated cell death pathways that are intricately linked to the inflammatory response.

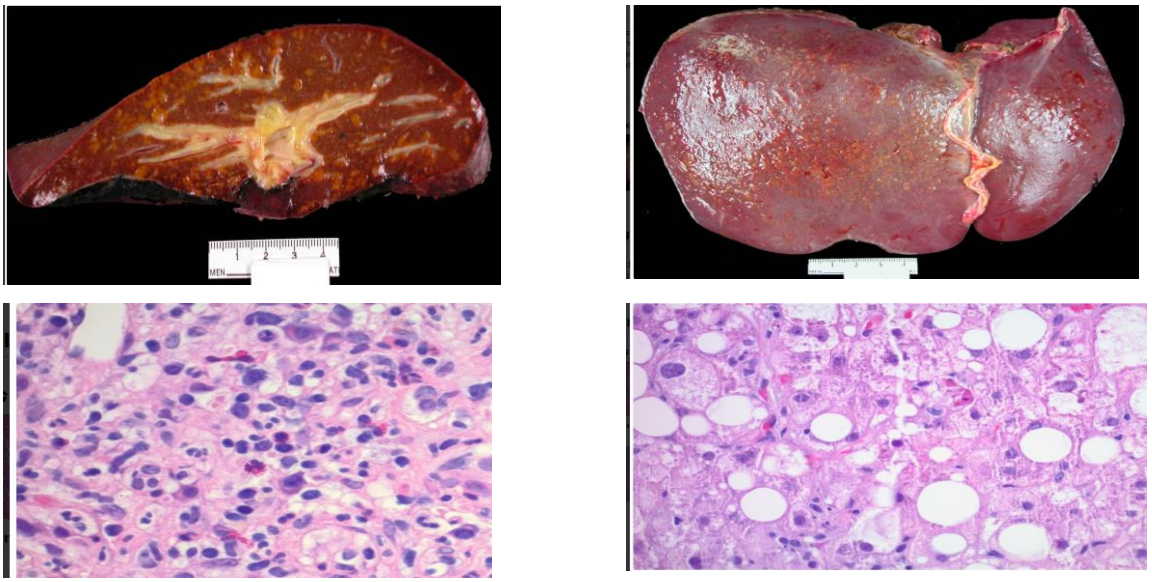


**Figure 18. Pathophysiology of liver Hepatities and necrosis cases**

## II.2.2. Cirrhosis

Cirrhosis represents the end-stage of chronic liver disease, characterized by the replacement of functional hepatic parenchyma with fibrotic scar tissue and regenerative nodules, leading to a profound distortion of the liver's architecture and subsequent organ failure. The pathophysiology of cirrhosis is a complex, multi-faceted process driven by chronic inflammation and persistent liver injury, which triggers the activation of hepatic stellate cells (HSCs). Once activated, HSCs transdifferentiate into myofibroblast-like cells, becoming the primary source of extracellular matrix (ECM) proteins, predominantly collagen, that accumulate in the liver. This fibrotic process is further exacerbated by a dysregulated immune response, involving both innate and adaptive immunity, and the translocation of gut-derived pathogens and their products, which fuel a pro-inflammatory environment. The progressive accumulation of ECM disrupts the intricate vascular architecture of the liver, leading to portal hypertension, a major driver of cirrhosis-related complications. While historically considered irreversible, recent evidence suggests that early-stage cirrhosis may be reversible if the underlying etiological agent is effectively treated, highlighting the dynamic nature of this devastating disease (Fig. 19).

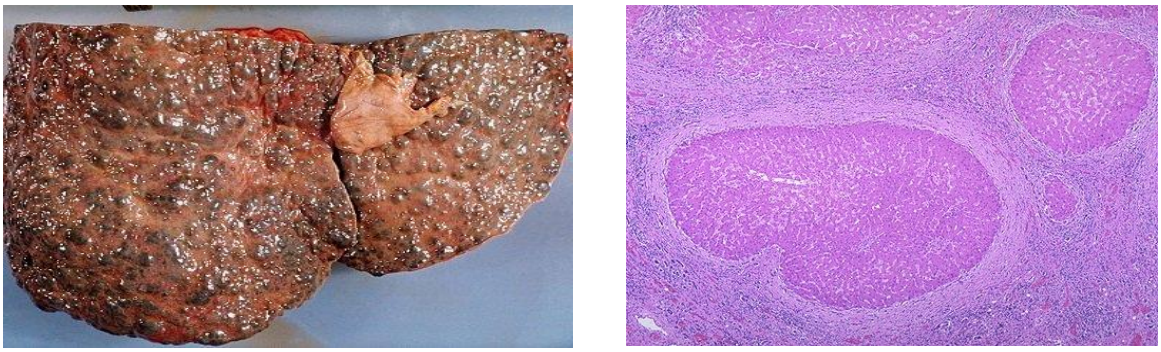


**Figure 19. Cirrhosis disease**

## II.2.3. Fibrosis

Liver fibrosis, a wound-healing response to chronic liver injury, represents a major global health burden. It is a dynamic and complex process characterized by the excessive accumulation of extracellular matrix (ECM) proteins, which distorts the normal liver architecture and can ultimately lead to cirrhosis, liver failure, and hepatocellular carcinoma. Understanding the diverse etiologies and the intricate histopathological changes associated with liver fibrosis is crucial for the development of effective diagnostic and therapeutic strategies. The causes of liver fibrosis are numerous and varied, with chronic insults of different origins converging on a common fibrogenic pathway. Globally, the most prevalent causes are chronic viral hepatitis B and C, alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). Chronic viral infections trigger a persistent inflammatory response that, over decades, leads to the gradual replacement of functional

liver tissue with scar tissue. ALD, resulting from excessive alcohol consumption, induces direct hepatotoxicity and metabolic disturbances that fuel inflammation and fibrosis. NAFLD, closely linked to the metabolic syndrome, is rapidly becoming the leading cause of chronic liver disease in many parts of the world. Other significant causes include autoimmune diseases such as autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, where immune-mediated destruction of hepatocytes or bile ducts incites a fibrotic response. Genetic and metabolic disorders, including hemochromatosis and Wilson's disease, as well as chronic exposure to certain drugs and toxins, also contribute to the burden of liver fibrosis. The histopathology of liver fibrosis reflects the liver's response to persistent injury and the subsequent activation of a complex cellular and molecular cascade. The central event in liver fibrogenesis is the activation of hepatic stellate cells (HSCs), which reside in the perisinusoidal space of Disse. In a healthy liver, HSCs are quiescent and serve as the primary storage site for vitamin A. Upon chronic liver injury, various signaling molecules, including reactive oxygen species (ROS), cytokines, and growth factors released from injured hepatocytes and inflammatory cells, trigger the transdifferentiation of quiescent HSCs into proliferative, contractile, and fibrogenic myofibroblasts. These activated HSCs are the primary source of the excessive ECM, producing large quantities of type I and III collagen, fibronectin, and other matrix components that form the fibrous scar. The pattern of fibrosis deposition on a liver biopsy can often provide clues to the underlying etiology. In chronic viral hepatitis, fibrosis typically begins in the portal tracts, leading to portal expansion and the formation of fibrous septa that bridge adjacent portal tracts or portal tracts and central veins (bridging fibrosis). In ALD and NAFLD, the initial fibrotic lesions are often observed in the centrilobular region, with a characteristic "chicken-wire" pattern of perisinusoidal fibrosis. As the disease progresses, regardless of the initial pattern, the fibrous septa become more extensive, eventually encircling nodules of regenerating hepatocytes, a hallmark of cirrhosis. The use of special stains, such as Masson's trichrome and Sirius red, is essential for the histological assessment of fibrosis, as they highlight the collagenous scar tissue in blue or red, respectively. While liver biopsy remains the gold standard for staging fibrosis, it is an invasive procedure with potential complications. Therefore, non-invasive methods, including serum biomarkers and imaging techniques, are increasingly used for the diagnosis and monitoring of liver fibrosis. Histologically, fibrosis is semi-quantitatively staged using various scoring systems, such as the METAVIR and Ishak scoring systems, which grade the extent of fibrosis from mild to cirrhosis. Importantly, liver fibrosis is no longer considered a passive and irreversible process. With the effective treatment of the underlying cause, such as viral eradication in hepatitis C or lifestyle

modifications in NAFLD, even advanced fibrosis can regress, highlighting the remarkable plasticity of the liver.

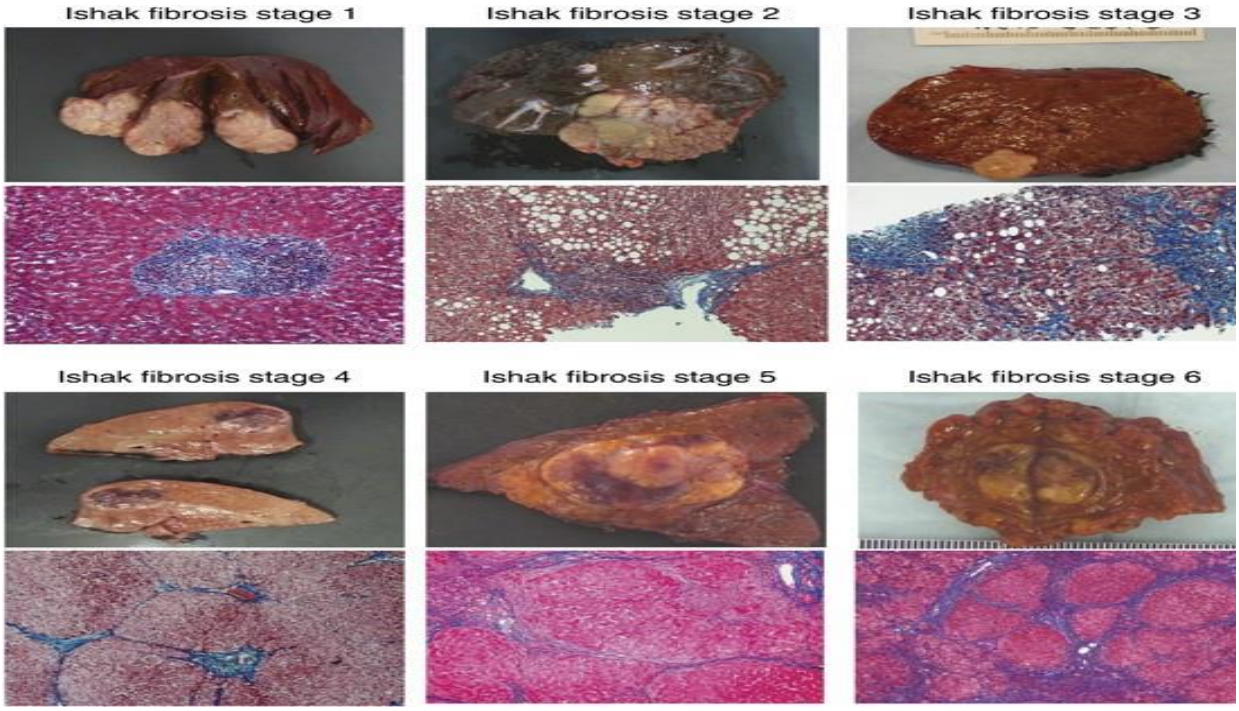



**Figure 20. Fibrosis**

## II.2.4. Hyperbilirubinemia

Hyperbilirubinemia refers to elevated levels of bilirubin in the bloodstream and is classified based on the type of bilirubin—**unconjugated** or **conjugated**—and the anatomical origin of the dysfunction: **prehepatic** or **posthepatic**.

**Prehepatic Causes**

- **Unconjugated Hyperbilirubinemia** arises primarily from increased bilirubin production due to hemolysis or ineffective erythropoiesis. Conditions such as *sickle cell disease*, *hereditary spherocytosis*, and *thalassemia* lead to excessive breakdown of red blood cells, overwhelming the liver's conjugation capacity.
- **Conjugated Hyperbilirubinemia** in this context may result from inherited defects in bilirubin transport (e.g., *MRP-2 mutations* in *Dubin-Johnson* and *Rotor's syndromes*) or hepatocellular damage due to *viral hepatitis* or *cirrhosis*, impairing bilirubin excretion.

**Posthepatic Causes**

- **Unconjugated Hyperbilirubinemia** may be seen in neonates due to physiologic immaturity of UDP-glucuronosyltransferase (UGT). Genetic deficiencies such as *Crigler-Najjar syndrome* (types I and II) and *Gilbert's syndrome* also impair bilirubin conjugation.
- **Conjugated Hyperbilirubinemia** typically results from biliary obstruction or cholestatic disorders. Conditions like *gallstones*, *biliary tumors*, *primary biliary cirrhosis*, and *primary sclerosing cholangitis* hinder bile flow, leading to accumulation of conjugated bilirubin in the blood.

**Table 1. Hyperbilirubinemia-related diseases**

| Type of Hyperbilirubinemia | Unconjugated (Indirect) Bilirubinemia | Conjugated (Direct) Bilirubinemia |
|---|---|---|
| **Prehepatic** | **Hemolytic anemias**<br>• Sickle cell disease<br>• Hereditary spherocytosis<br>**Ineffective hematopoiesis**<br>• Thalassemia | |
| **Hepatic** | **Physiologic jaundice** (low UGT activity)<br>• Neonates<br>**Hereditary** (UGT mutations)<br>• Crigler-Najjar syndrome (type 1 and 2)<br>• Gilbert's syndrome | **Hereditary** (MRP-2 mutations)<br>• Dubin-Johnson syndrome<br>• Rotor's syndrome<br>**Liver disease**<br>• Hepatitis (viral, toxin)<br>• Cirrhosis |
| **Posthepatic** | | **Biliary tract disease**<br>• Gallstones<br>• Tumors (bile duct, gallbladder, or pancreas)<br>• Primary biliary cirrhosis<br>• Primary sclerosing cholangitis |

This classification aids in differential diagnosis and guides targeted investigations based on the biochemical profile and clinical context. Let me know if you'd like this adapted into a diagnostic flowchart or translated for patient education.

**Scientific Interpretation of Liver Function Tests Across Pathologies**

Liver diseases manifest with distinct biochemical profiles that reflect the underlying pathophysiology. **Serum alanine aminotransferase (ALT)** is a marker of hepatocellular injury, while **alkaline phosphatase (ALP)** elevation suggests cholestasis or biliary obstruction. **Total bilirubin** reflects hepatic clearance and conjugation capacity, and **serum bile acids (SBA)**—both preprandial and postprandial—indicate hepatic uptake and portal circulation integrity.

- **Acute Hepatitis/Hepatic Necrosis** shows the most pronounced elevations in ALT (↑↑ to ↑↑↑) and SBA (↑↑ to ↑↑↑), consistent with massive hepatocyte damage and impaired bile acid clearance.
- **Chronic Hepatitis** and **Cirrhosis** exhibit moderate increases in ALT and SBA, reflecting ongoing inflammation and fibrosis with partial functional compromise.
- **Congenital Portosystemic Shunt (CPSS)** presents with normal to mildly elevated ALT, but markedly increased SBA (↑↑↑), due to bypassing of hepatic clearance mechanisms.
- **Biliary Tract Obstruction** is characterized by severe ALP and bilirubin elevation (↑↑ to ↑↑↑), with moderate SBA increases, indicating impaired bile flow.
- **Nonobstructive Biliary Tract Disease** and **Hepatic Neoplasia** show mild to moderate increases in ALT, ALP, and SBA, with variable bilirubin levels depending on the extent of parenchymal or ductal involvement.

Table 2. Key laboratory findings across a spectrum of liver-related conditions

| Laboratory Test | Acute Hepatitis/ Hepatic Necrosis | Chronic Hepatitis | Cirrhosis | CPSS | Biliary Tract Obstruction | Nonobstructive Biliary Tract Disease | Hepatic Neoplasia |
|---|---|---|---|---|---|---|---|
| ALT | ↑↑-↑↑↑ | ↑-↑↑↑ | N-↑↑ | N-↑ | N-↑↑ | N-↑↑ | N-↑↑ |
| ALP | ↑-↑↑ | ↑-↑↑ | N-↑↑ | N-↑ | ↑↑↑ | ↑-↑↑↑ | N-↑↑ |
| Total bilirubin | N-↑↑↑ | N-↑↑ | N-↑↑↑ | N | ↑↑-↑↑↑ | N | N-↑ |
| Preprandial SBA | N-↑↑ | N-↑↑ | ↑-↑↑↑ | N-↑↑ | ↑↑-↑↑↑ | N | N-↑ |
| Postprandial SBA | N-↑↑ | N-↑↑ | ↑-↑↑↑ | ↑↑-↑↑↑ | ↑↑-↑↑↑ | N | N-↑ |
| Ammonia | N-↑↑ | N-↑↑ | N-↑↑ | ↑-↑↑↑ | N | N | N-↑ |

↑, Mild increase; ↑↑, moderate increase; ↑↑↑, severe increase; ALP, serum alkaline phosphatase activity; ALT, serum alanine aminotransferase activity; CPSS, congenital portosystemic shunt; N, within the reference interval; SBA, serum bile acid concentration.

This pattern-based approach aids clinicians in differentiating hepatocellular from cholestatic and vascular liver disorders, guiding further imaging and histological evaluation.

## II.2.5. Diabetes

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Clinically, patients may present with fatigue, pruritus, blurred vision, polyuria, polydipsia, delayed wound healing, and increased body weight, reflecting the systemic impact of impaired glucose metabolism. Preventive strategies

focus on glycemic control through regular physical activity and dietary modifications, which are essential for reducing disease onset and progression. Several risk factors contribute to the development of diabetes, including age over 40 years, obesity, dyslipidemia, genetic predisposition, and arterial hypertension, all of which promote insulin resistance or pancreatic β-cell dysfunction. If left untreated, diabetes can lead to multisystem complications such as neuropathy, vasculopathy, retinopathy, cardiovascular disease, nephropathy, and diabetic foot syndrome. These complications arise from chronic hyperglycemia-induced oxidative stress, endothelial dysfunction, and microvascular damage, underscoring the importance of early diagnosis and comprehensive management to prevent long-term morbidity.

### II.2.5.1. Unusual symptoms of diabetes

Unusual symptoms of diabetes often reflect the systemic and insidious nature of chronic hyperglycemia and its impact on multiple organ systems. Neurological manifestations such as mental changes, fatigue, and leg pain or cramps may result from early diabetic neuropathy and impaired glucose utilization in neural tissues. Ocular symptoms, including vision changes, are commonly due to fluctuating blood glucose levels affecting the lens and retina. Oral health complications like dry mouth and periodontitis arise from reduced salivary flow and increased susceptibility to infection. Dermatological signs such as skin tags, pigmentation changes, and hair loss are linked to insulin resistance and microvascular dysfunction. Unexplained weight loss may indicate catabolic metabolism in the context of insulin deficiency, while increased urination reflects osmotic diuresis secondary to hyperglycemia. Additionally, recurrent infections and sexual health disturbances are associated with immune dysregulation and vascular compromise. Recognizing these atypical presentations is crucial for early diagnosis and comprehensive management of diabetes mellitus.

### II.2.5.2. Types of Diabetes

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In healthy individuals, insulin produced by pancreatic β-cells binds to insulin receptors on target cells, facilitating glucose uptake and utilization. In Type 1 diabetes, autoimmune destruction of β-cells leads to absolute insulin deficiency, preventing insulin-mediated glucose transport into cells and resulting in marked hyperglycemia. In contrast, Type 2 diabetes is defined by insulin resistance, wherein peripheral tissues fail to respond adequately to circulating insulin despite its presence, leading to impaired glucose uptake and progressive β-cell dysfunction. These distinct pathophysiological mechanisms

necessitate tailored therapeutic strategies, including exogenous insulin administration for Type 1 diabetes and insulin sensitizers or secretagogues for Type 2 diabetes.

### II.2.5.3. Relation between gut, liver and Diabetes

Diet-induced intestinal epithelial barrier (IEB) dysfunction plays a pivotal role in the pathogenesis of insulin resistance and liver injury through a gut-liver axis mechanism. Consumption of high-fat, processed foods compromises the integrity of the IEB, facilitating translocation of bacterial lipopolysaccharides (LPS) across the gut vascular barrier (GVB) into the portal circulation. Upon reaching the liver, LPS activates nuclear factor kappa B (NF-κB) signaling in hepatocytes and immune cells, leading to the release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines not only impair insulin signaling pathways, contributing to systemic insulin resistance, but also promote M1 macrophage polarization and further cytokine amplification. In adipose tissue, elevated TNF-α and IL-6 suppress insulin-like growth factors (IGF-1 and IGF-2), exacerbating metabolic dysfunction. Concurrent hepatic inflammation and hepatocyte damage stimulate hepatic stellate cell (HSC) proliferation and liver sinusoidal endothelial cell (LSEC) capillarization, culminating in fibrotic remodeling and compromised hepatic microcirculation. This integrated inflammatory cascade underscores the critical role of gut-derived endotoxemia in metabolic disease progression (Fig; 21).

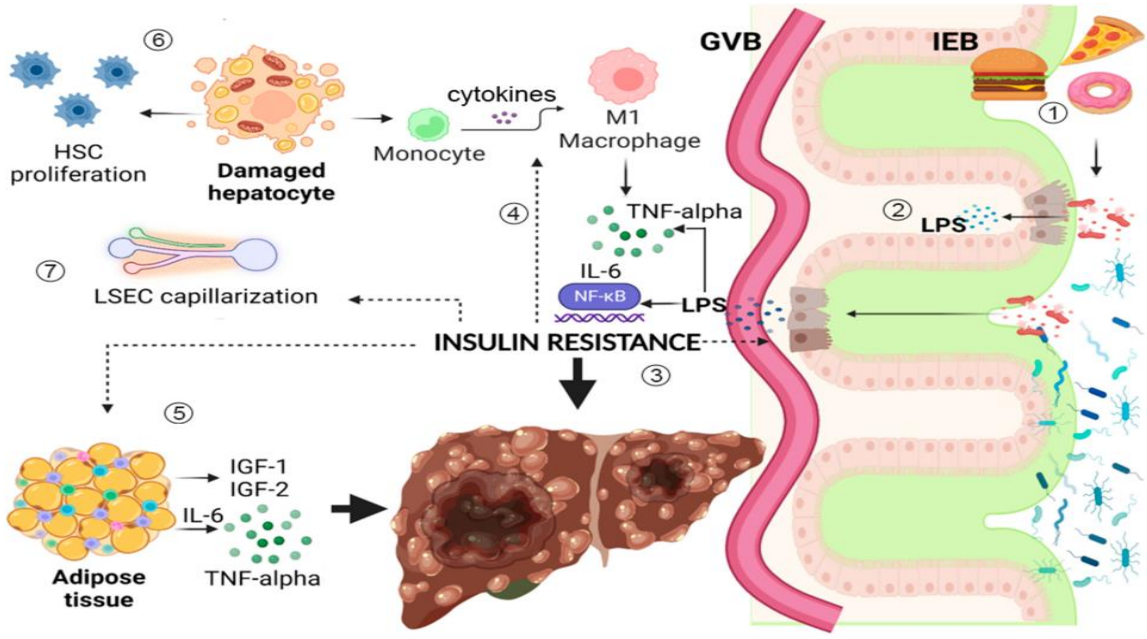



**Figure 21. The pathophysiological cascade linking intestinal epithelial barrier (IEB) dysfunction to insulin resistance and hepatic injury.**

### II.2.5.4. Diabetes complications and cardiovascular disease

Insulin resistance is a central feature of metabolic syndrome and plays a critical role in the pathogenesis of type 2 diabetes and cardiovascular disease (CVD). In adipose tissue, insulin resistance leads to elevated levels of non-esterified fatty acids (NEFA) and reduced adiponectin, contributing to hepatic triglyceride accumulation and impaired insulin signaling. Genetic predisposition and acquired factors, including insulin deficiency, exacerbate hepatic insulin resistance and promote hyperglycemia. Concurrently, excessive intake of saturated fats and sugars, physical inactivity, and increased body mass index (BMI) and waist circumference impair insulin sensitivity in skeletal muscle. These metabolic disturbances enhance de novo lipogenesis, resulting in elevated very-low-density lipoprotein triglycerides (VLDL-TG), reduced high-density lipoprotein cholesterol (HDL-C), and increased small dense low-density lipoprotein particles (LDL-T), all of which are atherogenic. Insulin resistance also affects platelets, increasing their aggregation potential and contributing to vascular dysfunction through the actions of glucose, insulin, acute phase proteins, and coagulation factors. Collectively, these alterations define the metabolic/insulin resistance syndrome, significantly increasing the risk of developing type 2 diabetes and CVD (Fig. 22).

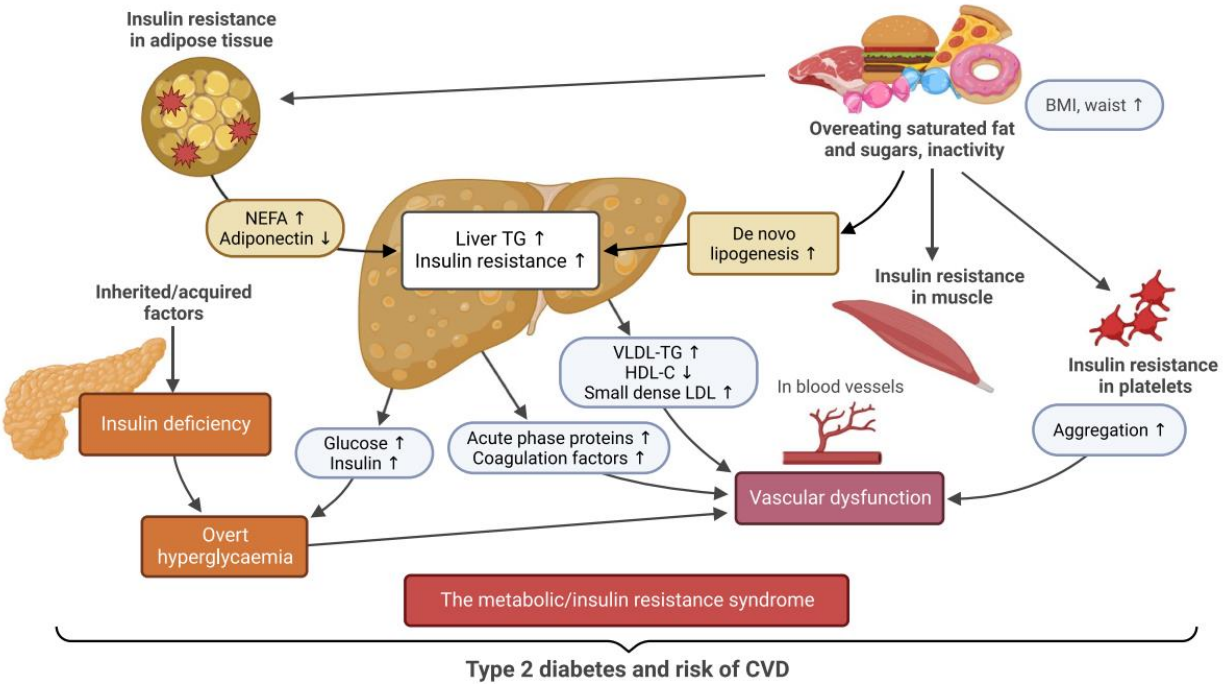



**Figure 22. The complex interplay between insulin resistance, type 2 diabetes, and cardiovascular disease (CVD)**

## II.2.6. Gallbladder gallstones

Bile produced by hepatocytes is transported via the hepatic ducts and stored in the gallbladder, where it is concentrated and released through the cystic duct into the common bile duct. The common bile duct merges with the pancreatic duct and empties into the duodenum, facilitating lipid digestion. The presence of gallstones—solid concretions typically composed of cholesterol or bilirubin—within the gallbladder or cystic duct can obstruct bile flow, leading to clinical conditions such as biliary colic, acute cholecystitis, or obstructive jaundice. In severe cases, migration of gallstones into the common bile duct may precipitate cholangitis or pancreatitis due to shared ductal anatomy. Understanding the spatial and functional dynamics of the biliary system is essential for diagnosing and managing hepatobiliary disorders.

### II.2.6.1.Symptoms

Gallstone pain, also known as biliary colic, typically presents as sudden and rapidly intensifying pain localized in the upper right quadrant of the abdomen or centrally beneath the sternum. This visceral pain may radiate to the back, particularly between the shoulder blades, or extend to the right shoulder due to shared neural pathways via the phrenic nerve. Accompanying symptoms often include nausea and vomiting, reflecting autonomic nervous system involvement. The duration of pain episodes can range from several minutes to a few hours, commonly triggered by fatty meals that stimulate gallbladder contraction. These clinical features are indicative of transient obstruction of the cystic duct by gallstones and are critical for the diagnosis and management of cholelithiasis.

### II.2.6.2. Risk factors for gallstones

Demographic and Genetic Factors:

* Gender: Women are more susceptible than men due to hormonal influences like pregnancy and the use of oral contraceptives.

* Age: The likelihood of developing gallstones increases after the age of 40.

* Ethnicity: Certain ethnic groups, such as Native Americans and Mexican-Americans, have a higher genetic predisposition.

* Family History: A family history of gallstones increases an individual's risk.

Lifestyle and Dietary Factors:

* Obesity: Being overweight is a significant risk factor as it can increase cholesterol levels in bile.

* Diet: Diets high in fat and cholesterol and low in fiber contribute to gallstone formation.

* Rapid Weight Loss: Losing weight too quickly can cause the liver to release more cholesterol into the bile.

* Sedentary Lifestyle: Lack of physical activity is also a risk factor.

Medical Conditions and Medications:

* Diabetes: Individuals with diabetes often have higher levels of triglycerides, a type of blood fat, which

is a risk factor for gallstones.

* Blood Disorders: Conditions like sickle cell anaemia can lead to the formation of pigment gallstones.

* Liver Disease: Liver cirrhosis and other liver diseases can increase the risk.

* Crohn's Disease: This inflammatory bowel disease can affect the absorption of bile acids.

* Medications: Some cholesterol-lowering drugs can increase the amount of cholesterol in bile.

* Total Parenteral Nutrition (TPN): Being fed intravenously can lead to the formation of gallstones.

### II.2.6.3. Types of gallstones

Gallstone formation is a multifactorial process influenced by biochemical composition, anatomical location, and underlying pathophysiological mechanisms. Cholesterol stones, which account for approximately 80% of cases, primarily arise in the gallbladder due to abnormal cholesterol metabolism and bile supersaturation. In this context, cholesterol precipitates in the presence of calcium ions, forming insoluble complexes alongside bile salts and lecithin. Black pigment stones, comprising around 10% of cases, also originate in the gallbladder and are typically associated with chronic hemolysis. The breakdown of erythrocytes leads to elevated levels of unconjugated bilirubin, which combines with calcium to form calcium bilirubinate, resulting in dark, dense stones. Mixed or brown pigment stones, also representing about 10% of cases, predominantly form within the biliary ducts and are linked to bacterial infection or parasitic infestation. These conditions promote the enzymatic degradation of lecithin via β-glucuronidase, generating fatty acids and unconjugated bilirubin that precipitate with calcium to form softer, heterogeneous stones. Each type of gallstone reflects distinct metabolic and infectious etiologies, with implications for diagnosis, treatment, and prevention strategies (Fig. 23).

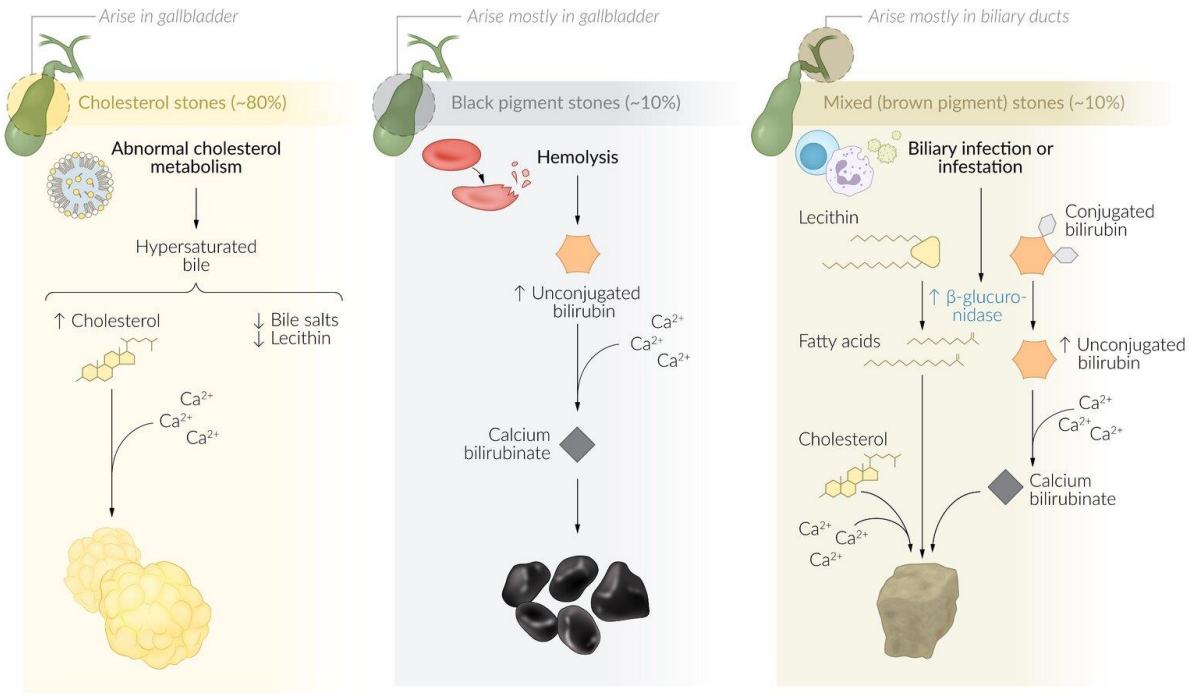



**Figure 23. Gallstone types and formation**

### II.2.6.4. Gallstone-related disorders

Gallstone-related disorders encompass a spectrum of hepatobiliary conditions, each defined by distinct anatomical involvement, pathophysiological mechanisms, clinical presentations, laboratory findings, and imaging characteristics.

**Cholelithiasis** refers to the presence of gallstones within the gallbladder, typically resulting from bile stasis, supersaturation with cholesterol, and impaired gallbladder motility. Most cases are asymptomatic; however, symptomatic individuals may experience right upper quadrant (RUQ) pain lasting less than six hours, known as biliary colic. Laboratory parameters are generally within normal limits, and ultrasonography reveals echogenic stones with posterior acoustic shadowing.

**Choledocholithiasis** involves gallstones that have migrated into the common bile duct, often originating from the gallbladder. Clinically, patients present with prolonged RUQ pain exceeding six hours and may exhibit jaundice. Laboratory findings include elevated total bilirubin, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and transaminases (AST, ALT). Imaging modalities such as ultrasound may show a dilated common bile duct and intraductal stones, while magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) confirm ductal obstruction via filling defects.

**Acute cholecystitis** is characterized by acute inflammation of the gallbladder secondary to cystic duct obstruction by a gallstone. Patients typically present with RUQ pain, fever, and a positive Murphy sign. Laboratory evaluation reveals leukocytosis and elevated C-reactive protein (CRP).

Ultrasonography demonstrates gallbladder wall thickening and pericholecystic fluid, while hepatobiliary iminodiacetic acid (HIDA) scanning shows nonvisualization of the gallbladder beyond four hours, indicating functional obstruction.

**Acute cholangitis** is a bacterial infection of the biliary tract precipitated by biliary obstruction, often due to gallstones. The classical clinical presentation includes Charcot's triad: RUQ pain, fever, and jaundice. In severe cases, Reynold's pentad—Charcot's triad plus hypotension and altered mental status—may be observed. Laboratory findings include leukocytosis and elevated levels of GGT, ALP, AST, ALT, and total bilirubin. MRCP is recommended when the diagnosis remains uncertain, providing non-invasive visualization of the biliary tree.

These conditions represent progressive stages of gallstone-related pathology, each requiring specific diagnostic and therapeutic approaches to prevent complications such as sepsis, biliary cirrhosis, or pancreatitis.

# References


- Longnecker, D. S. (2021). Anatomy and histology of the pancreas (Version 2.0). The Pancreapedia: Exocrine Pancreas Knowledge Base. https://pancreapedia.org/reviews/anatomy-and-histology-of-pancreas.
- Trefts, E., Gannon, M., & Wasserman, D. H. (2017). The liver. Current Biology, 27(21), R1147–R1151.
- Koyama, Y., & Brenner, D. A. (2017). Liver inflammation and fibrosis. Journal of Clinical Investigation, 127(1), 55–64.
- Garbuzenko, D. V., Arefyev, N. O., & Belov, D. V. (2022). Pathophysiological mechanisms of hepatic stellate cells activation in liver fibrosis. World Journal of Gastroenterology, 28(16), 1666–1685.
- Lee, Y. A., Wallace, M. C., & Friedman, S. L. (2015). Pathobiology of liver fibrosis: A translational success story. Gut, 64(5), 830–841.
- Singh, A., Koritala T., & Jialal I. (2023). Unconjugated hyperbilirubinemia. In StatPearls. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK549796/
- Chawla, A., Chawla, R., & Jaggi, S. (2016). Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian Journal of Endocrinology and Metabolism, 20(4), 546–551.
- Portincasa, P., Moschetta, A., & Palasciano, G. (2006). Cholesterol gallstone disease. The Lancet, 368(9531), 230–239.

# Chapter III Physiopathology of Kidneys

# III.1. Generalities on the urinary system

The urinary system is responsible for filtering blood, removing metabolic waste, regulating fluid and electrolyte balance, and maintaining acid–base homeostasis. It consists of:

- **Kidneys**: Filter blood to produce urine by removing urea, excess salts, and water.
- **Ureters**: Muscular tubes that transport urine from the kidneys to the bladder.
- **Urinary bladder**: A hollow organ that stores urine until excretion.
- **Urethra**: A tube that carries urine from the bladder to the external environment.

Urine formation involves three key processes: glomerular filtration, tubular reabsorption, and tubular secretion.

# III.2. Differences Between Male and Female Urinary Systems

| Feature | Male | Female |
|---|---|---|
| **Urethra length** | ~20 cm; passes through prostate and penis | ~4 cm; opens anterior to vaginal opening |
| **Urethral function** | Dual: urinary and reproductive | Solely urinary |
| **Bladder position** | Anterior to rectum, superior to prostate | Anterior to uterus and vagina |
| **Risk of UTI** | Lower due to longer urethra | Higher due to shorter urethra |

These anatomical differences influence clinical presentations, such as urinary tract infections being more common in females, and prostate-related urinary issues occurring exclusively in males. Let me know if you'd like diagrams or a deeper dive into renal physiology.

# III.3. Overview of Kidney and Nephron Anatomy

The kidney is encapsulated by a fibrous layer and organized into an outer cortex and inner medulla. Within the cortex reside the glomeruli and convoluted tubules, while the medulla contains the renal pyramids, loops of Henle, and collecting ducts. Urine formed in the nephrons drains through the renal papillae into minor calyces, which converge into major calyces and ultimately the renal pelvis, leading to the ureter. The nephron, the functional unit of the kidney, comprises a glomerulus enclosed by Bowman’s capsule, followed by tubular segments specialized for selective

reabsorption and secretion. Blood enters the glomerulus via afferent arterioles and exits through efferent arterioles, which give rise to either peritubular capillaries in cortical nephrons or vasa recta in juxtamedullary nephrons. These vascular networks facilitate countercurrent exchange and maintain osmotic gradients critical for water reabsorption. The arcuate and interlobular arteries and veins delineate vascular territories between cortex and medulla, while stellate veins drain superficial cortical blood. This intricate architecture supports the kidney's role in filtration, homeostasis, and endocrine regulation (Fig. 24).

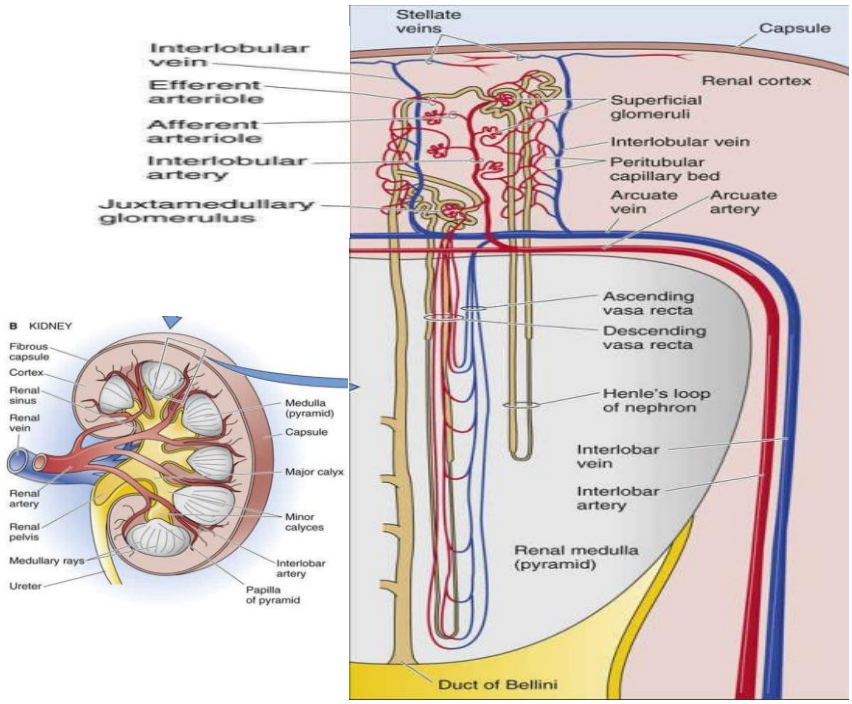



**Figure 24. Kidney and Nephron Anatomy**

The nephron spans distinct regions of the kidney, beginning in the renal cortex and extending into the medulla. Two primary nephron types are depicted: superficial nephrons, which reside predominantly in the cortex, and juxtamedullary nephrons, which extend deep into the inner medulla and play a critical role in urine concentration. Each nephron initiates with the Bowman's capsule, surrounding the glomerulus, where blood filtration occurs. The filtrate then passes through the proximal convoluted tubule (PCT), proximal straight tubule (PST), and the loop of Henle, which includes descending and ascending limbs—thin and thick segments—critical for establishing the medullary osmotic gradient. The distal convoluted tubule (DCT) and macula densa contribute to electrolyte regulation and tubuloglomerular feedback. Urine flows through the connecting tubule (CNT), initial collecting tubule (ICT), and cortical collecting tubule (CCT), eventually reaching the outer medullary collecting duct (OMCD) and inner medullary collecting duct (IMCD), terminating at the duct of Bellini. This pathway reflects the nephron's role in

filtration, reabsorption, secretion, and final urine concentration, coordinated by vascular and tubular interactions across cortical and medullary zones (Figure 25).

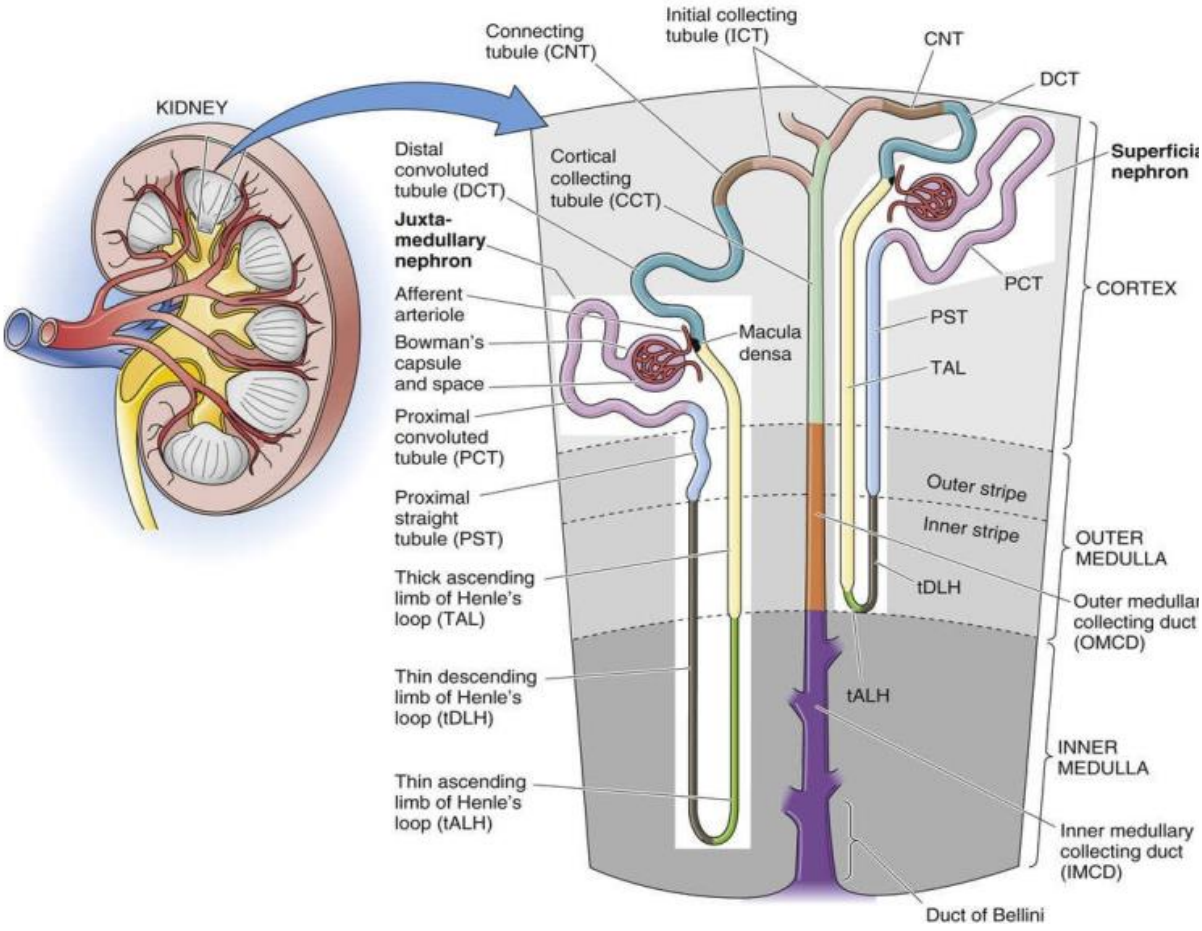



**Figure 25. Physiology of the nephron**

## 3.1. Function of the Nephron

Filtration begins at the glomerulus, where blood enters through the afferent arteriole and exits via the efferent arteriole. The glomerular capillaries filter plasma into Bowman's space, initiating the formation of the filtrate. In the proximal convoluted tubule, essential solutes such as bicarbonate ($HCO_3^-$), sodium ($Na^+$), chloride ($Cl^-$), glucose, amino acids, and water are reabsorbed primarily through active transport mechanisms. The filtrate then enters the loop of Henle, where the descending limb permits passive water reabsorption, while the ascending limb facilitates active reabsorption of $Na^+$, $Cl^-$, and potassium ($K^+$), contributing to the medullary osmotic gradient. In the distal convoluted tubule, sodium and chloride are actively reabsorbed under the influence of aldosterone, while calcium reabsorption is regulated by parathyroid hormone (PTH). The final segment, the collecting duct, adjusts urine concentration in response to vasopressin (antidiuretic hormone, ADH), which promotes water reabsorption through aquaporin channels. This hormonally regulated fine-tuning ensures homeostasis of fluid volume, osmolality, and electrolyte balance (Fig. 26).

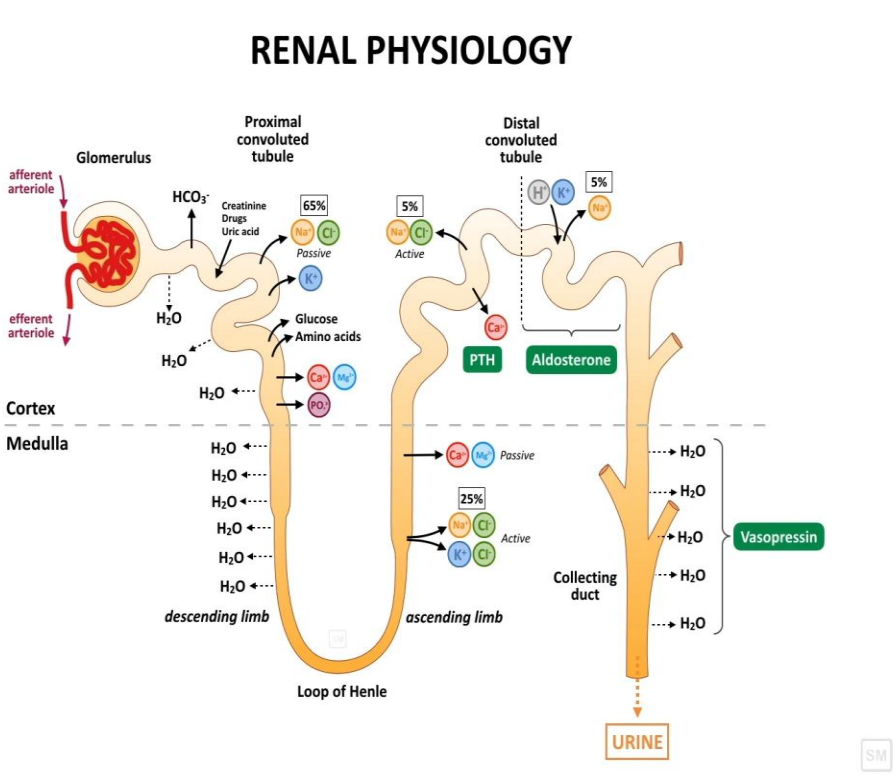



**Figure 26. Filtration of the blood by the nephron unit**

## 3.2. The renin–angiotensin system

The renin–angiotensin system (RAS) is a critical hormonal cascade that regulates blood pressure, fluid balance, and systemic vascular resistance. It is activated in response to a drop in blood pressure or reduced extracellular fluid volume. The process begins with the release of renin from the juxtaglomerular cells of the kidney. Renin acts enzymatically on angiotensinogen, a glycoprotein produced by the liver, converting it into angiotensin I. This inactive precursor is then cleaved by angiotensin-converting enzyme (ACE), primarily released from the pulmonary endothelium, to form angiotensin II, a potent vasoconstrictor.

Angiotensin II exerts multiple physiological effects: it induces vasoconstriction of arterioles, thereby increasing systemic vascular resistance and elevating blood pressure. Additionally, it stimulates the adrenal cortex to secrete aldosterone, a mineralocorticoid hormone that promotes sodium and water reabsorption in the distal nephron, particularly in the collecting ducts. This reabsorption contributes to increased intravascular volume and further supports blood pressure restoration. The RAS is tightly regulated and plays a central role in cardiovascular homeostasis, with dysregulation implicated in hypertension, heart failure, and renal pathologies (Fig. 27).

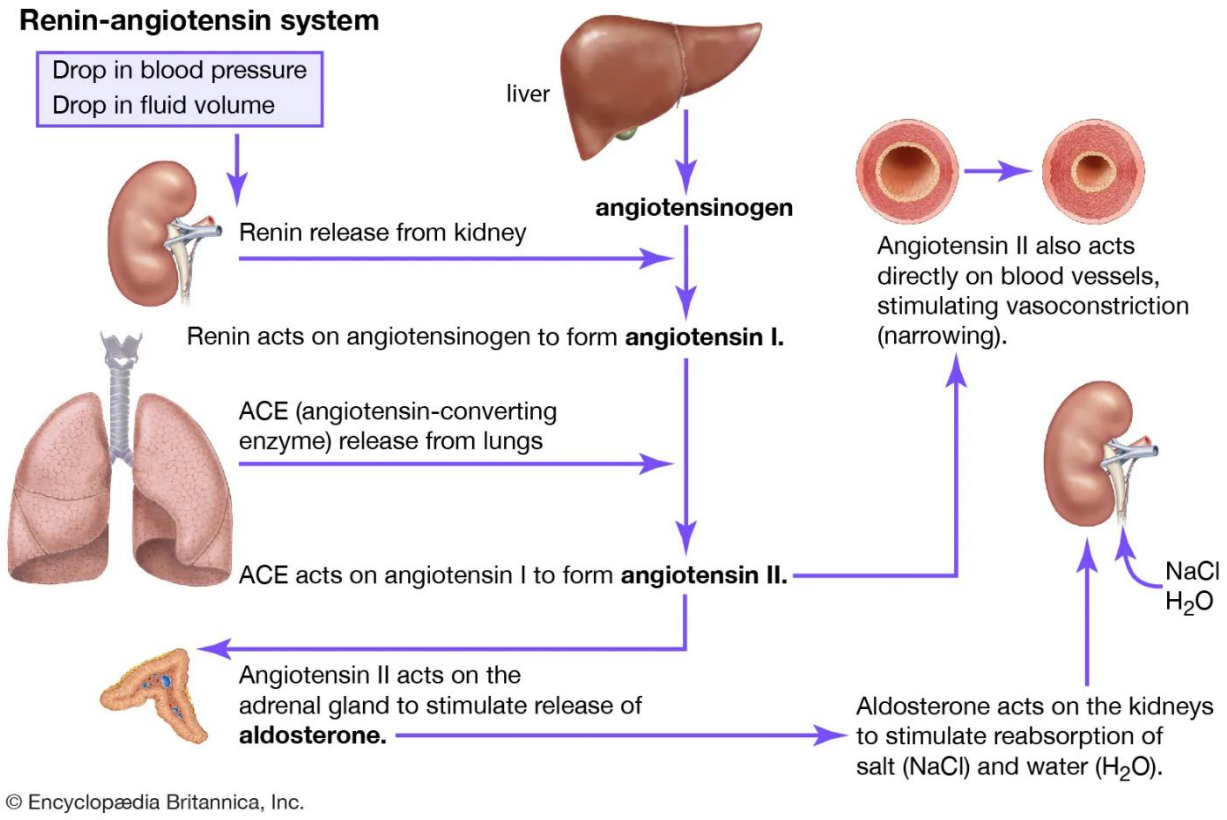



**Figure 27. The renin angiotensin system**

## 3.3. Urinary and blood analysis

Urinary and blood analyses are crucial for diagnosing and monitoring diseases of the urinary system, including infections and kidney failure. These tests provide a wealth of information about kidney function, inflammation, and the presence of metabolic abnormalities.

### 3.3.1. Urine Analysis

Urinalysis is a fundamental test that examines the physical, chemical, and microscopic properties of urine.

*1. Macroscopic and Dipstick Analysis*

Color and Clarity: Changes in color or clarity can indicate dehydration, bleeding, or infection.

pH: Abnormal pH may suggest kidney stones or tubular acidosis.

Protein: The presence of protein (proteinuria), particularly albumin, is a key indicator of kidney damage. The albumin-to-creatinine ratio (ACR) is a sensitive test for early detection.

Glucose: High levels of glucose in the urine are a sign of uncontrolled diabetes, a major risk factor for kidney disease.

Nitrites and Leukocyte Esterase: These are markers of a urinary tract infection (UTI).

*2. Microscopic Analysis*

Red and White Blood Cells: An increased number of red blood cells (hematuria) or white blood cells (pyuria) can indicate a variety of conditions, including infections, stones, or tumors.

Casts: These are cylindrical structures formed in the kidneys and can indicate underlying kidney disease.

Crystals: The presence of certain crystals can indicate a risk of kidney stone formation.

*3. Advanced Urine Tests*

Urine Culture: This test is used to identify the specific bacteria causing a UTI and to determine the most effective antibiotic for treatment.

24-Hour Urine Collection: This measures the total amount of a substance, such as protein, excreted in the urine over a 24-hour period, providing a more accurate assessment of kidney function.

Novel Biomarkers: Recent research has identified several new urinary biomarkers for the early detection and monitoring of kidney disease:

Kidney Injury Molecule-1 (KIM-1): A marker for acute tubular injury.

Dickkopf-3 (DKK3): Associated with the progression of chronic kidney disease (CKD).

Uromodulin (UMOD): Levels of this protein may be altered in certain kidney diseases.

### 3.3.2. Blood Analysis

Blood tests for kidney function primarily measure the levels of waste products and electrolytes in the blood.

*1. Standard Blood Tests*

Blood Urea Nitrogen (BUN): Urea is a waste product of protein metabolism that is filtered by the kidneys.

Elevated BUN levels can indicate decreased kidney function.

Serum Creatinine: Creatinine is a waste product from muscle metabolism. Like BUN, elevated creatinine levels suggest impaired kidney function.

Estimated Glomerular Filtration Rate (eGFR): This is considered the best overall indicator of kidney function. It is a calculation based on the serum creatinine level, age, sex, and race. A low eGFR indicates that the kidneys are not filtering waste as well as they should.

*2. Advanced Blood Tests*

Cystatin C: This is another protein that is filtered by the kidneys. Because its level is not affected by muscle mass, it can be a more accurate indicator of kidney function than creatinine in some individuals.

Neutrophil Gelatinase-Associated Lipocalin (NGAL): This is a marker of acute kidney injury.

Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR): This is an emerging biomarker that may be associated with the progression of kidney disease.

# III.4. Urinary system disorders

## 4.1. Urinary Tract Infection (UTI)

A urinary tract infection (UTI) is a microbial invasion of any part of the urinary system, including the urethra, bladder, ureters, and kidneys. The vast majority of UTIs are caused by bacteria, with Escherichia coli being the most common pathogen, which typically migrates from the gastrointestinal tract to the urethra. Causes and risk factors include female anatomy (a shorter urethra), sexual activity, certain types of birth control, urinary catheters, and conditions that cause incomplete bladder emptying. Symptoms of a lower UTI (cystitis) include a painful or burning sensation during urination (dysuria), a frequent and urgent need to urinate, cloudy or strong-smelling urine, and pelvic pain. If the infection ascends to the kidneys (pyelonephritis), symptoms can become more severe, including fever, chills, flank pain, nausea, and vomiting. Recent research highlights the increasing prevalence of multidrug-resistant bacteria in UTIs and explores the role of the urobiome in infection susceptibility.

## 4.2. Cystitis

Cystitis is the inflammation of the urinary bladder, most frequently caused by a bacterial UTI. The primary causative agent is Escherichia coli, which enters the urethra and colonizes the bladder. Besides bacterial infection, cystitis can also be caused by certain medications, radiation therapy, or chemical irritants. Symptoms are characteristic of a lower UTI and include dysuria, urinary frequency and urgency, suprapubic pain, and urine that may be cloudy, bloody (hematuria), or malodorous. A low-grade fever may be present, but a high fever could indicate that the infection has spread to the kidneys. Recent guidelines from the Infectious Diseases Society of America (IDSA) in 2024 and 2025 provide updated recommendations for the treatment of antimicrobial-resistant gram-negative infections, including complicated and uncomplicated cystitis, reflecting the evolving landscape of antibiotic resistance.

## 4.3. Pyelonephritis

Pyelonephritis is a serious infection of the kidney and renal pelvis, representing an upper urinary tract infection. It typically results from bacteria, most commonly E. coli, ascending from the bladder to the kidneys. Causes include untreated or undertreated cystitis, urinary tract obstructions (like kidney stones or an enlarged prostate), and vesicoureteral reflux (the backward flow of urine). Symptoms are often systemic and more severe than those of a lower UTI, including

high fever, shaking chills, severe flank pain, nausea, and vomiting, in addition to classic urinary symptoms like dysuria and urgency. Recent studies and guidelines emphasize the importance of prompt and appropriate antibiotic treatment to prevent complications such as renal scarring and sepsis, especially in high-risk populations like pregnant women and children.

## 4.4. Glomerulonephritis

Glomerulonephritis is a group of diseases characterized by inflammation of the glomeruli, the kidney's filtering units. This inflammation impairs the kidney's ability to filter waste and fluid from the blood. Causes are varied and can be primary (originating in the kidney) or secondary to other illnesses. Common causes include infections (like post-streptococcal glomerulonephritis), autoimmune diseases (such as lupus nephritis and IgA nephropathy), and vasculitis. Symptoms include hematuria (cola-colored urine), proteinuria (foamy urine), edema (swelling) in the face, hands, and feet, and hypertension. Recent advancements in treatment, particularly for IgA nephropathy, include the FDA approval of targeted-release budesonide and sparsentan, which have shown to reduce proteinuria and slow the progression of kidney disease.

## 4.5. Nephrotic Syndrome

Nephrotic syndrome is a clinical syndrome defined by a collection of signs resulting from damage to the glomeruli, leading to excessive protein loss in the urine. It is scientifically characterized by heavy proteinuria (>3.5 g/24h), hypoalbuminemia (low blood albumin), peripheral edema, and hyperlipidemia. Primary causes are kidney diseases that directly affect the glomeruli, such as minimal change disease (most common in children), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy. Secondary causes include systemic diseases like diabetes mellitus, lupus, and amyloidosis. The cardinal symptom is significant edema, often starting around the eyes and progressing to the lower extremities, accompanied by foamy urine and fatigue. Recent research has focused on genetic causes and targeted therapies, with promising results from clinical trials on drugs like obinutuzumab for idiopathic nephrotic syndrome in children.

## 4.6. Urinary Tract Obstruction

Urinary tract obstruction is a condition where the flow of urine is blocked, either partially or completely, at any point in the urinary tract. This blockage causes urine to back up, leading to increased pressure and potential damage to the urinary system, including hydronephrosis and kidney failure. Causes can be intrinsic, such as kidney stones (urolithiasis), tumors, or strictures (narrowing of the ureter or urethra), or extrinsic, such as an enlarged prostate (BPH), abdominal tumors, or retroperitoneal fibrosis. Symptoms depend on the location and severity of the

obstruction and can include pain in the flank or abdomen, difficulty urinating, a weak urine stream, and a feeling of incomplete bladder emptying. An acute, complete obstruction can cause severe pain and is a medical emergency. Recent literature reviews emphasize the importance of timely diagnosis and management to prevent irreversible kidney damage.

## 4.8. Urolithiasis

Urolithiasis refers to the formation of stones (calculi) within the urinary tract. These stones are formed from mineral and salt deposits that crystallize in concentrated urine. The most common cause is a combination of factors including dehydration, diet (high in sodium, protein, and oxalate), and metabolic abnormalities (such as hypercalciuria). Certain medical conditions like gout, hyperparathyroidism, and recurrent UTIs can also predispose individuals to stone formation. The hallmark symptom of a kidney stone passing into the ureter is renal colic, an excruciatingly severe, intermittent pain in the flank that may radiate to the groin. Other symptoms include hematuria, nausea, vomiting, and painful urination. The European Association of Urology (EAU) and the American Urological Association (AUA) regularly update their guidelines on the management of urolithiasis, with the most recent EAU guidelines published in 2025, reflecting advancements in minimally invasive surgical techniques and metabolic evaluation for prevention.

## 4.7. Hydronephrosis

Hydronephrosis is the swelling or distention of a kidney due to the backup of urine, and it is a direct consequence of urinary tract obstruction. It is not a disease in itself but a physical result of an underlying condition that prevents urine from draining properly from the kidney. The causes are the same as those for urinary tract obstruction, including kidney stones, tumors, BPH, strictures, and congenital abnormalities. In many cases, especially if it develops gradually, hydronephrosis can be asymptomatic. When symptoms do occur, they are often related to the underlying cause and can include flank pain, nausea, fever (if infection is present), and changes in urinary habits. Recent research has focused on the management of antenatal hydronephrosis (detected in fetuses), with studies aiming to refine risk stratification and determine the optimal timing for intervention to prevent long-term kidney damage.

## 4.9. Renal Failure (Acute and Chronic)

Renal failure, or kidney failure, is a condition in which the kidneys lose their ability to adequately filter waste products from the blood. It is classified as either acute or chronic.

* **Acute Renal Failure** (Acute Kidney Injury - AKI): This is a sudden and rapid loss of kidney function that occurs over hours to days. It is often reversible if treated promptly. Common causes include severe dehydration, shock, sepsis, acute tubular necrosis (often due to toxins or ischemia),

and urinary tract obstruction. Symptoms can include a significant decrease in urine output, fluid retention causing swelling in the legs and feet, fatigue, and confusion.

*** Chronic Renal Failure** (Chronic Kidney Disease - CKD): This is a gradual and progressive loss of kidney function over a period of months to years. The most common causes are diabetes and hypertension, which slowly damage the kidneys over time. Other causes include glomerulonephritis and polycystic kidney disease. CKD is often asymptomatic in its early stages, but as it progresses, symptoms may include fatigue, swelling, changes in urination, and nausea. Recent breakthroughs in CKD management include the use of SGLT2 inhibitors and GLP-1 receptor agonists, which have been shown to slow the progression of diabetic kidney disease, and advancements in xenotransplantation offer hope for future treatment options.

# References


- Biga, L. M., Dawson, S., Harwell, A., Hopkins, R., Kaufmann, J., LeMaster, M., Matern, P., Morrison-Graham, K., Quick, D., & Runyeon, J. (n.d.). *Anatomy & Physiology*. OpenStax, Oregon State University.
- Barrett, K. E., Barman, S. M., Brooks, H. L., & Yuan, J. X.-J. (2019). *Ganong's review of medical physiology* (26th ed.). McGraw-Hill Education.
- Boron, W. F., & Boulpaep, E. L. (2017). *Medical physiology* (3rd ed.). Elsevier.
- Kibble, J. D. (2013). *The big picture: Physiology (2nd ed.)*. McGraw-Hill Education.
- https://www.britannica.com/science/renin-angiotensin-system. Updated; Oct. 14, 2025.
- National Institute of Diabetes and Digestive and Kidney Diseases. (2023). Kidney disease tests & diagnosis. U.S. Department of Health and Human Services. https://www.niddk.nih.gov/health-information/kidney-disease/tests
- National Kidney Foundation. (2024). Kidney tests. https://www.kidney.org/atoz/content/kidneytests
- Peña-Polanco, D., et al. (2023). Novel biomarkers for the prediction of chronic kidney disease progression. Journal of Clinical Medicine, 12(13), 4393.
- Zhang, D., et al. (2023). Advances in biomarkers for early diagnosis of chronic kidney disease. Frontiers in Physiology, 14, 1195849.
- Levin, A., et al. (2024). Kidney Disease: Improving Global Outcomes (KDIGO) 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International, 105(4S), S117-S314.
- Khan, A. M. (2023). Obstructive uropathy. In StatPearls. StatPearls Publishing.
- Herrington, W. G., Staplin, N., Wanner, C., Green, J. B., Hauske, S. J., Emberson, J. R., Preiss, D., Judge, P., Mayne, K. J., Ng, S. Y. A., Baigent, C., & Landray, M. J. (2023). Empagliflozin in patients with chronic kidney disease. New England Journal of Medicine, 388(2), 117-127.

# Chapter IV: Phyiopathology of Lungs

# IV.1. Generalities

## IV.1.1. Human respiratory system

The human respiratory system is responsible for taking in oxygen and expelling carbon dioxide from the body. It is divided into the upper and lower respiratory tracts. The upper tract includes the nose, nasal cavity, mouth, sinuses, pharynx (throat), and larynx (voice box). Air travels from the nose and mouth through the pharynx and larynx, then moves into the trachea, which is supported by cartilaginous rings. The trachea then splits into two main bronchi, each leading to a lung (Fig. 28).

Inside the lungs, the bronchi branch into smaller bronchioles, ending in tiny air sacs known as alveoli. Gas exchange takes place in the alveoli, where oxygen passes into the blood and carbon dioxide is removed. The lungs are divided into lobes—three on the right and two on the left. The diaphragm, a large muscle below the lungs, aids breathing by contracting and relaxing during respiration.

This system also contains various anatomical features such as the paranasal sinuses, vocal folds, and multiple lobes and fissures within each lung. The close association between the alveoli and capillary networks allows for efficient oxygen and carbon dioxide exchange between the air and the bloodstream

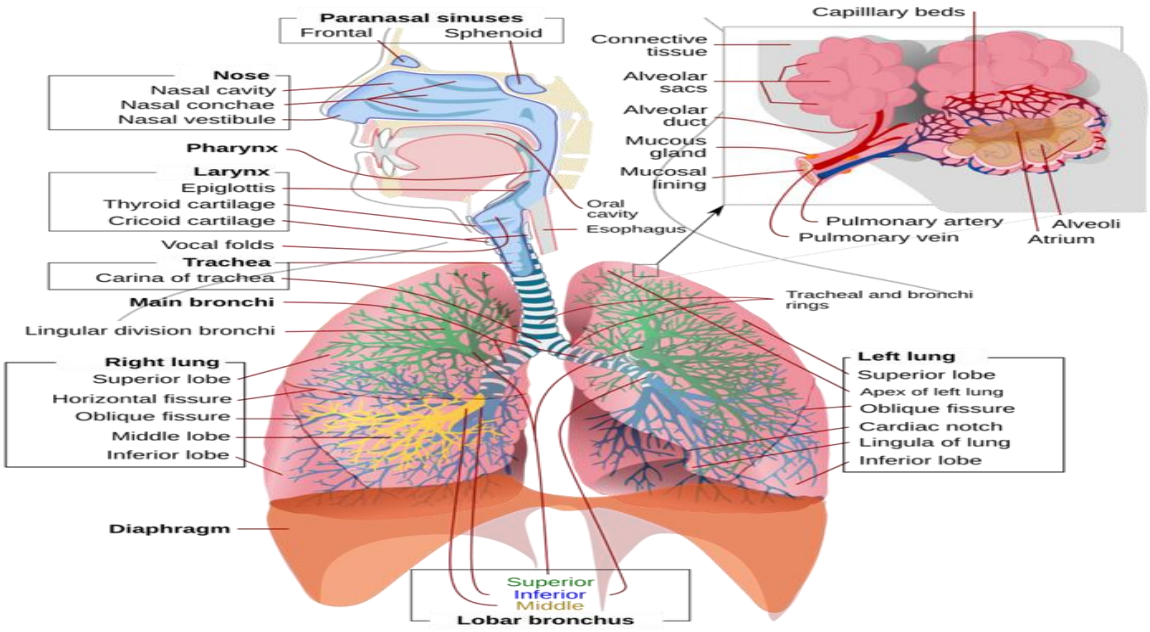



**Figure 28. Respiratory system**

## IV.1.2. Oxygen transportation system

Oxygen enters the lungs and diffuses into the blood, where it binds to haemoglobin. The oxygen-rich blood is pumped by the left heart to tissues, supplying cells with oxygen for metabolism. Cells produce carbon dioxide as a waste product, which diffuses into the blood and is transported back to the lungs by the right heart. Here, carbon dioxide is expelled during exhalation. The respiratory centers in the medulla of the brain monitor oxygen, carbon dioxide, and pH levels in the blood, adjusting motor signals to respiratory muscles to regulate breathing rates and efficiency. Thus, the diagram captures the coordination between the lungs, heart, blood, and control centers that sustains cellular respiration and homeostasis (Fig. 29).

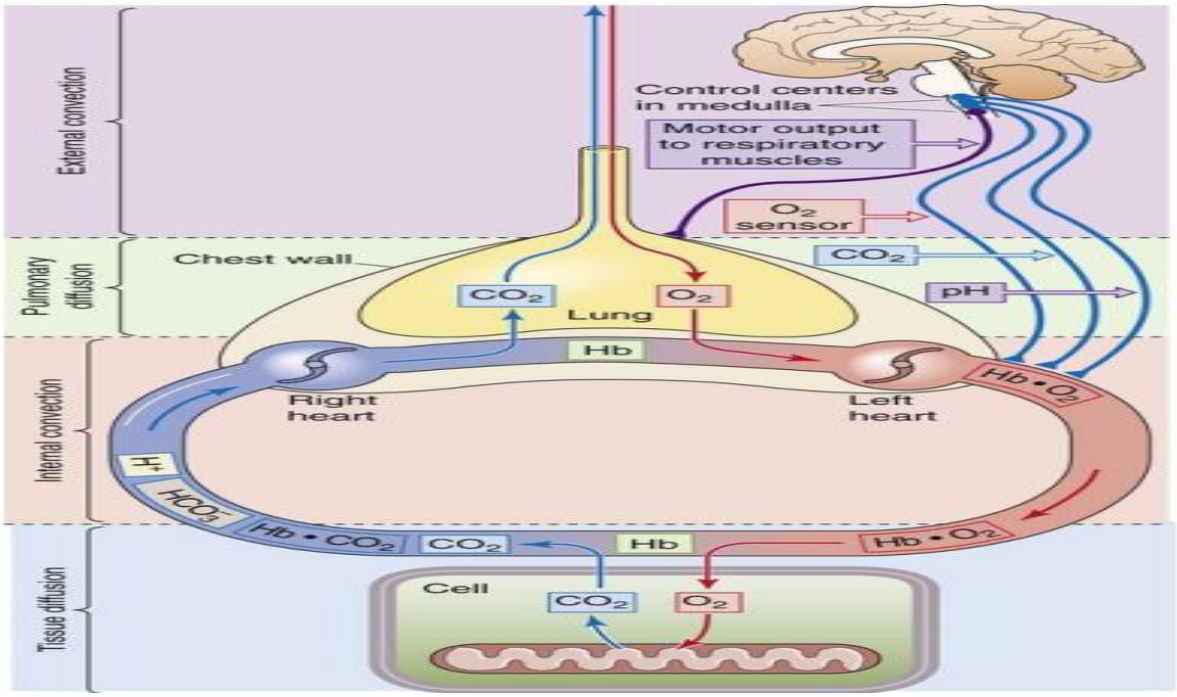



**Figure 29. The integrated process of oxygen and carbon dioxide transport in the body as controlled by the brain.**

The upper conducting airways, comprising the trachea and bronchi, are supported by cartilage and function as anatomical dead space where no gas exchange occurs. As airways branch further into bronchioles, cartilage is absent and smooth muscle fibres become prominent. The terminal bronchioles give rise to respiratory bronchioles, which lead to alveolar ducts and finally to alveolar sacs. Gas exchange primarily occurs in the alveolar air spaces, where alveoli are closely associated with capillaries. The inset shows a microscopic view of the alveolar wall, highlighting type I pneumocytes, endothelial cells, interstitial spaces, and red blood cells involved in the process of oxygen and carbon dioxide transfer between air and blood.

The lung receives blood from two distinct systems. The primary system is the pulmonary circulation, which is responsible for gas exchange. Deoxygenated blood is delivered from the

right heart through the Pulmonary Artery to the dense capillary networks surrounding the alveoli. After oxygenation occurs at the alveolar level, the newly oxygenated blood returns almost entirely to the left heart via the Pulmonary Veins. The second system is the bronchial circulation, which serves a nutritive function. Oxygenated blood (from the systemic circulation) travels through the Bronchial Artery to supply the supporting tissue of the lung, specifically the conducting airways (bronchi and bronchioles). This bronchial blood supply is necessary because the tissues of the conducting airways are too thick to receive adequate oxygen directly from the air inside them. The phenomenon known as the bronchial shunt occurs because most of the deoxygenated blood that has supplied the conducting airways does not return to the right heart via systemic veins; instead, it drains directly into the Pulmonary Veins. This results in a small amount of deoxygenated blood mixing with the highly oxygenated blood returning from the alveoli just before it reaches the left heart. This normal, physiological mixing causes the systemic arterial blood to have an oxygen saturation slightly less than 100%.

## IV.1.3. CO2 exchange process

Carbon dioxide CO2 transport involves a continuous exchange process between the body's tissues and the lungs. In the systemic capillaries at the tissues, CO2 produced by cell metabolism rapidly diffuses into the systemic capillary and then into the red blood cell (RBC). Inside the RBC, the enzyme carbonic anhydrase quickly catalyzes the conversion of CO2 and water into carbonic acid HCO3-, which immediately dissociates into a bicarbonate ion HCO3- and a hydrogen ion H+. The majority of the HCO3- diffuses out into the plasma, and to maintain electrical balance, a chloride ion Cl- moves into the RBC—a process known as the Chloride Shift. The resultant $\text{H}^+$ is buffered by hemoglobin (Hb), preventing a drop in blood pH. This CO2 is then transported primarily as bicarbonate HCO3- in the plasma to the lungs. In the pulmonary capillaries near the alveolus, this process reverses due to the lower CO2 concentration (partial pressure) in the alveolus. HCO3- moves back into the RBC (the reverse Chloride Shift), where it recombines with the H+ released from haemoglobin to reform H2CO3-. Carbonic anhydrase converts this back into CO2 and H2O, allowing CO2 to diffuse out of the blood and into the alveolus for exhalation (Fig. 30).

Gas exchange is driven by partial pressure gradients (P) across the entire circulatory system. In the lungs (external respiration), deoxygenated blood $P_{O2} = 40 \P_{CO2} = 46 \mmHg$ equilibrates with alveolar air $P_{O2} = 105 \P_{CO2} = 40 \mmHg$, causing O2 to diffuse into the blood and CO2 to diffuse out. In the tissues (internal respiration), oxygenated blood PO2 = 100 \mmHg releases $O_2$ to the cells $P_{O2} < 40 \mmHg$ and picks up CO2 ($P_{CO2} > 46 \mmHg$), completing the

cycle as blood returns to the heart with partial pressures of $P_{O2}$ = 40 \mmHg and $P_{CO2}$ = 46 \mmHg.

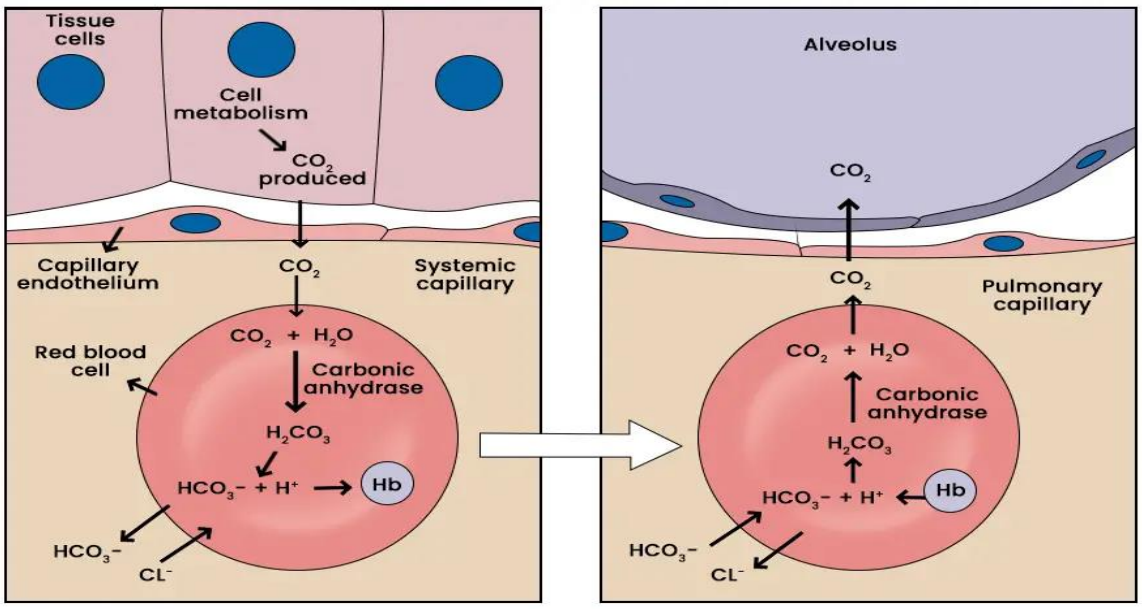



**Figure 30. CO2 transfer via red blood cells**

## IV.2. Pulmonary system and aging

Aging results in significant structural and functional deterioration across the entire respiratory system, affecting the airways and the gas-exchange units.

In the Upper and Lower Airways, the primary defense mechanism, mucociliary clearance, becomes impaired. This is due to a reduction in the number of basal cells (precursors for epithelial cells) and a decrease in the ciliary beat frequency of the ciliated cells. These changes compromise the ability of the respiratory system to effectively remove inhaled particles and pathogens. Furthermore, the supportive tissue below the epithelium (submucosa) in both the upper and lower airways undergoes detrimental changes, characterized by alterations in the extracellular matrix (ECM). In the upper airway, specific ECM components (such as GLEI/ARSMG) accumulate, and in the lower airway, general ECM changes affect structures supported by smooth muscle and fibroblasts, contributing to airway remodelling and stiffness.

At the level of the Alveolar Space, the core unit for gas exchange, aging leads to reduced efficiency and structural integrity. There is a notable loss or decrease in alveolar septae (the walls separating alveoli), and a corresponding reduction in the elasticity of the lung tissue (Tab. 3). This loss of structure results in a condition sometimes referred to as 'senile emphysema', leading to the enlargement of the alveolar space. This enlargement directly decreases the total surface area available for gas exchange. Finally, the interstitial tissue surrounding alveolar cells

and capillaries also undergoes changes in extracellular matrix composition, contributing to the overall stiffening and reduced compliance of the ageing lung (Fig. 31).

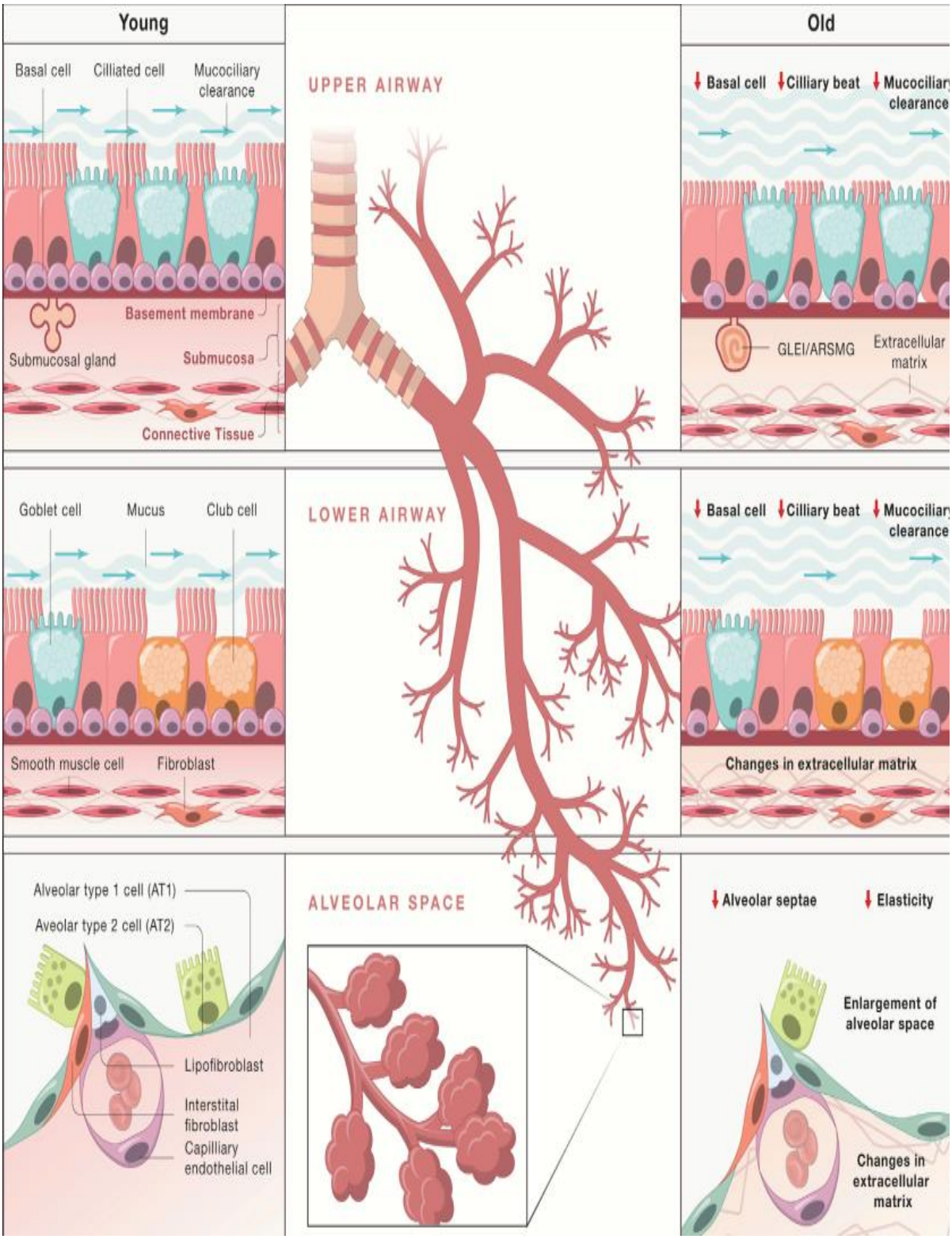



**Figure 31. Effects of age on the respiratory system**

Table 3. Age related changes in pulmonary system cells

| Cell | Localization in human lung | Function | Age-related changes |
|---|---|---|---|
| Basal cells | Trachea, bronchi, bronchioles | Multipotent progenitor. Self-renewal and differentiation into club cells, goblet cells and neuroendocrine cells. Differentiation to ciliated cells after injury. | Decrease in the number of basal cells. Less proliferative phenotype (stem cell exhaustion). |
| Club cells | Bronchi, bronchioles, respiratory bronchioles | Progenitor. Self-renewal. Differentiation into goblet and ciliated cells. De-differentiation into basal cells after injury. Club cells secrete primary components of the fluid lining the respiratory bronchioles, they play a key role in the biotransformation of xenobiotics, oxidative stress reduction, and immunomodulation. | Reduced self-renewal and differentiation. Increased apoptosis. |
| Ciliated cells | Trachea, bronchi, bronchioles | Ciliated cells have a critical biomechanical role as a component of mucociliary clearance. There is increasing recognition that airway ciliated cells sense and respond to both mechanical and irritant stimulation. | Slow ciliary beat frequency. Decrease in the number of ciliated cells. |
| Glandular-like epithelial invaginations | Trachea, bronchi | Arise from basal cells during aging and contribute to homeostasis and repair. | Appearance of age-related GLEI/ARSMG. |
| SMG myoepithelial cells | Trachea, bronchi | SMG-derived myoepithelial cells display multipotency and contribute to basal and luminal cell types of the SMGs and surface airway epithelium. | Not described. |
| Alveolar type 2 cells | Alveolar parenchyma | Progenitor AT2: self-renewal and differentiation into AT1 cells. "Mature" AT2: synthesis and secretion of surfactant proteins and phospholipids. Innate immune response. | Impaired differentiation into AT1 cells. Senescence. Endoplasmic reticulum stress. Increase of MHC class I genes. Altered lipid metabolism, increased cholesterol biosynthesis. |
| Alveolar type 1 cells | Alveolar parenchyma | Gas exchange | Reduced number of AT1, uniform airspace enlargement. |

## IV.3. Other functions of the pulmonary system

The lungs play several crucial, multifaceted roles in maintaining and regulating systemic blood pressure. First, the pulmonary circulation contributes to overall cardiovascular function by regulating pulmonary vascular resistance and blood flow within the lungs. Second, the lungs

are actively involved in modulating vascular tone through the production of signalling molecules, such as nitric oxide, which acts as a powerful vasodilator to help dilate blood vessels, thereby reducing vascular resistance and lowering systemic blood pressure. Third, the respiratory system is a critical component of the Renin-Angiotensin-Aldosterone System (RAAS), a major hormonal cascade for blood pressure control; specifically, the lungs house the Angiotensin-Converting Enzyme (ACE), which catalyses the conversion of the inactive hormone angiotensin I to angiotensin II, a potent vasoconstrictor that significantly regulates blood pressure. Finally, breathing patterns directly influence blood pressure via neural feedback, with deep, slow breathing generally helping to lower blood pressure, while rapid or shallow breathing tends to raise it.

# IV.4. Some physiopathology of the respiratory system

## IV4.1. Asthma

Asthma is a pervasive, chronic respiratory disease affecting millions worldwide. It is characterised by three core features: chronic airway inflammation, airway hyperresponsiveness, and variable, often reversible, airflow obstruction. Far from being a simple breathing disorder, asthma is fundamentally an immunological disease driven by a complex, overzealous response to environmental triggers. Understanding the symptoms, causes, and the specific mechanisms of immune system intervention is crucial for effective management of this condition.

The clinical presentation of asthma is marked by a set of classic and distressing symptoms that reflect the underlying narrowing of the bronchial tubes. The most recognisable symptom is wheezing, a high-pitched whistling sound typically heard during exhalation, caused by air being forced through constricted airways. This is frequently accompanied by shortness of breath (dyspnea), which can range from mild difficulty to a severe, life-threatening sensation of suffocation. Patients also often report chest tightness—a feeling of pressure or constriction across the chest—and a persistent, recurrent coughing that tends to worsen during the night or early morning hours.

The aetiology of asthma is multifactorial, stemming from an interplay between genetic susceptibility and environmental factors. Causes and risk factors include a strong genetic predisposition; individuals with a family history of asthma or other allergic conditions (atopy) are significantly more vulnerable. This inherent sensitivity is often brought to the fore by environmental triggers that induce inflammation or bronchospasm. These triggers encompass a wide range of allergens such as pollen, pet dander, mold, and dust mites, as well as irritants like tobacco smoke, air pollution, and chemical fumes. Furthermore, factors such as respiratory viral

infections (especially in early childhood), physical exertion (exercise-induced bronchoconstriction), and certain medications (e.g., NSAIDs or beta-blockers) can provoke acute exacerbations.

The core pathology of asthma lies in the exaggerated and chronic involvement of the immune system. The disease is classified as a chronic Type 2 T-helper cell (TH2) inflammatory disorder. The process begins during the sensitization phase, where the airway is exposed to an allergen. T cells are activated and differentiate into TH2 cells, the orchestrators of the allergic cascade. These TH2 cells release a cocktail of inflammatory cytokines, most notably Interleukin-4 (IL-4) and IL-13, which drive B cells to produce high quantities of the antibody Immunoglobulin E (IgE) specific to the invading allergen. These IgE antibodies attach themselves to the surface of mast cells embedded in the airway tissue. Crucially, TH2 cells also release Interleukin-5 (IL-5), which recruits and activates eosinophils—white blood cells central to chronic airway inflammation and associated tissue damage.

#### IV.4.1.1. Airway Pathology and Structural Changes in Severe Asthma

When the sensitized individual is subsequently re-exposed to the allergen, the allergen binds to the IgE on the mast cells, triggering the rapid degranulation of these cells in the effector phase. Mast cells immediately dump vast amounts of inflammatory mediators, including histamine, leukotrienes, and prostaglandins, into the surrounding tissue. It is these substances that precipitate the acute asthma attack by causing simultaneous bronchoconstriction (rapid airway muscle contraction), vasodilation (leading to airway swelling), and excessive mucus hypersecretion, all of which combine to severely obstruct airflow (Fig. 32 a).

Over the long term, the persistent immune activation leads to a destructive process known as airway remodelling, which fundamentally changes the airway's structure compared to a healthy state. Key features of this remodelling include: Airway smooth muscle exhibiting hyperresponsiveness, chronic constriction, and significant thickening; Sub-epithelial inflammation and fibrosis, involving deposition of connective tissue under the epithelium; Mucus hypersecretion and impaired clearance, resulting in thick mucus plugs within the lumen; and a dramatic increase in inflammatory cells, specifically eosinophils and/or neutrophils, accumulating within the airway lumen and the tissue walls. This remodelling increases airway reactivity and leads to a fixed, irreversible component of airflow limitation, highlighting why asthma management must address the underlying immune-driven inflammation and not just the acute bronchospasm (Fig. 32 b).

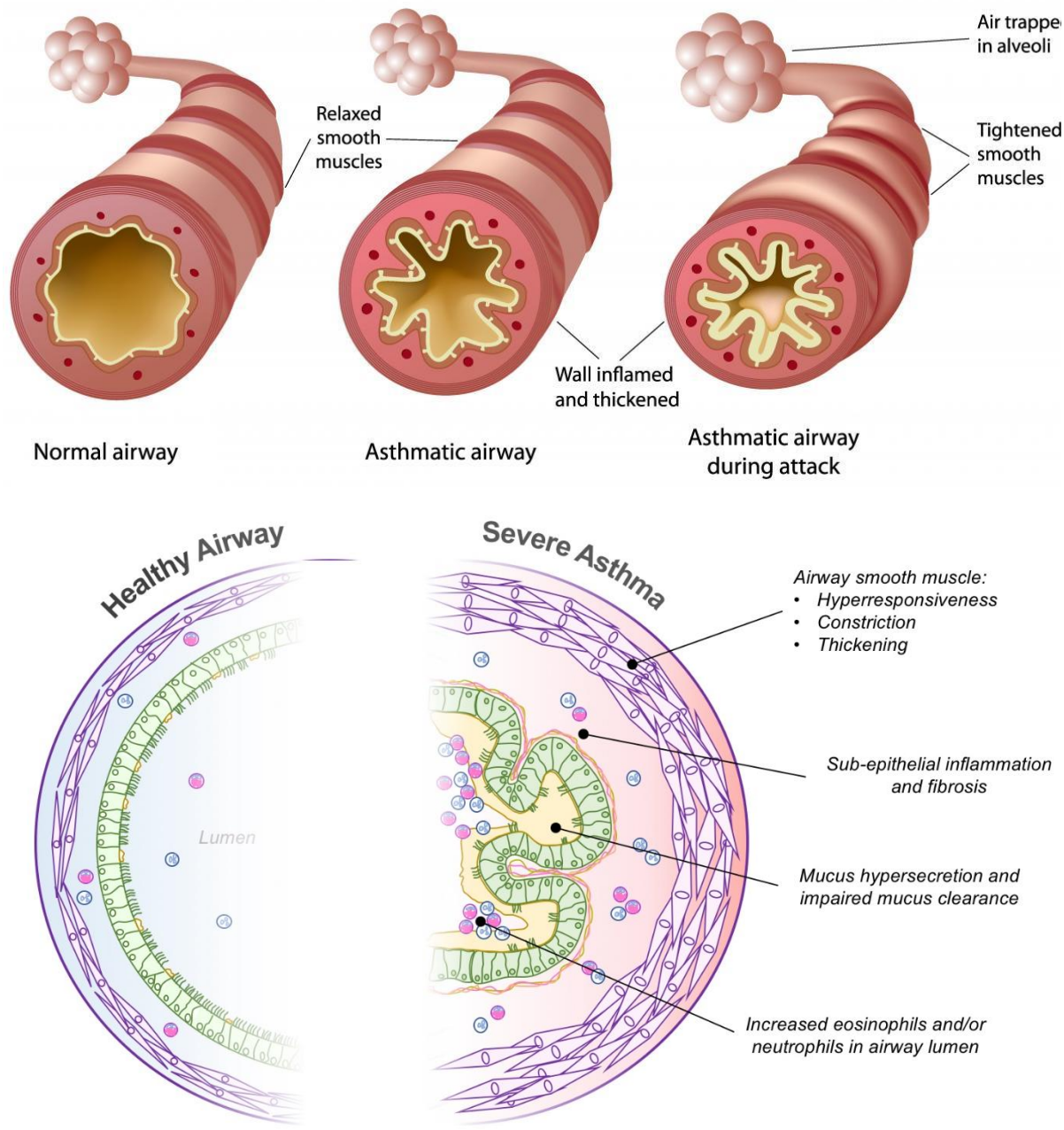



**Figure 32. Airway's pathology and structural changes in severe asthm**

In the sensitisation phase, allergens penetrate through a damaged epithelium with loosened tight junctions and stimulate epithelial cells to release thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33, which activate dendritic cells, basophils, and innate lymphoid cells type 2 (ILC2). Activated dendritic cells migrate to draining lymph nodes, present antigen via MHC class II to naïve CD4+ T cells, and—with co-stimulatory molecules such as CD80, CD86, and OX40L plus basophil-derived IL-4—drive differentiation of naïve T cells into Th2 and T follicular helper (TFH) cells. Th2 and TFH cells then secrete IL-4, IL-5, IL-9, IL-13, and IL-21, promoting B-cell activation, class-switch recombination to IgE, and plasma cell

differentiation, while ILC2-derived IL-5 and IL-13 contribute further to eosinophil recruitment and epithelial barrier changes, including mucus secretion and wider tight junction opening. In the effector phase, allergen-specific IgE produced by plasma cells binds to high-affinity FcεRI receptors on mast cells and basophils, leading to their sensitization; upon re-exposure to the allergen, cross-linking of IgE triggers mast cell and basophil degranulation, releasing mediators such as histamine and prostaglandin D2 (PGD2) that cause smooth muscle contraction, enhanced mucus secretion, and amplification of the Th2 cytokine milieu (IL-4, IL-5, IL-9, IL-13), thereby sustaining eosinophilic inflammation and the clinical manifestations of allergic disease (Fig. 33).

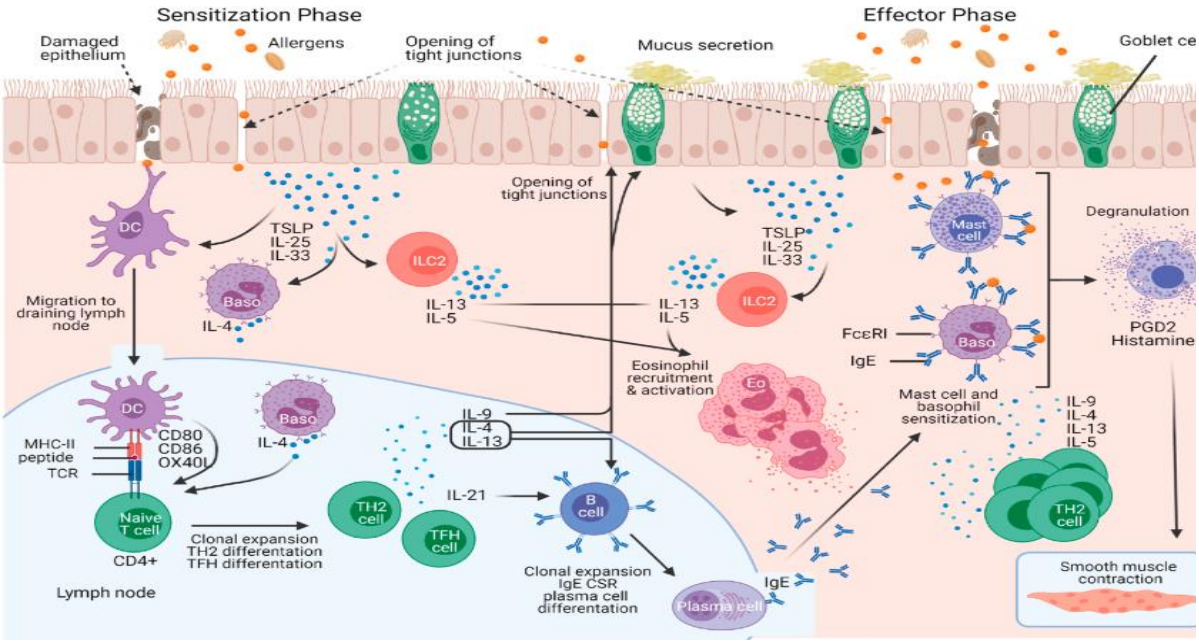



**Figure 33. The immunologic cascade of allergic response in the mucosa.**

## IV.4.2. Chronic obstructive pulmonary disease

Chronic Obstructive Pulmonary Disease (COPD) is depicted as a progressive respiratory condition characterized by significant structural damage and airflow obstruction. The pathophysiology involves three primary mechanisms: chronic bronchitis, chronic obstructive bronchiolitis, and emphysema. In chronic bronchitis, the airway becomes severely blocked by mucus hypersecretion and inflammatory exudate, while chronic obstructive bronchiolitis is marked by mucosal inflammation and fibrosis that thickens and narrows the airway walls. Simultaneously, emphysema causes the destruction of the alveolar sacs, drastically reducing the surface area available for gas exchange. Crucially, the disease leads to the disruption of alveolar attachments—the elastin fibres that provide structural support—causing the airways to

lose their elasticity and collapse. Together, these pathological changes result in narrowed bronchioles and trapped air, which significantly impairs the patient's ability to breathe (Fig. 34).

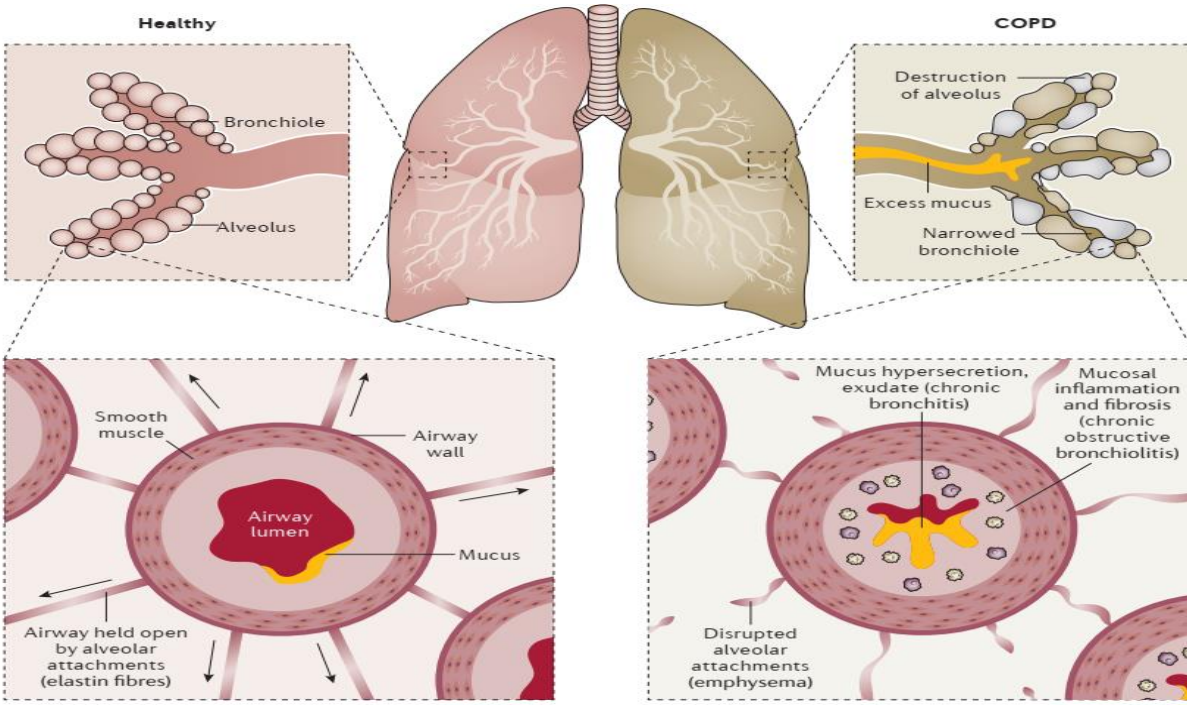



**Figure 34. Structural damage in Chronic Obstructive Pulmonary Disease**

The process is initiated by the inhalation of cigarette smoke or biomass fuels, which activate the inflammasome and Toll-like receptors (TLRs) within epithelial cells and alveolar macrophages. This initial insult leads to a state of heightened oxidative stress and corticosteroid resistance, while simultaneously impairing the phagocytic ability of macrophages, which allows for persistent bacterial colonization. As these activated "sentinel" cells release a variety of chemotactic factors, they recruit a diverse array of immune cells—including neutrophils, monocytes, and various T-lymphocyte subsets to the lung tissue. Once recruited, these inflammatory cells release potent proteases, such as neutrophil elastase and matrix metalloproteinases (MMP9), which overwhelm the body's natural antiprotease defences. This biochemical imbalance leads to the three hallmark structural pathologies of the disease: the destruction of alveolar walls known as emphysema, the thickening and scarring of small airways through fibrosis, and chronic mucus hypersecretion from overactive goblet cells. To counter this progression, the diagram maps various therapeutic interventions to specific stages of the pathway, ranging from primary prevention through smoking cessation and nicotine antagonists to targeted pharmacological treatments like PDE4 inhibitors, antioxidants, and mucoregulators. Furthermore, the model suggests future regenerative strategies, such as the use

of stem cells and retinoic acid, aimed at repairing the underlying structural damage to the lung architecture (Fig. 35).

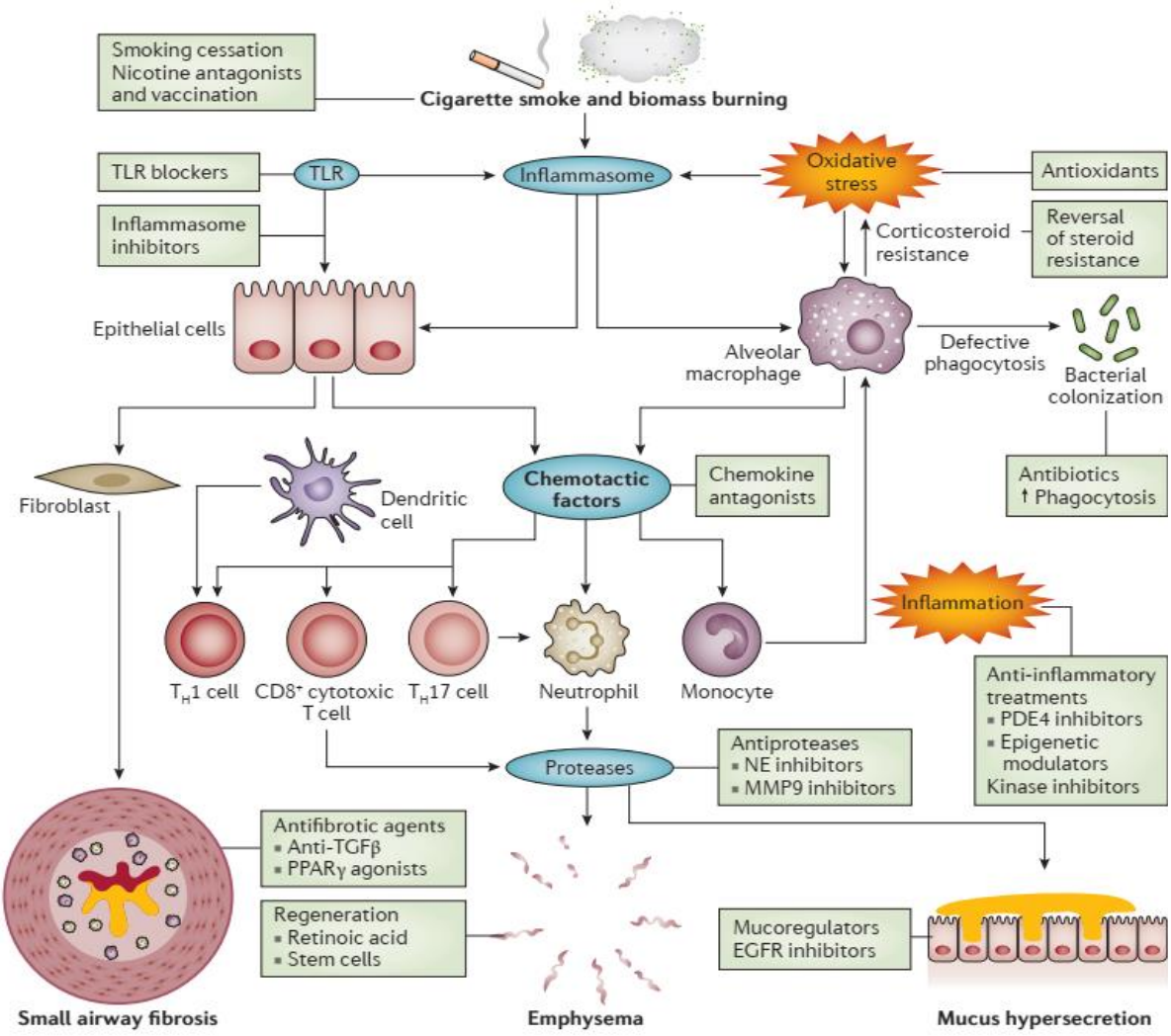



**Figure 35. Triggers of chronic obstructive pulmonary disease and treatments**

## IV.4.3. Pneumonia

Pneumonia is an acute respiratory infection characterised by inflammation of the pulmonary parenchyma, specifically the microscopic air sacs known as the alveoli. In a healthy state, the alveolus is clear, lined with Type I and Type II pneumocytes and a thin surfactant layer, allowing for efficient gas exchange with the adjacent capillary. However, when pneumonia occurs, pathogens—such as bacteria, viruses, or fungi—infiltrate the alveolar space, triggering an intense inflammatory cascade (Fig. 36).

The alveolar epithelium responds to this invasion by secreting mucins to bind pathogens, while resident alveolar macrophages begin phagocytosing the bacteria. This immune activation causes the interstitial space to widen—a condition known as an edematous interstitium—and leads to gap formation between inflamed endothelial cells in the capillary. These gaps allow

neutrophils and platelets to migrate from the blood into the alveolar space. As the infection progresses, the alveolus becomes filled with "consolidation," a dense mixture of activated neutrophils releasing cytokines, cellular debris, and fibrin. This fluid and cellular accumulation physically obstructs the air sac, severely impairing the lung's ability to transfer oxygen into the bloodstream and resulting in the clinical symptoms of the disease.

Because this fluid and cellular accumulation physically obstructs the air sac and prevents oxygen from reaching the bloodstream, it manifests in several recognisable clinical symptoms. Common symptoms include a persistent cough that may produce thick, colored phlegm (sputum), a high fever often accompanied by sweating and shaking chills, and stabbing chest pain that worsens when breathing deeply or coughing. As the lungs struggle to maintain oxygen levels, patients typically experience shortness of breath (dyspnea), rapid breathing (tachypnea), and significant fatigue. In severe cases or in older adults, pneumonia can also lead to confusion or changes in mental awareness due to decreased oxygen saturation in the blood.

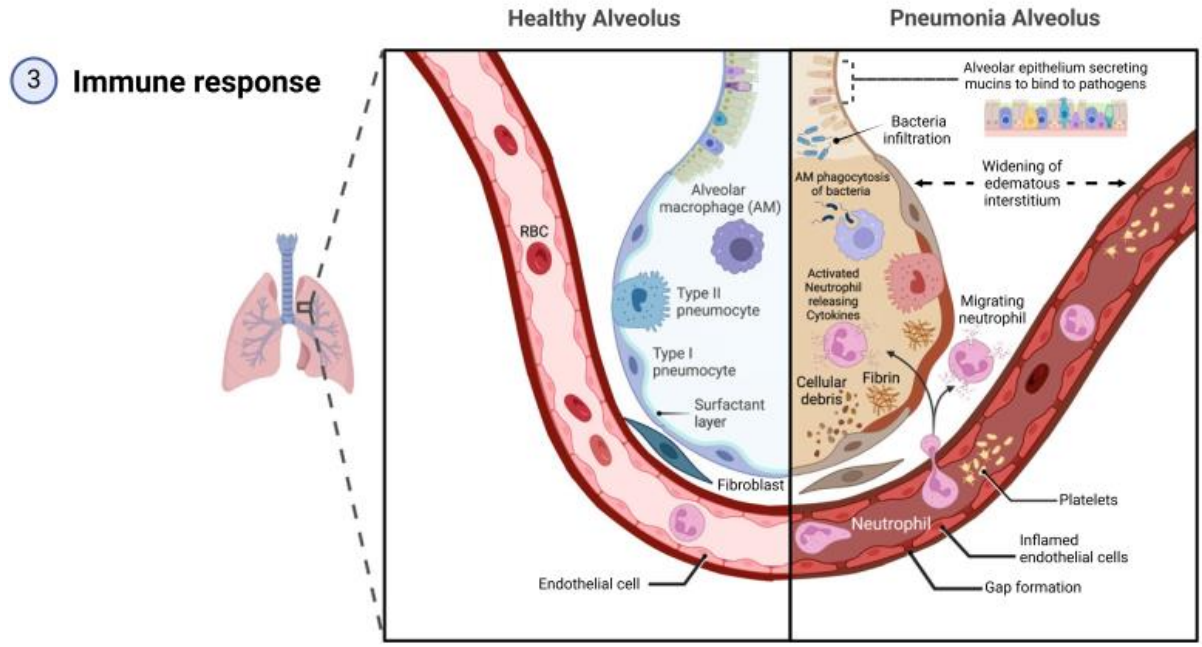



**Figure 36. Immune response during pneumonia**

## IV.4.4. Tuberculosis

Tuberculosis (TB) is a highly infectious bacterial disease caused by Mycobacterium tuberculosis that primarily attacks the lungs, though it can spread to other parts of the body. The provided illustration details the lifecycle of the infection by contrasting Latent infection with Active disease. In the latent stage, the bacteria enter the alveolus and are engulfed by alveolar macrophages and monocytes into phagosomes. Dendritic cells then migrate to the lymph nodes for T-cell priming to initiate an immune response. This results in the formation of

a granuloma—a specialized immunological structure composed of T cells, B cells, and interstitial macrophages that effectively "walls off" the bacteria, keeping the infection contained and asymptomatic (Fig. 37).

However, if the immune system weakens, the condition progresses to Active disease. In this phase, the structural integrity of the granuloma fails, allowing the bacteria to multiply rapidly and escape into the lung parenchyma and airways. The illustration shows these bacteria being shed from the broken granuloma, leading to infectiousness and the spread to regional lymph nodes. Clinically, this progression manifests as severe symptoms, including a chronic cough that may produce blood (hemoptysis), chest pain, unintentional weight loss, drenching night sweats, and persistent fever. Because active TB allows the bacteria to be expelled into the air via coughing or sneezing, prompt diagnosis and long-term antibiotic treatment are essential to prevent transmission and further lung tissue necrosis.

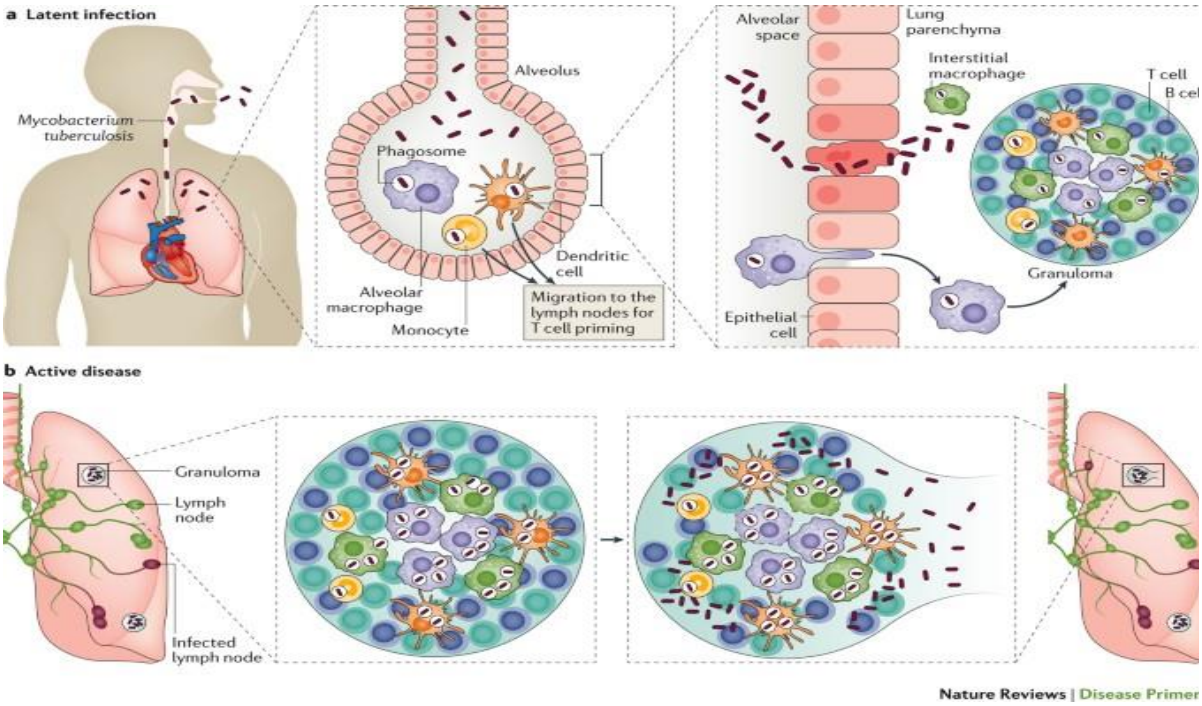



**Figure 37. Tuberculosis infection disease**

## IV.4.5. Lung cancer

Lung cancer is a malignant condition characterized by the uncontrolled growth of abnormal cells in the tissues of the lung, typically beginning in the cells lining the air passages. The provided illustration outlines the mechanisms linking COPD to cancer, demonstrating how the chronic state of a COPD lung can transition into a cancerous one. The chronic inflammation associated with COPD triggers a cascade of proteinases and cytokines, which lead to an altered cell cycle and significant genetic and epigenetic changes. These molecular shifts disrupt normal

cell regulation, eventually causing a tumor to form, as seen in the "COPD and Cancer" lung (Fig. 38).

It starts with Normal alveoli, which then progress to Emphysema with Atypical Alveolar Hyperplasia. In this middle stage, immune cells like T cells, neutrophils, and macrophages are present alongside abnormal cell growth (hyperplasia) within the damaged air sacs. This environment serves as a precursor to the final stage, where a distinct tumor develops within the lung tissue.

Because these tumors occupy space and damage lung architecture, they produce various clinical symptoms. Common symptoms of lung cancer include a persistent cough that does not go away or changes over time, coughing up blood (hemoptysis), and constant chest pain that is often made worse by deep breathing or coughing. As the disease advances, patients may experience unexplained weight loss, loss of appetite, and significant shortness of breath. Other signs can include recurrent respiratory infections like bronchitis or pneumonia, as well as hoarseness or wheezing caused by the tumor obstructing major airways.

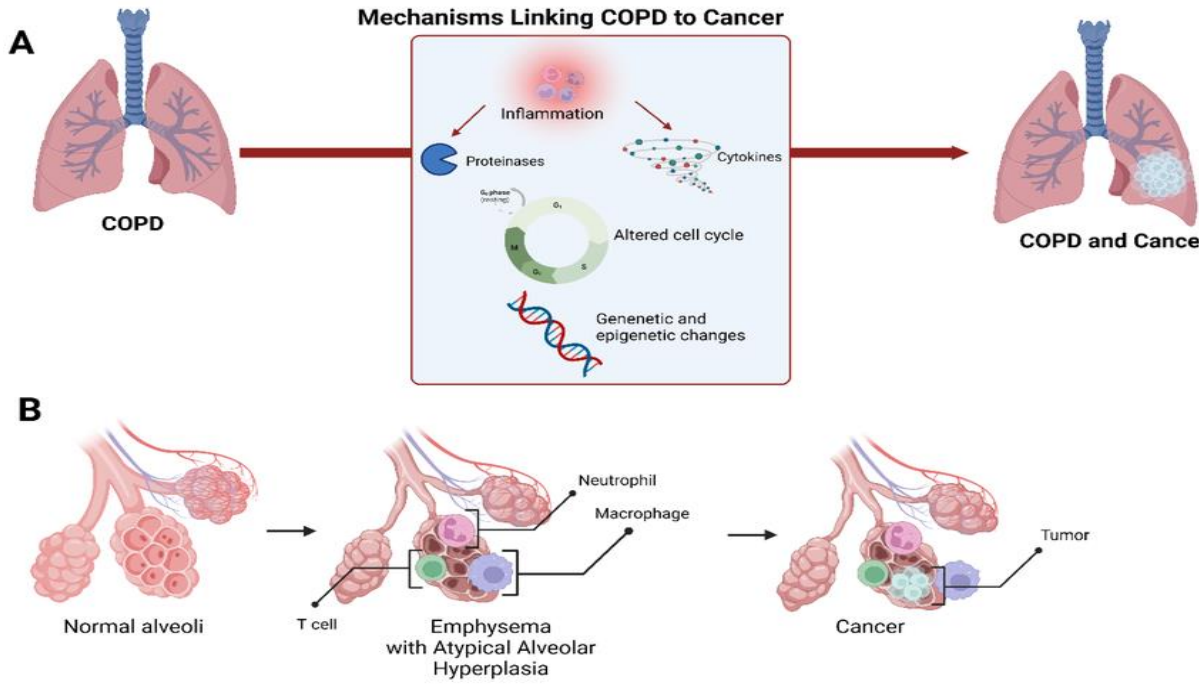



**Figure 38. Mechanism linking COPD to cancer**

## IV.4.6. Pulmonary Fibrosis

Pulmonary fibrosis is a chronic and progressive lung disease characterised by the scarring and thickening of the deep lung tissues, specifically the pulmonary parenchyma. The provided illustration contrasts a Healthy Alveolus with one affected by Idiopathic Pulmonary Fibrosis (IPF), a specific and severe form of the disease. In the healthy state, the alveolus maintains a

delicate balance with clear Type I and Type II epithelial cells and minimal connective tissue. However, as shown on the right, pulmonary fibrosis is driven by a combination of genetic factors, aging, and environmental triggers like smoking, which lead to significant epithelial cell damage and the exhaustion of stem cells. The diagram details how this cellular damage activates a cascade of growth factors, including TGFb PDGF, and CTGF. These signals trigger the excessive deposition of extracellular matrix and collagen by myofibroblasts, creating a stiffened scaffold that replaces the normally elastic lung tissue. This process of "autophagy" and matrix stiffness fundamentally alters the alveolar structure, making it difficult for the air sacs to expand.As the lung tissue becomes increasingly scarred and rigid, oxygen cannot easily pass through the thickened alveolar walls into the bloodstream, resulting in distinct clinical symptoms. The most common sign is a persistent, dry, hacking cough that does not produce phlegm. Patients typically experience worsening shortness of breath (dyspnea), especially during physical activity, along with shallow breathing and significant fatigue. Over time, the lack of oxygen can lead to "clubbing," a widening and rounding of the tips of the fingers or toes. Additionally, patients may notice unexplained weight loss and aching muscles or joints as the body struggles with the chronic lack of oxygenation (Fig. 39).

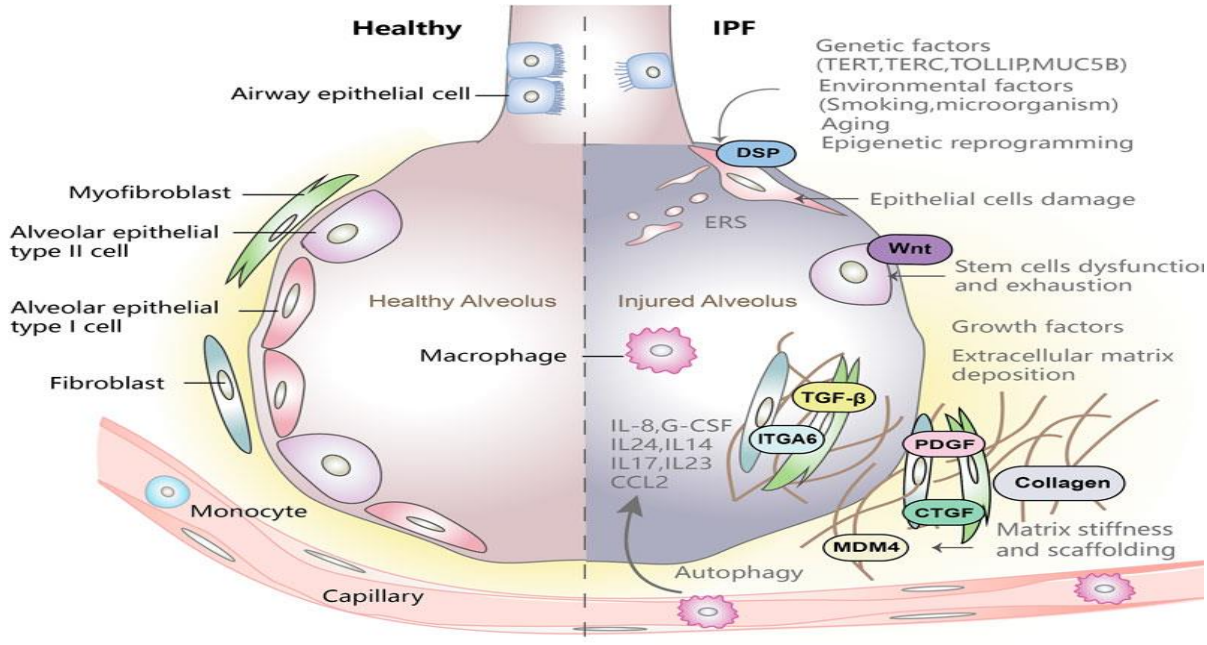



**Figure 39. Pulmonary fibrosis**

## IV.4.7. Obstructive Sleep Apnea

Sleep Apnea, specifically Obstructive Sleep Apnea (OSA), is a common yet serious sleep disorder characterised by repeated interruptions in breathing during sleep due to the partial or complete collapse of the upper airway. The condition is often driven by a decrease in airway size and an increase in resistance and collapsibility. This can be caused by morphological abnormalities, such as compromised craniofacial structures, adipose soft tissue deposition (often seen in obesity), or airway mucosal oedema resulting from fluid shifts. Furthermore, sleep onset—particularly during REM sleep—leads to decreased ventilatory drive and reduced upper airway dilator muscle activity, making the airway prone to closure. The "vicious cycle" of a sleep apnea event begins with the onset of intermittent hypoxia (low oxygen), which leads to a drop in ventilatory drive and muscle tone. As respiratory effort decreases, carbon dioxide levels (PCO2) rise and oxygen levels (PO2) fall, eventually triggering an arousal or a brief awakening. This arousal temporarily increases ventilatory drive and opens the airway, often leading to hyperventilation. However, once the patient returns to sleep, the ventilatory drive drops again, leading back to hypoventilation and airway collapse, repeating the cycle throughout the night. The clinical symptoms of sleep apnea are a direct result of these frequent respiratory interruptions and sleep fragmentations. The most prominent sign is loud, chronic snoring, often punctuated by gasping or choking sounds as the person struggles to breathe. Partners may observe actual "apneic episodes" where the person stops breathing entirely for several seconds. During the day, patients suffer from excessive daytime sleepiness, significant fatigue, and difficulty concentrating or irritability. Other common symptoms include waking up with a very dry mouth or sore throat, and experiencing frequent morning headaches due to the nocturnal fluctuations in oxygen and carbon dioxide levels. Over time, untreated sleep apnea can lead to serious cardiovascular complications, such as high blood pressure and heart strain (Figure 40).

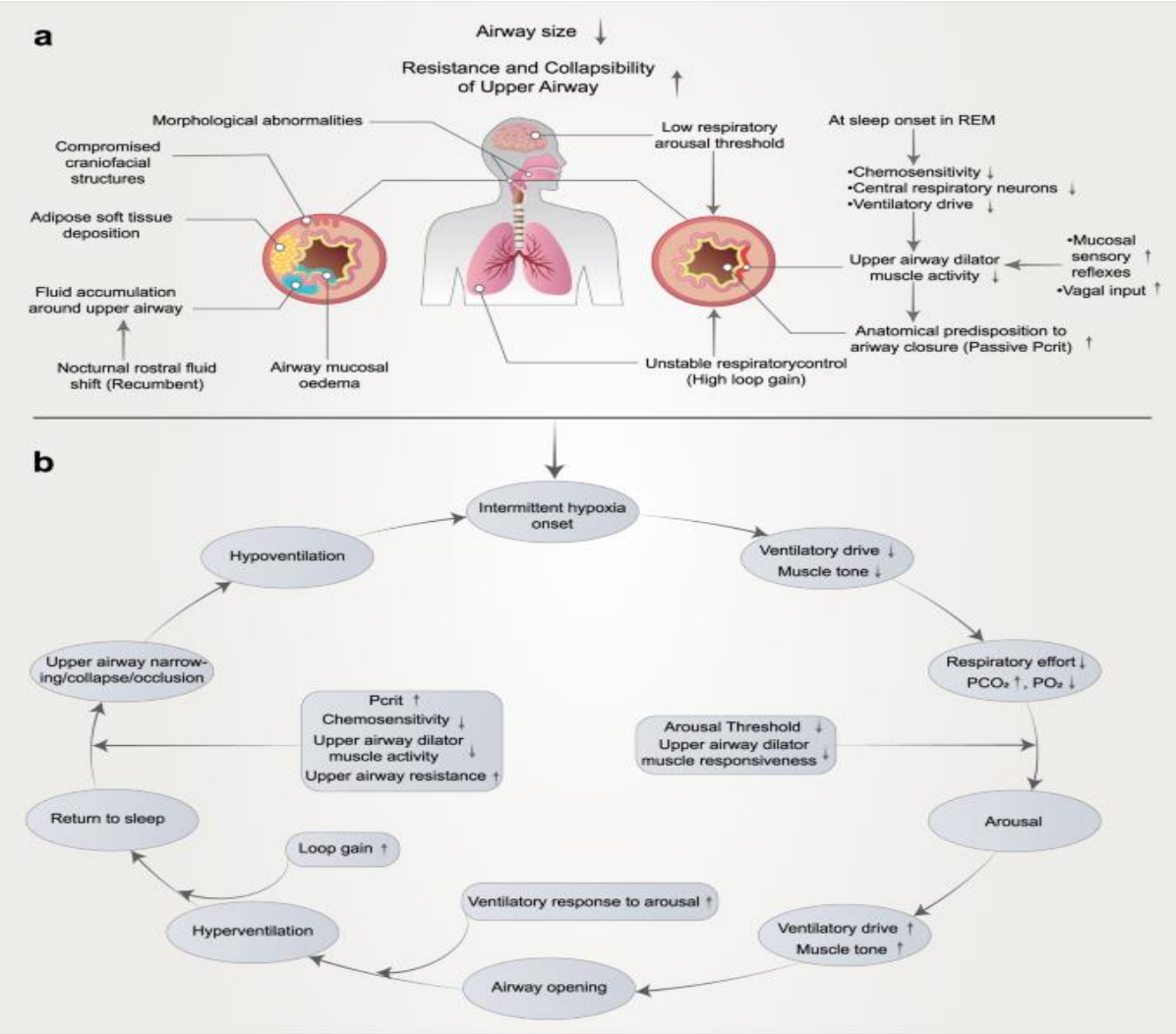



**Figure 40. Obstructive Sleep Apnea**

Obstructive Sleep Apnea Syndrome (OSAS) and Intermittent Hypoxia (IH), lead to chronic metabolic diseases. These disturbances trigger two primary pathological pathways: Sympathetic overactivity and a combination of oxidative stress and systemic inflammation. Increased sympathetic outflow to skeletal muscles, combined with inflammatory cytokines like TNF-a and IL-6, leads to pancreatic β-cell dysfunction and impaired glucose disposal. Consequently, the body suffers from decreased insulin sensitivity and impaired glucose tolerance, eventually culminating in Insulin Resistance and Type 2 Diabetes. The stress placed on the body increases the activity of SREBPs (sterol regulatory element-binding proteins) and decreases lipase activity. This biochemical shift results in a significant increase in total cholesterol, triglycerides, and "bad" cholesterol levels such as VLDL and LDL, while decreasing the levels of "good" HDL-C cholesterol. This state of Dyslipidemia, combined with the aforementioned glucose instability, creates a high-risk environment for cardiovascular

disease. Sleep apnea is not merely a respiratory issue but a systemic disorder that fundamentally alters the body's hormonal and metabolic balance (Fig. 41).

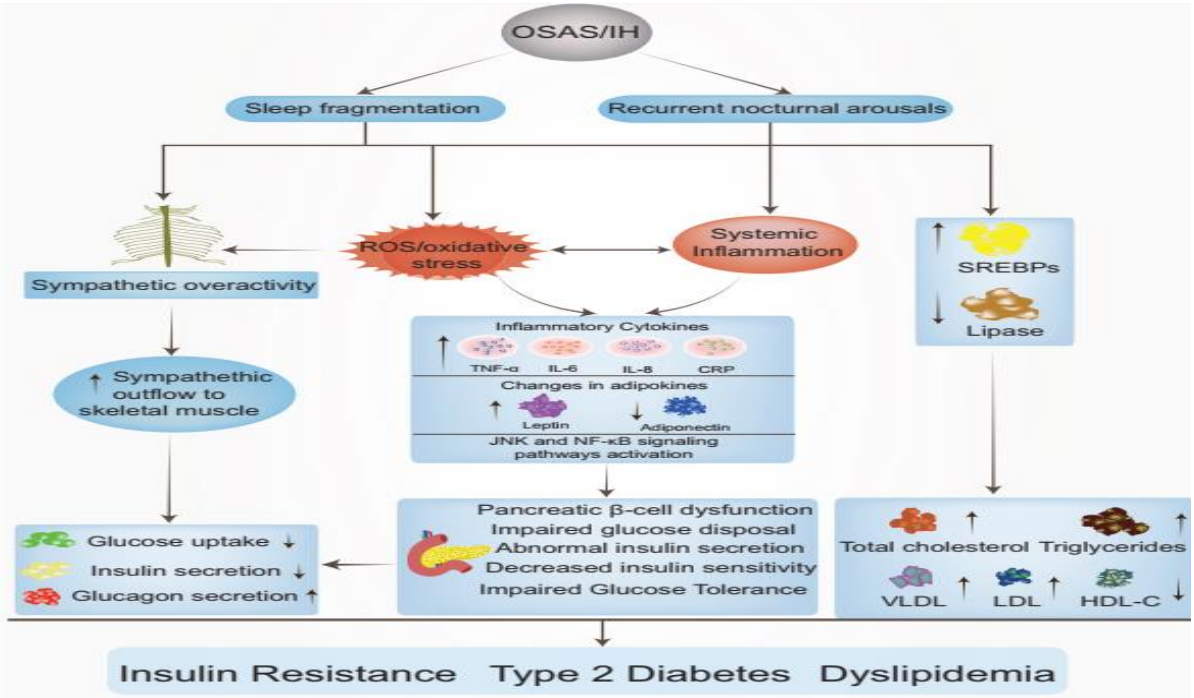



**Figure 41. Obstructive Sleep Apnea Syndrome and metabolic complications**

## IV.4.8. Interstitial Lung Disease

Interstitial Lung Disease (ILD) is a broad umbrella term for a large group of disorders that cause progressive scarring (fibrosis) of the lung tissue. This scarring primarily affects the interstitium, which is the delicate network of tissue that supports the air sacs (alveoli). As shown in the provided illustrations, particularly in the context of Rheumatoid Arthritis-associated ILD, the disease is driven by several complex pathogenic stages. It begins with initiation, where environmental factors like smoking or genetic variations cause epithelial damage and endothelial activation. This leads to the progression phase, characterized by the infiltration of immune cells such as T-cells, B-cells, and neutrophils, which release inflammatory cytokines and reactive oxygen species (ROS).

The hallmark of ILD is the failed resolution of this inflammation. Instead of healing normally, the body undergoes an Epithelial-Mesenchymal Transition (EMT) and a Fibroblast-Myofibroblast Transition (FMT). This results in the excessive deposition of fibrillar collagen and extracellular matrix (ECM) proteins, leading to matrix stiffness and scaffolding. This thickening of the interstitium creates a physical barrier that makes it increasingly difficult for oxygen to pass from the alveoli into the blood vessels (capillaries).

Because the lung tissue becomes stiff and less elastic, patients with ILD experience specific clinical symptoms. The most common sign is a progressive shortness of breath (dyspnea), which may initially only occur during exercise but eventually persists even at rest. A persistent, dry cough that does not produce mucus is also a frequent symptom. As the disease advances and oxygen levels in the blood drop, patients may experience significant fatigue, loss of appetite, and unexplained weight loss. In some cases, "clubbing" of the fingernails or toenails occurs due to chronic oxygen deprivation. If the ILD is related to an autoimmune condition like Rheumatoid Arthritis, patients may also experience joint pain and swelling alongside their respiratory issues (Fig. 42).

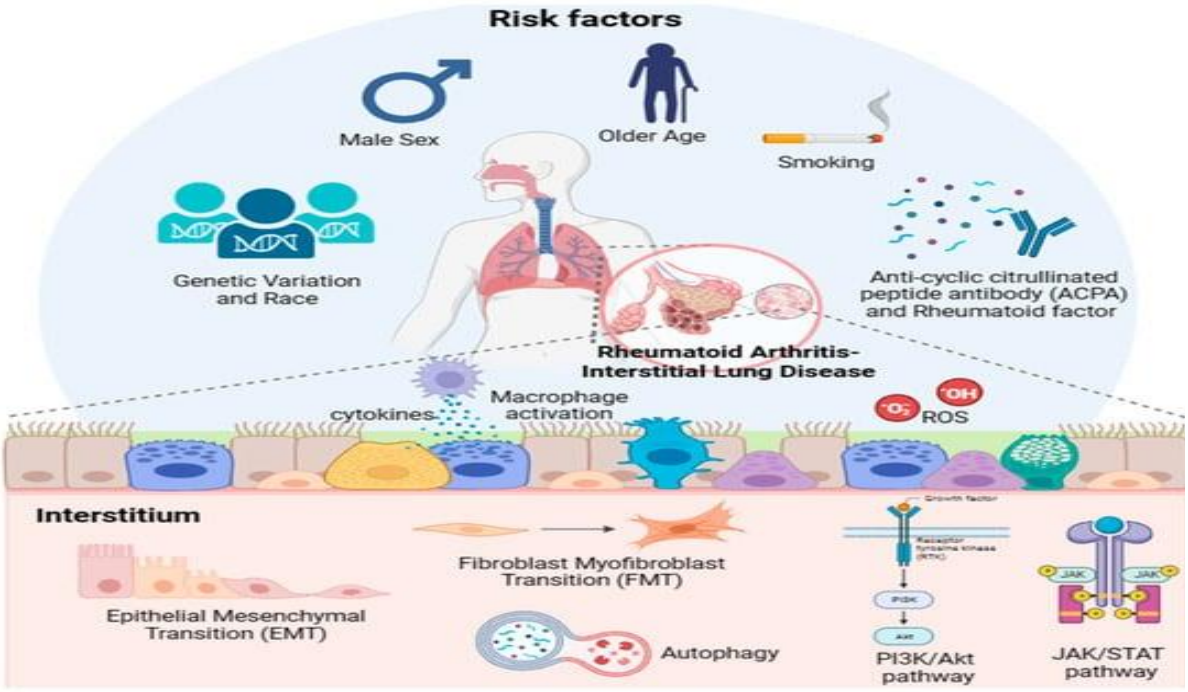



**Figure 42. Interstitial Lung Disease associated risk factor**

## IV.4.9. Silicosis

Silicosis is a type of occupational lung disease and a form of pneumoconiosis caused by the inhalation of crystalline silica dust. When these silica particles are inhaled into the lungs, they are taken up by epithelial cells and macrophages. This uptake triggers direct and indirect cytotoxicity, leading to cell death via apoptosis and necrosis. The resulting cellular damage recruits neutrophils and releases a flood of cytokines and chemokines, creating a state of chronic inflammation and oxidants that causes persistent lung injury (Fig. 43).

A critical aspect of silicosis is its link to cancer. The chronic inflammation and cellular stress induce genotoxicity, which causes DNA damage and changes in oncogene expression. These genetic alterations eventually lead to the transformation of healthy tissue into tumour cells.

Furthermore, chronic irritants drive a broader cycle of oxidative stress and protease release, culminating in the structural destruction of the lungs, including small airway fibrosis, emphysema, and mucus hypersecretion.

The symptoms of silicosis often develop slowly after years of exposure and are a direct result of the lungs becoming increasingly scarred and less able to exchange oxygen. Primary symptoms include a persistent, often "dry" cough and progressive shortness of breath (dyspnea), which may initially occur only during physical exertion but eventually happens at rest. Patients may also experience significant fatigue, chest pain, and unexplained weight loss. As the lung tissue continues to harden and oxygen levels drop, individuals may develop a bluish tint to the lips or skin (cyanosis). Because silicosis weakens the immune system's local defenses, as shown by the "defective phagocytosis" in the first diagram, patients are also at a significantly higher risk of developing secondary infections like tuberculosis or pneumonia.

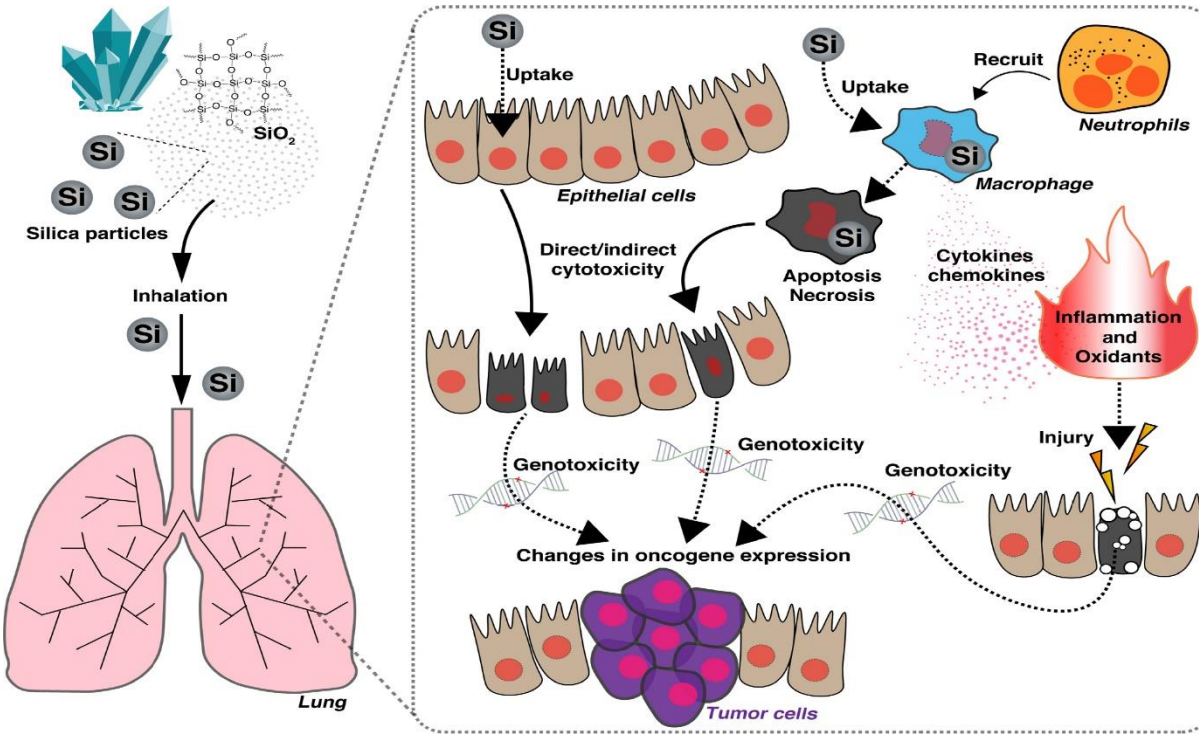



**Figure 43. Silicosis disease**

## References


- Kenhub. (2014). Respiratory system: Anatomy and functions. Kenhub GmbH. https://www.kenhub.com/en/library/anatomy/the-respiratory-system
- Stanford Children's Health. (2024). Anatomy of the respiratory system. Stanford Medicine Children's Health. https://www.stanfordchildrens.org/en/topic/default?id=anatomy-of-the-respiratory-system-85-P01300
- Rhoades, R. A., & Bell, D. R. (2013). Medical physiology: Principles for clinical medicine (4th ed.). Lippincott Williams & Wilkins. (Chapter on oxygen and carbon dioxide transport; overview consistent with StatPearls $CO_2$ transport.) See also:
- Rhoades, C. J., & Martin, T. J. (2023). Physiology, carbon dioxide transport. In StatPearls. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK532988/
- Janssens, J. P., Pache, J. C., & Nicod, L. P. (1999). Physiological changes in respiratory function associated with ageing. European Respiratory Journal, 13(1), 197–205. https://pubmed.ncbi.nlm.nih.gov/10065680/ (Pulmonary structure, function, and "senile emphysema" changes; consistent with.)
- Lambrecht, B. N., Hammad, H., & Fahy, J. V. (2019). The immunology of asthma. Nature Immunology, 20(10), 1360–1374. https://doi.org/10.1038/s41590-019-0476-1
- Patel, G. K., et al. (2021). Modulating Th2 cell immunity for the treatment of asthma. Frontiers in Immunology, 12, 637948. https://www.frontiersin.org/articles/10.3389/fimmu.2021.637948/full
- Barnes, P. J. (2016). Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. Journal of Allergy and Clinical Immunology, 138(1), 16–27. https://doi.org/10.1016/j.jaci.2016.05.011
- Kwak, N. D., et al. (2021). Synergistic cycles of protease activity and inflammation via PPARγ degradation in COPD. Experimental & Molecular Medicine, 53(5), 823–834. https://www.nature.com/articles/s12276-021-00626-7
- Marrie, T. J. (2010). Community-acquired pneumonia. Clinical Infectious Diseases, 51(Suppl. 4), S296–S304. https://doi.org/10.1086/655827 (Alveolar consolidation, neutrophils, impaired gas exchange, matching IV.4.3.) For didactic pathology text:
- BCcampus. (2022). Pathophysiology of pneumonia. In Pathology: Introduction to disease. https://pressbooks.bccampus.ca/dcbiol2200/chapter/pathophysiology-of-pulmonary-edema/

- Pai, M., Behr, M. A., Dowdy, D., et al. (2016). Tuberculosis. Nature Reviews Disease Primers, 2, 16076. https://doi.org/10.1038/nrdp.2016.76
- Travis, W. D., Costabel, U., Hansell, D. M., et al. (2013). An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. American Journal of Respiratory and Critical Care Medicine, 188(6), 733–748.

# Chapter V

# Hematopoietic and lymphatic systems physiopathology

# V.1. Generalities

## V.1.1. Haematopoietic system

The hematopoietic system is a complex and highly organised network of organs, tissues, and specialised stem-cell populations that are responsible for the continuous production, differentiation, and regulation of all blood cells throughout life. In essence, it ensures that the body maintains adequate numbers of erythrocytes (red blood cells), leukocytes (white blood cells), and platelets (thrombocytes) in circulation, which are indispensable for oxygen transport, immune defence, and hemostasis. Under normal physiological conditions, the hematopoietic system produces approximately $10^{11}$-$10^{12}$ new blood cells per day, a figure that may increase dramatically in response to stress, infection, haemorrhage, or hypoxia. This continuous turnover is coordinated by a hierarchy of hematopoietic stem cells (HSCs) and progenitor cells that reside mainly in the bone marrow, though certain lymphoid tissues also contribute to the final stages of maturation and activation of specific cell lineages.

The primary anatomical site of hematopoiesis in adults is the red bone marrow, which is found in the axial skeleton (skull, vertebrae, ribs, sternum, pelvis) and in the proximal ends of the long bones, such as the femur and humerus. Within the marrow, hematopoietic stem cells occupy specialised microenvironments called niches, where interactions with stromal cells, extracellular matrix proteins, and a variety of signalling molecules tightly regulate whether HSCs remain quiescent, self-renew, or commit to differentiation into specific blood-cell lineages. These niches provide structural support and deliver soluble factors such as stem-cell factor (SCF), interleukin-3 (IL-3), and other cytokines that act on receptors on HSCs to modulate their behaviour. In addition to the bone marrow, secondary lymphoid organs such as the spleen, lymph nodes, and mucosa-associated lymphoid tissue (MALT) play roles in the maturation and activation of lymphoid cells, particularly T and B lymphocytes, while also serving as reservoirs for monocytes and platelets.

At the cellular level, the hematopoietic system is organised around a single multipotent stem cell, the hematopoietic stem cell, which has the dual capacity for self-renewal and differentiation into all mature blood-cell types. From this common precursor, the system branches into two broad lineages: the myeloid lineage and the lymphoid lineage. The myeloid lineage gives rise to erythrocytes, megakaryocytes (which produce platelets), granulocytes (neutrophils, eosinophils, basophils), monocytes/macrophages, and dendritic cells, all of which are involved in oxygen transport, phagocytosis, inflammation, and antigen presentation. The lymphoid lineage, in contrast, produces T cells, B cells, and natural killer (NK) cells, which are central to adaptive and innate immunity, respectively. This bifurcation is not absolute at the earliest stages, as some

progenitors retain multilineage potential, but progressively, lineage-specific transcription factors such as GATA-1, PU.1, and Ikaros drive commitment toward distinct fates (Fig. 44).

One of the most striking features of the hematopoietic system is its dynamic responsiveness to changing physiological demands. For example, under conditions of hypoxia, tissues such as the kidney increase production of erythropoietin (EPO), a hormone that stimulates erythroid progenitors in the bone marrow to accelerate red-cell production and thus improve oxygen delivery. Similarly, in the setting of infection or tissue injury, the levels of granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin-6 (IL-6) rise, promoting the expansion and differentiation of granulocytes and monocytes to enhance inflammatory and phagocytic responses. Platelet production is regulated by thrombopoietin (TPO), which acts on megakaryocyte progenitors to generate more platelets when there is significant blood loss or vascular damage. In this way, the hematopoietic system functions not as a static factory but as a finely tuned, feedback-controlled system that preserves the balance between cell production, circulation, and destruction.

Beyond numerical homeostasis, the hematopoietic system also plays a critical role in immune surveillance and tolerance. Lymphoid progenitors give rise to naïve T and B cells that circulate between lymphoid organs and peripheral tissues, where they encounter antigens and either mount protective immune responses or undergo deletion/anergy to avoid autoimmunity. Dendritic cells, macrophages, and other antigen-presenting cells derived from the myeloid lineage serve as sentinels in tissues, sampling the environment and migrating to lymph nodes to present antigenic peptides to T cells, thereby bridging innate and adaptive immunity. Additionally, specialized subsets such as regulatory T cells and myeloid-derived suppressor cells help to modulate immune responses, preventing excessive inflammation and tissue damage. This integrative function of the hematopoietic system underscores its importance not only in defending against pathogens but also in maintaining overall immune homeostasis and preventing chronic inflammation or autoimmune disorders.

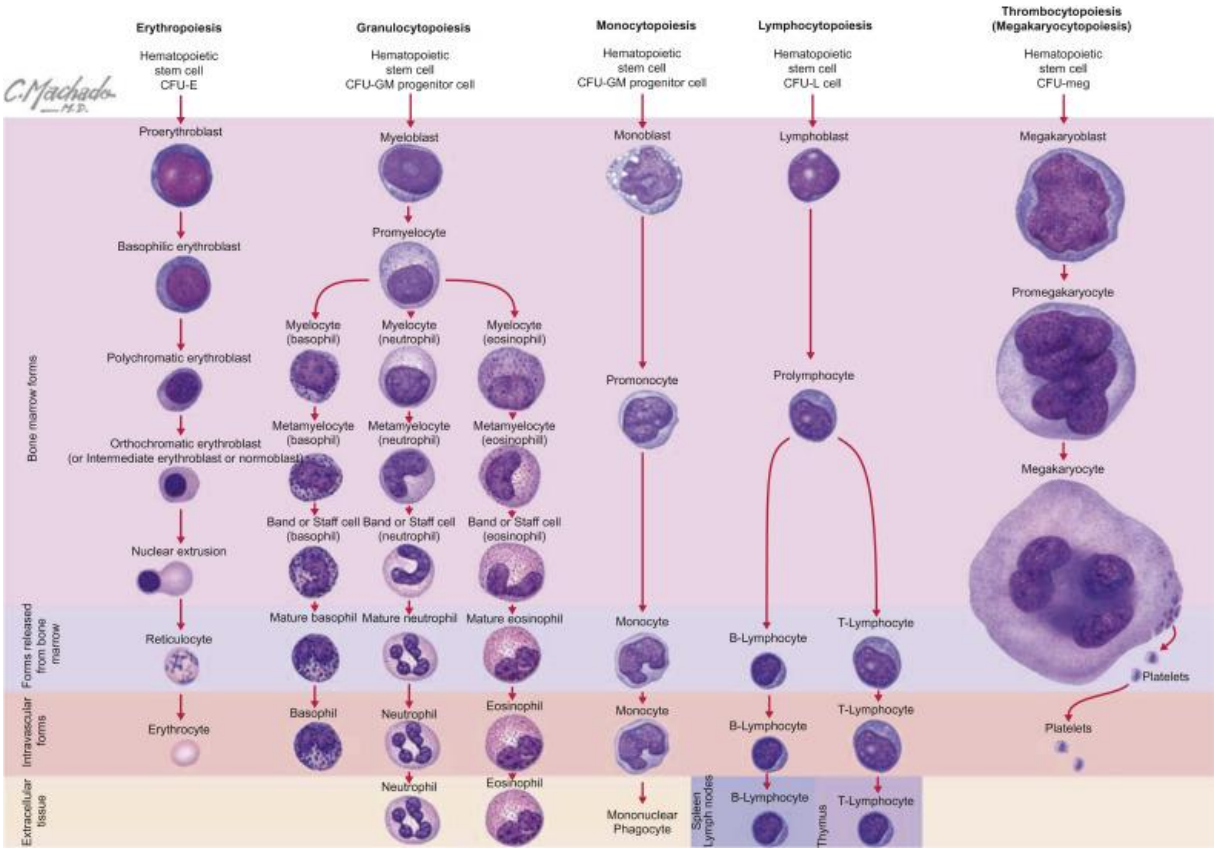



**Figure 44. Haematopoietic cells.**

## V.1.2. Lymphatic system

The lymphatic system is an essential part of the circulatory and immune systems, consisting of a vast network of lymphatic vessels, lymph nodes, and lymphoid organs such as the spleen, thymus, and tonsils. It functions primarily to maintain fluid balance by collecting excess interstitial fluid, now called lymph, from body tissues and returning it to the bloodstream. This system also plays a crucial role in immune surveillance and defence by transporting lymphocytes—white blood cells that fight infection—and filtering harmful substances like bacteria and damaged cells through lymph nodes. Additionally, the lymphatic system absorbs fats and fat-soluble vitamins from the digestive tract, facilitating their transport to the bloodstream. The flow of lymph is propelled mainly by muscle contractions and valves within the vessels, ensuring unidirectional movement. Overall, the lymphatic system not only helps regulate fluid levels and absorb nutrients but also is fundamental for immune system function and protection against disease

Lymphatic vessels have crucial functions in the maintenance of tissue fluid homeostasis, immune cell trafficking, and reverse cholesterol transport through scavenger receptor B1 (SR-BI)-mediated uptake of high-density lipoprotein (HDL) in all tissues (general functions), but they have also specialised functions in different organs (tissue-specific functions, depicted on the left). The organisation of the lymphatic vessel network is illustrated on the right. Lymphatic capillaries take

up fluid, macromolecules and HDL–cholesterol (HDL-C) from the interstitial tissue and provide an entry point for immune cells for trafficking to the lymph nodes (Fig. 45).

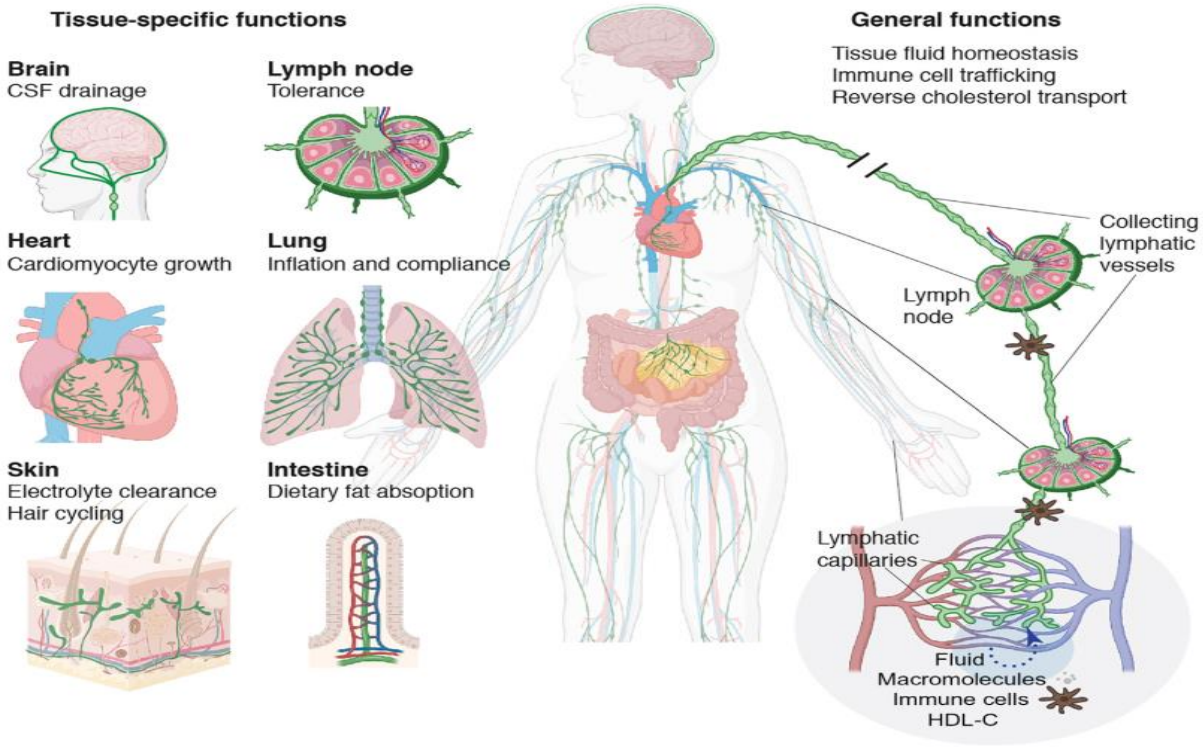



**Figure 45. Lymphatic system**

# V.2. Diseases of the hematopoietic system

## V.2.1. Aplastic Anaemia

Aplastic Anaemia is a severe condition resulting from damage to the bone marrow, which consequently leads to the reduced production of all blood cell types (red blood cells, white blood cells, and platelets). This production failure can be triggered by several factors: Autoimmune Disorders, where the immune system mistakenly attacks the bone marrow; Exposure to Toxins, such as benzene or certain pesticides; specific Medications, including chemotherapy drugs or antibiotics; Viral Infections like hepatitis, Epstein-Barr virus, or HIV; and Inherited Conditions, such as Fanconi anaemia or other genetic disorders. The symptoms of Aplastic Anaemia reflect the lack of circulating blood cells, including fatigue and weakness, shortness of breath, and pale skin (due to anaemia); frequent or prolonged infections (due to leukopenia); and unexplained bruising or bleeding, nosebleeds, or gum bleeding (due to thrombocytopenia). Treatment options focus on restoring cell counts and function, primarily through Blood Transfusions to manage symptoms temporarily, Immunosuppressive Drugs to stop the underlying immune attack on the

bone marrow, a Bone Marrow Transplant which offers a potential cure, especially for younger patients, and the use of Growth Factors to stimulate the remaining bone marrow to produce blood cells.

## V.2.2. Hemolytic Anaemia

Hemolytic Anaemia is a disorder characterized by the destruction (hemolysis) of red blood cells (RBCs) faster than the bone marrow can replace them. This RBC destruction can occur within the blood vessels (intravascular hemolysis) or in organs like the spleen and liver (extravascular hemolysis). The causes are separated into two main categories. Inherited Causes are due to genetic defects in the RBCs, including Hemoglobinopathies (Sickle cell anaemia, thalassemia), Membrane Defects (Hereditary spherocytosis, elliptocytosis), and Enzyme Deficiencies (G6PD deficiency, pyruvate kinase deficiency). Acquired Causes result from external factors, such as Immune-Mediated reactions (Autoimmune Hemolytic Anaemia, blood transfusion reactions), Infections (Malaria, babesiosis), exposure to Drugs and Toxins (Penicillin, dapsone, venoms), Mechanical Destruction (from prosthetic heart valves or microangiopathic hemolytic anaemia [MAHA]), and Paroxysmal Nocturnal Hemoglobinuria (PNH), a rare acquired stem cell disorder.

Symptoms include fatigue and weakness, pale or jaundiced skin (yellowing due to increased bilirubin), dark urine (from hemoglobin or bilirubin), an enlarged spleen (splenomegaly), rapid heartbeat, and shortness of breath. Untreated, complications like severe fatigue, gallstones, or heart problems may arise. Clinical diagnostics involve a Complete Blood Count (CBC), which typically shows low hemoglobin levels but an elevated reticulocyte count (indicating bone marrow compensation). A Peripheral Blood Smear reveals abnormal RBC shapes like spherocytes or schistocytes (fragmented cells). Serum Tests show an elevated Lactate Dehydrogenase (LDH) and Indirect Bilirubin (markers of cell destruction), and low Haptoglobin (due to binding with free hemoglobin). The Direct Antiglobulin Test (Coombs Test) is crucial, being positive for immune-mediated hemolysis and negative for non-immune causes. Specialized tests include the G6PD Activity Test, Hemoglobin Electrophoresis for hemoglobinopathies, Flow Cytometry for PNH, and Bone Marrow Aspiration to exclude marrow-related causes. Treatment is cause-specific and involves Medications like corticosteroids for autoimmune causes, folic acid supplements to support RBC production, Transfusions for severe anaemia, Plasma Exchange (for conditions like thrombotic thrombocytopenic purpura [TTP]), Splenectomy (for hereditary spherocytosis or refractory cases), Avoidance of Triggers (in G6PD deficiency), and Bone Marrow Transplant for severe inherited hemolytic anaemias.

## V.2.3. Leukopenia

Leukopenia is defined as a reduced number of white blood cells (WBCs), specifically when the total count falls below $4,000$ cells/$\mu$L. Because WBCs are crucial for the immune system, leukopenia significantly increases the risk of infections. Leukopenia can stem from Decreased Production of WBCs due to Bone Marrow Disorders (Aplastic anaemia, Myelodysplastic syndromes, Leukemia/lymphoma), Nutritional Deficiencies (Vitamin B12, folate, copper), or Medications (chemotherapy, immunosuppressive drugs, certain antibiotics/antiepileptics). It can also result from Increased Destruction of WBCs caused by Autoimmune Diseases (Lupus, rheumatoid arthritis), Infections (severe viral infections like HIV, hepatitis, Epstein-Barr virus, or sepsis), or certain Medications or Reactions (drug-induced leukopenia). Other mechanisms include Redistribution of WBCs due to stress, shock, or Splenic Sequestration (enlarged spleen trapping WBCs), and Genetic Disorders (Congenital Neutropenia).

Leukopenia is categorized based on the cell type affected: Neutropenia (low neutrophils, the most common type), Lymphopenia (low lymphocytes, seen in severe viral infections), or Monocytopenia (low monocytes). Symptoms are generally those of immune compromise: frequent or recurrent infections, fever, chills, or sweats, mouth ulcers or sores, and fatigue or weakness. Diagnostics begin with a CBC with Differential to confirm the low total WBC count and identify the specific low cell type. A Bone Marrow Aspiration and Biopsy helps identify underlying bone marrow disorders. Other tests include a Peripheral Blood Smear, Infection Screen (blood cultures, viral serologies), Autoimmune Markers (ANA test, rheumatoid factor), Nutritional Tests, and Genetic Testing for congenital causes. Treatment focuses on the underlying cause: Infection Management with antibiotics/antivirals, Stimulating WBC Production using Granulocyte Colony-Stimulating Factor (G-CSF) drugs (filgrastim, pegfilgrastim), Treating Underlying Causes (corticosteroids/immunosuppressants for autoimmune disorders, supplements for deficiencies, discontinuing causative medications), and Bone Marrow Transplant for severe, irreversible failure. Lifestyle recommendations include avoiding infection exposure and ensuring adequate nutrition.

## V.2.4. Thrombocytopenia

Thrombocytopenia is a condition characterized by a platelet count below the normal range (150,000 to 450,000 platelets per $\mu$L of blood). As platelets are crucial for clotting, this leads to excessive bleeding or bruising. Causes fall into four categories: Decreased Platelet Production (Bone Marrow Disorders like Aplastic anaemia, Leukemia, Myelodysplastic syndromes; Nutritional Deficiencies like Vitamin B12/folate; Viral Infections like HIV/hepatitis C; Medications like chemotherapy; and Chronic Alcohol Use). Increased Platelet Destruction (Immune-Mediated Destruction like Immune Thrombocytopenic Purpura (ITP), Drug-induced

thrombocytopenia [e.g., heparin-induced thrombocytopenia (HIT)], Infections like Sepsis, Pregnancy-Associated, and Autoimmune Diseases like Lupus/rheumatoid arthritis). Platelet Sequestration (enlarged spleen/splenomegaly trapping platelets, common in liver diseases). Lastly, Dilutional Thrombocytopenia can occur after massive blood transfusions.

Symptoms include easy bruising (ecchymosis), prolonged bleeding from cuts, spontaneous bleeding (like nosebleeds, bleeding gums), petechiae (tiny red spots on the skin), and heavy menstrual periods. Severe cases may involve blood in stool/urine or internal hemorrhages. Diagnosis is confirmed by a CBC showing a platelet count $<150,000/\mu$L. A Peripheral Blood Smear checks platelet appearance, and Bone Marrow Aspiration and Biopsy assesses production issues. Coagulation Tests (PT and aPTT) evaluate overall clotting function. Specific tests include Autoimmune Tests, Infection Screens (HIV, hepatitis C), and the Heparin Antibody Test for HIT. Treatment ranges from Observation for mild cases ($>50,000/\mu$L) to Medications like corticosteroids (for immune-mediated destruction), Immunoglobulin Therapy (IVIG), or Thrombopoietin Receptor Agonists (to stimulate production). Platelet Transfusions are used for severe bleeding, and Treating Underlying Conditions involves antibiotics for infections, stopping causative drugs, or Splenectomy for chronic ITP. Lifestyle modifications include avoiding activities or medications (aspirin, NSAIDs) that increase bleeding risk.

## V.2.5. Methemoglobinemia

Methemoglobinemia is defined by the production of an abnormal amount of methemoglobin, a form of hemoglobin with oxidized iron ($Fe^{3+}$ instead of $Fe^{2+}$) that cannot bind oxygen effectively. This reduces oxygen delivery and causes tissue hypoxia. The condition is most commonly Acquired from exposure to drugs and chemicals that oxidize hemoglobin, such as Medications (local anesthetics like benzocaine/lidocaine, dapsone, nitrates/nitrites, sulfonamides), Chemical Exposure (aniline dyes, nitrates in fertilizers), or Nitrates in Food/Water (causing "blue baby syndrome" in infants). Rarer Congenital Methemoglobinemia is caused by genetic defects like Hemoglobin M disease or a deficiency of the enzyme NADH-cytochrome b5 reductase, which normally reduces methemoglobin.

Symptoms are severity-dependent: Mild cases (<10) are often asymptomatic. Moderate cases (10–30%) show cyanosis (bluish discoloration), fatigue, dizziness, and headache. Severe cases (30–50%) involve shortness of breath, confusion, and palpitations. Life-Threatening cases (>50%) result in severe hypoxia, seizures, coma, and potentially death. Clinical diagnostics include an Arterial Blood Gas (ABG) (which may show normal oxygen saturation despite cyanosis), direct measurement of the Methemoglobin Level, and Co-oximetry, which quantifies methemoglobin. A CBC rules out other issues, and Genetic Testing is available for congenital forms. Treatment for

severe cases (>20% or symptomatic) is usually the intravenous administration of Methylene Blue, which reduces methemoglobin back to hemoglobin (though it is ineffective/contraindicated in G6PD deficiency). Ascorbic Acid (Vitamin C) is used when methylene blue is contraindicated, and Oxygen Therapy provides supplemental oxygen. Exchange Transfusion is rarely needed for life-threatening cases, and the underlying cause must be treated by discontinuing the offending agent.

Hypersensitivity Reactions Affecting Blood Cells

Hypersensitivity Reactions are immune system overreactions to allergens that can damage tissues and affect blood cells. They are categorized by the Gell and Coombs classification:

- Type I (Immediate Hypersensitivity): Mechanism involves IgE antibodies binding to mast cells/basophils, releasing histamine. Primarily affects eosinophils and basophils. Examples include Anaphylaxis, Allergic asthma, and Atopic dermatitis. Symptoms include swelling, itching, and potentially life-threatening systemic anaphylactic shock.
- Type II (Cytotoxic Hypersensitivity): Mechanism involves IgG or IgM antibodies binding to antigens on cell surfaces, leading to cell destruction by complement or phagocytosis. This type often targets RBCs, platelets, and leukocytes, causing Hemolytic Anaemia (e.g., Autoimmune Hemolytic Anaemia), Thrombocytopenia (e.g., ITP), and Leukopenia. Examples include Transfusion Reactions and Autoimmune Diseases like Myasthenia gravis.
- Type III (Immune Complex Hypersensitivity): Mechanism involves the formation of antigen-antibody complexes that deposit in tissues, causing inflammation. Affects leukocytes, RBCs, and platelets indirectly. Associated with systemic diseases like Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, and Serum sickness, causing organ damage (vasculitis, arthritis) and skin rashes.
- Type IV (Delayed-Type Hypersensitivity): Mechanism is mediated by T cells (CD4+ helper T cells and CD8+ cytotoxic T cells) rather than antibodies. Involves monocytes, macrophages, and T lymphocytes. Examples include Contact dermatitis, Tuberculin reactions, and Chronic transplant rejection. Symptoms are typically delayed (24-48 hours) and involve local inflammation.

Specific examples of these reactions affecting blood cells include Autoimmune Hemolytic Anaemia and Immune Thrombocytopenic Purpura (ITP) (both Type II), Agranulocytosis (severe reduction in neutrophils, Type II or IV, often drug- or autoimmune-induced), and Allergic Leukopenia (Type I). Diagnostics involve CBC, Antibody Tests (Direct Coombs Test), Skin Tests (Patch Testing for Type IV), Serology Tests (for immune complexes/autoantibodies), and Bone

Marrow Aspiration/Biopsy. Treatment focuses on Removing the Offending Agent, Pharmacological Treatments (Antihistamines for Type I; Corticosteroids/Immunosuppressive Drugs for Type II, III, IV), Plasmapheresis (to remove antibodies/immune complexes in severe Type II/III), and careful Blood Transfusions with cross-match testing.

# V.3. Lymphatic' system pathologies

## V.3.1. Lymphodema

Lymphedema is a chronic, progressive condition characterized by the abnormal accumulation of protein-rich lymphatic fluid in the interstitial tissue due to impaired lymphatic drainage. This impairment can arise from either congenital defects in the lymphatic system, termed primary lymphedema, or from acquired damage secondary to factors such as cancer treatment, infection, trauma, or surgery, known as secondary lymphedema. The pathological accumulation of lymph fluid leads to persistent swelling, typically of the extremities, accompanied by a sensation of heaviness, discomfort, and restricted mobility. Over time, this swelling may become associated with tissue fibrosis, skin thickening, recurrent infections like cellulitis, and in severe cases, disfigurement. The underlying pathophysiology involves a disruption in the balance between lymph production and clearance, resulting in lymphatic stasis and chronic edema. Recognition of lymphedema symptoms and risk factors—including malignancy, lymph node dissection, radiotherapy, and obesity—is crucial for early diagnosis and effective management. Although lymphedema is incurable, treatment strategies focus on symptom reduction, prevention of complications, and improvement of quality of life through methods such as compression therapy, manual lymphatic drainage, and exercise regimens. Comprehensive assessment and ongoing monitoring remain integral to managing this complex disorder effectively.

## V.3.2. Lymphoma

Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are distinct types of lymphatic system cancers that primarily affect lymphocytes, a kind of white blood cell. The hallmark of Hodgkin lymphoma is the presence of Reed-Sternberg cells, which are large, abnormal B lymphocytes identifiable under a microscope. This type tends to originate in lymph nodes located in the chest, neck, or underarms and typically spreads in a predictable, stepwise fashion from one lymph node region to adjacent areas. In contrast, non-Hodgkin lymphoma is more diverse, encompassing over 30 subtypes arising from either B cells or T cells, and its spread is less predictable, often affecting lymph nodes throughout the body and potentially invading other organs such as the lungs, liver, or bones.

Lymphoma, a cancer of the lymphatic system, presents with a variety of symptoms that can vary depending on the type and location of the disease. The most common symptom is painless swelling of lymph nodes, often found in the neck, armpits, or groin. Other general symptoms include unexplained fever, drenching night sweats, persistent fatigue, and unintentional weight loss. Some patients, particularly those with Hodgkin lymphoma, may experience itching of the skin. Additional symptoms can arise depending on the affected areas, such as cough, shortness of breath, or chest pain if lymph nodes in the chest are involved, and abdominal discomfort or swelling if lymph nodes in the abdomen are affected. Less commonly, lymphoma can cause bone pain, frequent infections, unusual bruising or bleeding due to low platelet counts, and swelling or tightness in limbs caused by lymphatic obstruction (lymphedema). Because these symptoms can be subtle and overlap with other conditions, it is important to seek medical evaluation if they persist or worsen.

Both HL and NHL share similar symptoms, including painless swelling of lymph nodes, fever, night sweats, unexplained weight loss, fatigue, and occasional rash. However, HL generally has a better prognosis, with a five-year survival rate exceeding 85-90%, while NHL's prognosis varies widely depending on the subtype, stage at diagnosis, and treatment response, with an average five-year survival around 70-75%. Risk factors for both include family history, certain infections, and possibly autoimmune conditions. Treatment approaches differ; HL is commonly treated with combinations of chemotherapy and radiation with high curative potential, whereas NHL treatment depends largely on the specific subtype and may include chemotherapy, immunotherapy, targeted therapies, or stem cell transplantation. The underlying biological differences and clinical behaviors between Hodgkin and non-Hodgkin lymphoma necessitate distinct diagnostic and therapeutic strategies tailored to each subtype's characteristics.

## V.3.3. Lymphadenitis

Lymphadenitis is the inflammation and infection of one or more lymph nodes, commonly occurring as a complication of bacterial infections. It causes the affected lymph nodes to become swollen, tender, and painful, often located near the site of an infection or inflammation in the body. The condition can result from various infectious agents including bacteria such as streptococcus or staphylococcus, viruses, fungi, or rarely from infections like tuberculosis or cat scratch disease. Clinically, lymphadenitis may present with symptoms such as fever, chills, and localized pain, and the swollen lymph nodes may feel hard or tender to touch. If untreated, lymphadenitis can lead to abscess formation or the spread of infection to surrounding tissues. It is important to distinguish lymphadenitis from lymphadenopathy, which refers more generally to swollen lymph nodes

without infection. Treatment typically involves antibiotics for bacterial causes, and prognosis depends on timely intervention and addressing the underlying infection.

## V.3.4. Lymphangitis

Lymphangitis is an acute inflammatory condition of the lymphatic vessels, generally caused by a bacterial infection that originates from a skin wound, abscess, or other localized infection. The lymphatic system, which plays a crucial role in immune function and fluid balance, consists of a network of vessels that transport lymph—a fluid containing immune cells—throughout the body. When bacteria, most commonly group A beta-hemolytic streptococci or Staphylococcus aureus, invade these vessels, they cause inflammation that manifests visibly as red, painful streaks extending along the skin from the site of infection toward nearby lymph nodes. These inflamed lymphatic channels become tender and warm, and the regional lymph nodes often swell and hurt as well.

Clinically, lymphangitis presents with not only localized redness and streaking but also systemic symptoms such as fever, chills, and malaise, indicating a spreading infection. The condition represents a warning sign that the underlying infection is worsening and may spread further into the bloodstream, potentially causing sepsis, a life-threatening systemic inflammatory response. Prompt diagnosis and treatment with appropriate antibiotics are essential to prevent such severe complications. Besides bacterial causes, lymphangitis can occasionally arise from fungal, viral, or parasitic infections, as well as non-infectious triggers like arthropod bites or allergic reactions. Due to the risk of rapid progression, medical attention should be sought immediately upon symptom onset. Treatment typically involves antibiotics, wound care, and supportive measures, with close monitoring to ensure the infection is controlled and does not advance to more serious conditions such as abscess formation or septicemia.

# References


- Mosaad, Y. M. (2014). Hematopoietic stem cells: An overview. Transfusion and Apheresis Science, 51(3), 68–82.
- Koury, M. J. (2014). Abnormal erythropoiesis and the pathophysiology of chronic anemia. Blood Reviews, 28(2), 49–66.
- de L. Thau, M., Reddy, V., & Singh, P. (2023). Physiology, lymphatic system. In StatPearls. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK557833/
- Young, N. S. (2018). Aplastic anemia. The New England Journal of Medicine, 379(17), 1643–1656.
- Barcellini, W., Fattizzo, B., Zaninoni, A., et al. (2020). Hemolytic anemias: Diagnosis and management. Hematology/Oncology Clinics of North America, 34(4), 655–675.
- Boxer, L. A. (2012). How to approach neutropenia. Hematology American Society of Hematology Education Program, 2012(1), 174–182. (Clinical approach to leukopenia/neutropenia.)
- Neunert, C., Terrell, D. R., Arnold, D. M., et al. (2019). American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Advances, 3(23), 3829–3866. https://ashpublications.org/bloodadvances/article/3/23/3829/429077/American-Society-of-Hematology-2019-guidelines-for
- Wright, R. O., Lewander, W. J., & Woolf, A. D. (1999). Methemoglobinemia: Etiology, pharmacology, and clinical management. Annals of Emergency Medicine, 34(5), 646–656. (Classic review of acquired and congenital methemoglobinemia.)
- Coombs, R. R. A., Gell, P. G. H., & Lachmann, P. J. (1975). The classification of allergic reactions responsible for clinical hypersensitivity and disease. In P. G. H. Gell, R. R. A. Coombs, & P. J. Lachmann (Eds.), Clinical aspects of immunology (3rd ed., pp. 761–781). Blackwell Scientific.
- Rockson, S. G. (2018). Lymphedema after cancer treatment. The New England Journal of Medicine, 379(20), 1937–1944. (Authoritative review on lymphedema pathophysiology and management.)

# Chapter VI

# Neurotoxicity

# VI.1. Generalities

## VI.1.1. The nervous system anatomy

The nervous system is anatomically divided into two major parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and the spinal cord, which are protected by the skull and vertebral column respectively. The brain is the control center, while the spinal cord serves as a communication pathway between the brain and the body. The PNS comprises nerves that connect the CNS to the rest of the body, including somatic nerves that control muscles and sensory organs, and the autonomic nerves that regulate involuntary functions like heart rate and digestion (Fig. 46).

The CNS is further organized with the brain divided into regions such as the forebrain, midbrain, and hindbrain. The brain is composed of several key parts that work together to control different functions. The cerebrum, the largest part, is divided into two hemispheres and four lobes (frontal, parietal, temporal, occipital) responsible for thinking, memory, sensory processing, and voluntary movement. Beneath the cerebrum is the cerebellum, which manages balance and coordination. The brainstem, consisting of the midbrain, pons, and medulla oblongata, connects the brain to the spinal cord and controls vital automatic functions such as breathing and heart rate. Central to the brain is the diencephalon, which includes the thalamus, acting as a relay station for sensory and motor signals, and the hypothalamus, which regulates autonomic and endocrine functions. Together, these parts form an integrated system essential for bodily and cognitive processes (Fig. 47).

The spinal cord is segmented into cervical, thoracic, lumbar, sacral, and coccygeal regions with corresponding spinal nerves. The spinal cord contains gray matter with neurons and white matter for transmission of nerve signals. The PNS includes cranial nerves and spinal nerves that branch out to various body parts to carry sensory input to the CNS and motor commands back to muscles and glands.

The autonomic nervous system, a part of the PNS, is subdivided into the sympathetic and parasympathetic systems. The sympathetic system prepares the body for 'fight or flight' responses, increasing heart rate and metabolism, while the parasympathetic system promotes rest and digestion, slowing heart rate and conserving energy.

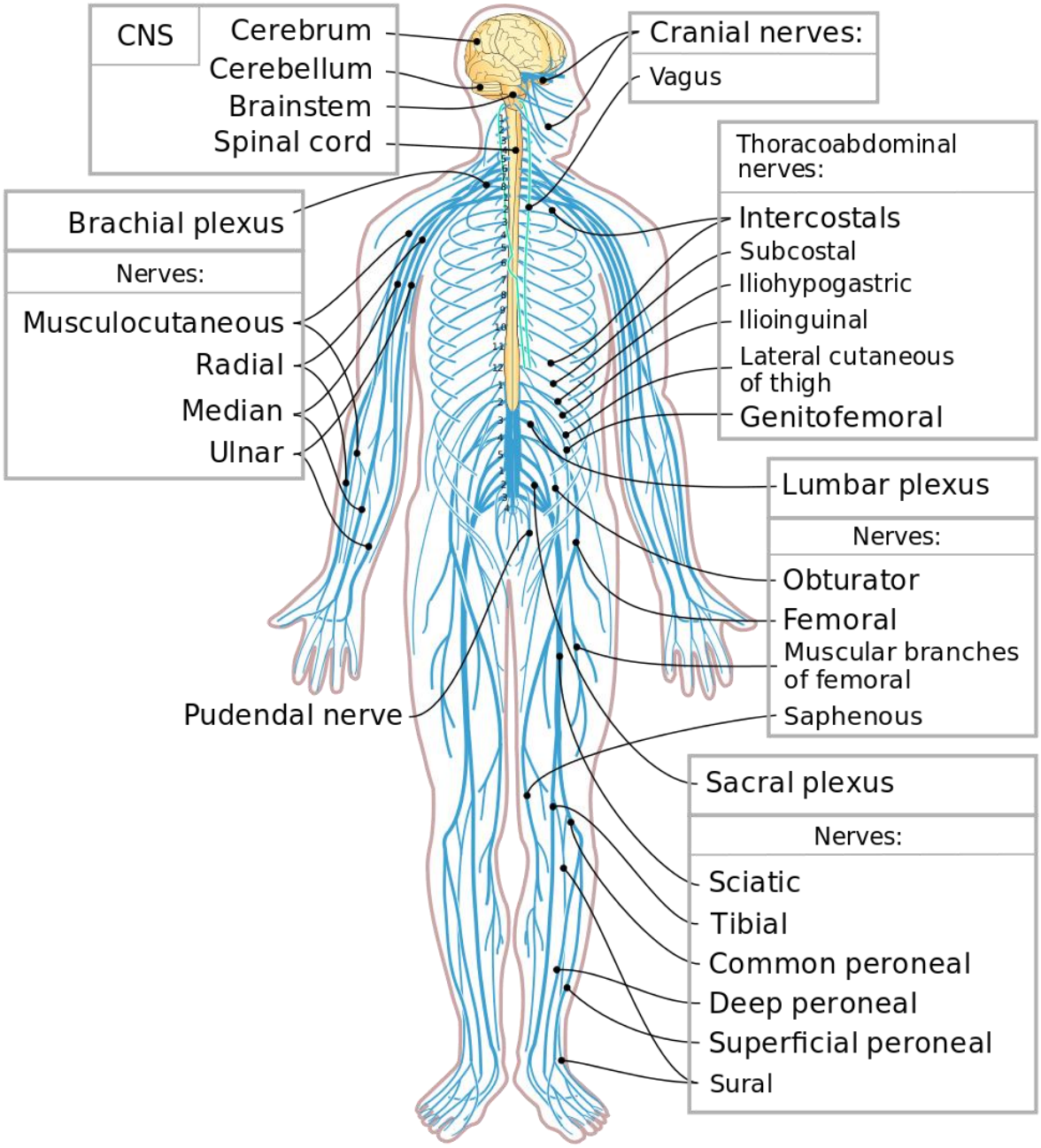



**Figure 46. The nervous system**

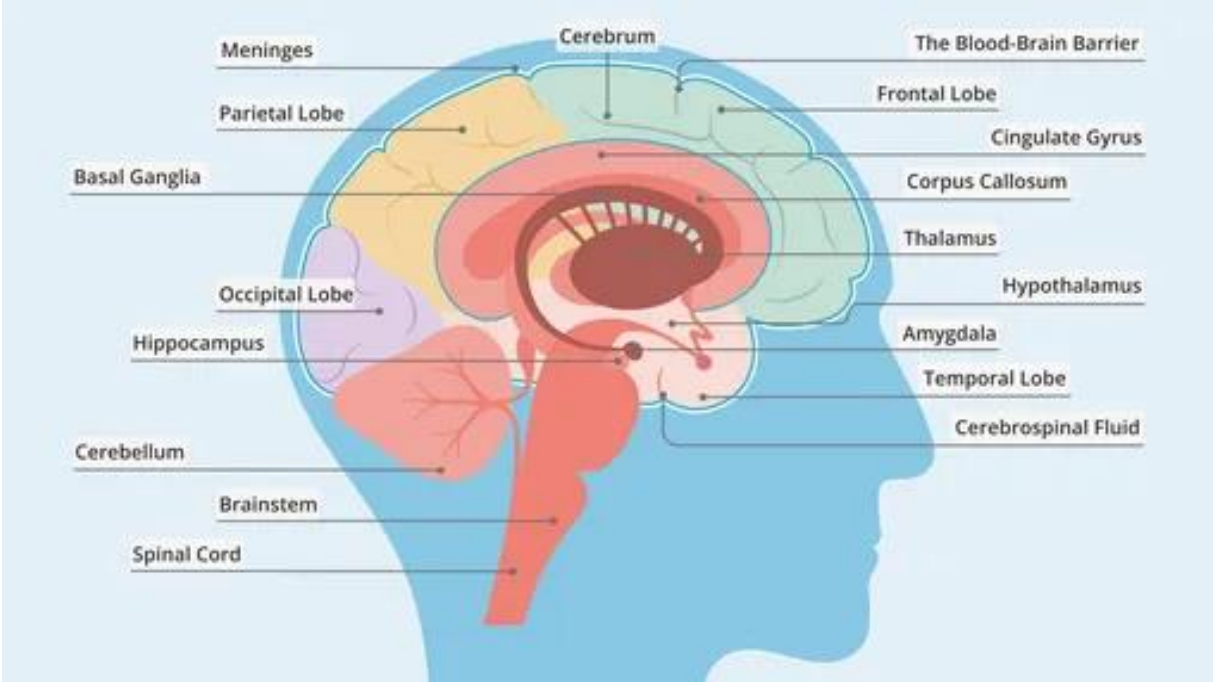


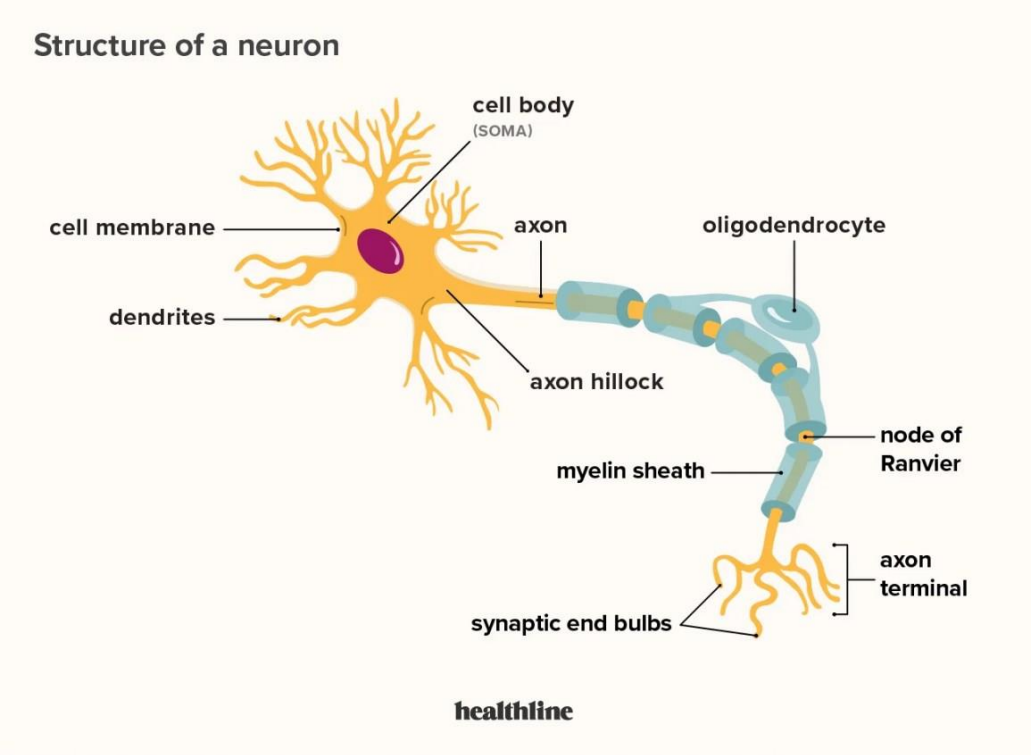

**Figure 47. Brain composition**

## VI.1.2. Cells of the nervous system

The nervous system is composed primarily of two types of cells: neurons and glial cells.

Neurons are the fundamental signalling units of the nervous system responsible for transmitting electrical and chemical signals. They consist of a cell body (soma), dendrites that receive signals, and a single axon which transmits impulses to other neurons or effector cells. Neurons are classified by function into sensory neurons (carrying signals from sensory receptors to the CNS), motor neurons (transmitting commands from the CNS to muscles and glands), and interneurons (connecting neurons within the CNS to facilitate complex processing). They differ in shape, size, and neurotransmitter types, supporting a wide array of neural functions.

Glial cells, also known as neuroglia, provide critical support and protection for neurons. In the central nervous system (CNS), main glial types include astrocytes, which regulate the extracellular environment and maintain the blood-brain barrier; oligodendrocytes, which form the myelin sheath that insulates CNS axons; microglia, which act as immune cells performing surveillance and cleanup; and ependymal cells, which line cavities and help circulate cerebrospinal fluid. In the peripheral nervous system (PNS), Schwann cells myelinate axons, and satellite cells support neuron cell bodies within ganglia, maintaining their environment (Fig. 48).



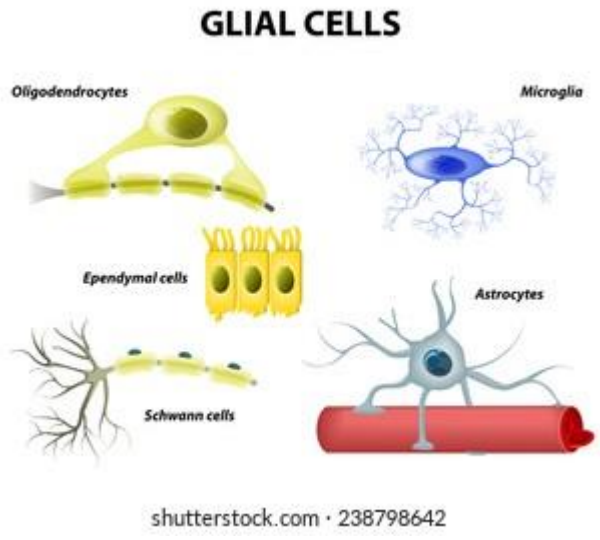




**Figure 48. Neurons and glial cells**

# VI.2. Physiopathology of the nervous system

## VI.2.1. Perinatal brain injuries

Perinatal brain injuries are brain damage that occurs around the time of birth and can lead to lifelong physical, cognitive, and developmental impairments. The main types include hypoxic-ischemic encephalopathy (HIE), caused by oxygen deprivation leading to brain cell death; intracranial hemorrhage, which is bleeding inside the brain; perinatal arterial ischemic stroke,

where blood flow to parts of the brain is blocked; cerebral sinovenous thrombosis, involving blood clots in the brain's venous system; and periventricular leukomalacia, characterized by white matter damage near the brain's ventricles often linked to premature birth. Causes include maternal factors like smoking, anemia, infections, placental abruption, umbilical cord complications, and trauma during delivery. Diagnosis typically relies on clinical assessment, neuroimaging (ultrasound, MRI), and EEG. Early intervention is critical for managing seizures, preventing further injury, and supporting neurodevelopment.

## VI.2.2. Traumatic brain injury

Traumatic brain injury (TBI) is damage to the brain caused by an external force such as a blow, jolt, or penetrating injury to the head. It can range from mild concussion to severe brain damage, leading to bruising, bleeding, torn tissues, and swelling inside the skull. Symptoms vary by severity but often include loss or alteration of consciousness, headaches, dizziness, confusion, memory problems, seizures, vision or hearing disturbances, and changes in mood or behavior. Severe cases may involve prolonged unconsciousness or coma. Diagnosis is done through neurological exams and imaging like CT scans or MRIs. Treatment depends on severity and may involve rest, medications for pain or seizures, surgery to relieve pressure or repair damage, and rehabilitation therapies to aid recovery. Preventive measures include wearing helmets, seatbelts, and avoiding risky behaviors to reduce the risk of head injury.

TBI can be classified into three main categories based on the type of injury involved: skull fractures, parenchymal injuries, and traumatic vascular injuries.

**Skull fracture injuries** involve breaks or cracks in the skull bone caused by direct impact. These include linear fractures (simple cracks), depressed fractures (where a portion of the skull is pushed inward), and comminuted fractures (where the bone is shattered into pieces). Basilar skull fractures affect the base of the skull and can damage structures like cranial nerves and lead to cerebrospinal fluid leaks. Skull fractures may increase the risk of underlying brain injuries such as hematomas and contusions.

**Parenchymal injuries** refer to direct damage to the brain tissue itself. This category includes contusions, which are bruises of the brain caused by bleeding and swelling either at the site of impact (coup injury) or on the opposite side (contrecoup injury). Diffuse axonal injury is another type, involving widespread injury to nerve fibers caused by shearing forces from rapid acceleration, deceleration, or rotational movements. Concussions, a form of mild TBI and the most common type, also belong here. Concussions result from a blow or jolt to the head causing temporary brain dysfunction, with symptoms ranging from brief loss of consciousness to dizziness, confusion, and headaches. There are subtypes of concussion, including mild concussion, classical

concussion with brief loss of consciousness, and complex concussion involving prolonged neurological symptoms or seizures. Repeated concussions can lead to cumulative neurological damage, including chronic traumatic encephalopathy.

**Traumatic vascular injuries** involve damage to the brain's blood vessels resulting in hemorrhages or hematomas. Examples include epidural hematomas (bleeding between the skull and dura mater), subdural hematomas (bleeding beneath the dura mater), subarachnoid hemorrhage (bleeding in the space surrounding the brain), and intracerebral hematomas (bleeding within the brain tissue). These vascular injuries increase intracranial pressure, which can worsen neuronal injury and impair brain function.

## VI.2.3. Infections of the CNS

**Meningitis** is an inflammation of the meninges, the protective membranes covering the brain and spinal cord, which can occur as a serious complication following traumatic brain injury (TBI). Post-traumatic meningitis is typically caused by bacterial infection entering through a skull fracture or cerebrospinal fluid (CSF) leakage, such as rhinorrhea or otorrhea, which creates a pathway for pathogens. It presents diagnostic and treatment challenges compared to community-acquired meningitis and is associated with increased mortality and prolonged hospital stays.

Clinically, meningitis after TBI can lead to symptoms including fever, headache, neck stiffness, altered mental status, seizures, and nausea. The infection causes inflammation and swelling of the brain tissues, increasing the risk of brain injury and long-term neurological consequences such as cognitive impairments, motor deficits, hearing loss, epilepsy, and behavioral problems. Prompt diagnosis often requires analysis of CSF obtained by lumbar puncture, along with blood cultures and imaging to identify underlying fractures or abscesses.

Treatment involves aggressive antibiotic therapy tailored to the causative bacteria, sometimes requiring prolonged hospitalization and supportive care.

Meningitis can be classified into several types based on its cause:

**Bacterial meningitis**: Caused by bacterial infections such as Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae. It is a severe, potentially life-threatening condition that requires prompt antibiotic treatment.

**Viral meningitis**: More common but usually less severe than bacterial meningitis. It is caused by viruses like enteroviruses, herpes simplex virus, and mumps virus. Symptoms often resolve without specific treatment.

**Fungal meningitis**: Caused by fungi such as Cryptococcus neoformans and Histoplasma. This type is more common in immunocompromised individuals and requires antifungal therapy.

Parasitic meningitis: Rare and caused by parasites like *Angiostrongylus cantonensis* or Taenia solium. It can cause severe neurological symptoms.

**Tuberculous** meningitis: Results from infection by Mycobacterium tuberculosis. It has a slow onset and requires prolonged treatment with antitubercular drugs.

**Noninfectious (chemical or aseptic) meningitis**: Inflammation due to cancer, autoimmune diseases, drugs, or injury but without an infectious cause.

## VI.2.4. Peripheral neuropathy diseases

Peripheral neuropathy is a frequent neurological problem in primary care, particularly in older adults, with a prevalence of about 2.4% in the general population, rising to around 8% in people over 55 years of age. It refers to disorders of the peripheral nerves that produce symptoms such as pain, paresthesia (tingling, numbness, crawling sensations), sensory loss, weakness, and gait disturbance, but similar complaints may also arise from lesions in the plexus, nerve roots, spinal cord, or central sensory and motor pathways. A careful history and examination are therefore essential to suggest that the problem truly lies in peripheral nerves, especially in geriatric patients, for whom clinicians must decide when to suspect neuropathy from symptoms, when and how to screen high-risk but asymptomatic patients (for example, those with diabetes), how to counsel and treat confirmed cases, and when to refer for specialist assessment.

The pattern of nerve involvement strongly shapes the clinical picture: length-dependent neuropathies affect the longest fibers first, causing distal symptoms in the feet and legs, whereas non–length-dependent neuropathies may involve proximal and distal limbs, trunk, or face regardless of fiber length. Predominant large-fiber involvement leads to weakness and sensory ataxia, while small-fiber involvement causes pain and allodynia (pain from normally non-painful stimuli) with little or no weakness. The commonest pattern is a length-dependent, predominantly sensory neuropathy of both small and large fibers, but some patients have focal or multifocal involvement of individual large nerves (mononeuropathy simplex or multiplex), and autonomic fibers may be affected either along with other fibers or in isolation, leading to orthostatic hypotension, sweating abnormalities, sphincter dysfunction, and sexual dysfunction.

Several historical elements help narrow the cause of neuropathy. An acute onset with rapid progression suggests conditions such as Guillain-Barré syndrome, toxic neuropathy from chemotherapy or critical illness, vasculitis, or infection, whereas a subacute course can point to chronic inflammatory demyelinating neuropathy, paraneoplastic neuropathy, or nutritional deficiency, and a slowly progressive chronic course is typical of diabetes, long-term alcohol use, or hereditary neuropathies. Important comorbidities and exposures to inquire about include diabetes mellitus, chronic alcohol use, thyroid disease, renal failure, recent weight loss or

gastrointestinal disease with possible vitamin B1 or B12 deficiency, malignancy and chemotherapy, HIV infection, autoimmune or rheumatologic disease, and environmental or occupational exposure to toxins such as heavy metals or pesticides.

Medications are a frequent and sometimes overlooked cause, so clinicians should review drugs such as certain antimicrobials (for example, fluoroquinolones, metronidazole, nitrofurantoin, isoniazid, ethambutol, linezolid), chemotherapeutic agents (vincristine, taxanes, platinum drugs, thalidomide, bortezomib), amiodarone, high-dose pyridoxine supplements, older antiretrovirals (zalcitabine, didanosine, stavudine, lamivudine), some statins, various immunosuppressants, and agents like phenytoin, levodopa, and disulfiram. A family history of similar problems suggests hereditary neuropathy, which often presents earlier in life but can appear later in milder forms and may explain some previously "cryptogenic" cases.

Symptomatically, many patients describe tingling and numbness in the feet, sharp or electric-shock pains in the toes, a stocking-like sensation, and mild imbalance that worsens in the dark or with eyes closed, reflecting distal sensory loss and ataxia. Positive symptoms, driven by abnormal or excessive nerve activity, include burning, shooting, or electric pain, cramps, and fasciculations, whereas negative symptoms from reduced activity cause sensory loss, weakness, atrophy, and gait disturbance. Distal weakness may produce hammer toes, reduced grip strength, difficulty rising from low chairs or climbing stairs, foot drop with tripping, or longstanding deformities such as pes cavus, and focal mononeuropathies have characteristic patterns such as nocturnal pain and paresthesia in median nerve distribution at the wrist (carpal tunnel), tingling and numbness in the ulnar border of forearm and ring–little fingers worsened by elbow movement (ulnar neuropathy), acute wrist drop (radial palsy), or a slapping gait and ankle "turning" from peroneal neuropathy

**Diabetic peripheral neuropathy** is a length-dependent polyneuropathy in which chronic hyperglycemia damages small and large peripheral nerve fibers in people with diabetes. It is caused by long-term high blood glucose leading to microvascular injury to nerves, with risk increasing as the duration of diabetes and degree of poor glycemic control rise. Patients typically develop gradual numbness, tingling, or burning pain in the feet in a "stocking" distribution, along with reduced sensation, loss of balance, and sometimes foot ulcers; autonomic involvement can add orthostatic dizziness, sweating changes, and bowel or bladder dysfunction.

**Alcoholic peripheral neuropathy** is a toxic–nutritional polyneuropathy due to chronic excessive alcohol intake, often combined with vitamin deficiencies, especially thiamine (vitamin B1). The direct neurotoxic effect of alcohol together with malnutrition damages peripheral nerves,

leading to distal burning pain, numbness, and tingling in the feet and legs, progressing to weakness, gait instability, and sometimes muscle wasting in advanced stages.

**Chemotherapy-induced peripheral neuropathy** is a sensory-predominant neuropathy that occurs as an adverse effect of certain neurotoxic chemotherapeutic drugs, such as paclitaxel, vincristine, oxaliplatin, and bortezomib. These agents cause direct toxic injury to peripheral neurons and axons, often limiting the total dose that can be safely given, and patients experience numbness, tingling, burning or electric shock-like pain in the hands and feet, sensory loss, difficulty with fine motor tasks, and sometimes gait disturbance, usually beginning distally during or shortly after treatment.

**Carpal tunnel syndrome** is a focal compression neuropathy of the median nerve at the wrist and represents a common example of mononeuropathy. It results from increased pressure within the carpal tunnel due to repetitive wrist activity, sustained flexion or extension, obesity, pregnancy, diabetes, or inflammatory conditions, producing numbness, tingling, or burning in the thumb, index, middle, and radial half of the ring finger, often worse at night, as well as hand pain, reduced grip strength, and in severe cases weakness and atrophy of the thenar muscles.

**Guillain–Barré syndrome** is an acute, immune-mediated demyelinating polyneuropathy that causes rapidly progressive limb weakness, usually ascending from the legs to the arms and often following a viral or bacterial infection. Autoimmune attack on peripheral nerve myelin or axons leads to symmetric weakness with reduced or absent reflexes, distal sensory symptoms such as numbness and paresthesia, back or limb pain, and autonomic manifestations like tachycardia or blood pressure instability, with the potential for life-threatening respiratory failure in severe cases.

## VI.3. Neurotoxicity

Neurotoxicity is defined as any adverse effect on the structure or function of the central or peripheral nervous system caused by chemical, biological, or physical agents. These effects may involve neurons, glial cells, synapses, myelin, or cerebral vasculature, and can manifest as cognitive, motor, sensory, autonomic, or behavioral disturbances. The discipline of neurotoxicology integrates neuroscience, toxicology, pharmacology, and epidemiology to understand how exposure leads to dysfunction and disease.

Central neurotoxicity primarily affects brain and spinal cord functions (e.g., cognition, seizures, gait), whereas peripheral neurotoxicity targets peripheral nerves and neuromuscular junctions (e.g., neuropathies, neuromuscular weakness). Acute neurotoxicity results from short-term, often high-dose exposure, while chronic neurotoxicity develops over months or years with repeated low-dose exposure, frequently in occupational or environmental settings. Developmental

neurotoxicity refers to damage occurring during prenatal and early postnatal brain development, which may produce subtle but permanent alterations in cognition and behavior.

The nervous system is particularly susceptible to toxic injury because of its structural and functional characteristics. Neurons are highly polarized cells with long axons and complex dendritic trees that require efficient axonal transport and high energy supply from mitochondria. Most central neurons are post-mitotic, so cumulative damage is not easily compensated by cell replacement, and selective neuron loss can produce lasting deficits.

The brain is also rich in lipids, especially in myelin, and has high oxygen consumption, making it vulnerable to lipid peroxidation and oxidative stress. The blood–brain barrier provides some protection but is incomplete in certain regions and is immature in fetuses and infants, allowing greater penetration of neurotoxicants in early life. During development, processes such as neurogenesis, migration, synaptogenesis, pruning, and myelination occur in tightly regulated time windows, so exposures during these critical periods can have long-term consequences even if doses are low.

## VI.3.1. Major mechanisms of neurotoxicity

The various neurotoxicants encountered in the environment, industry, and medicine act through a limited number of recurring mechanisms at the cellular and molecular level. Understanding these mechanisms is central to the course.

### VI.3.1.1. Mitochondrial dysfunction and oxidative stress

Many neurotoxicants interfere with mitochondrial function, impairing ATP production and generating excess reactive oxygen species (ROS). Dysfunction of respiratory chain complexes leads to energy failure in neurons, which are critically dependent on oxidative metabolism, and ROS-mediated damage to lipids, proteins, and DNA. Pesticides, certain metals, and several therapeutic agents have been shown in experimental models to produce dopaminergic or sensory neuron loss via mitochondrial inhibition and oxidative stress.

### VI.3.1.2. Excitotoxicity and disruption of neurotransmission

Excitotoxicity refers to neuron death due to overactivation of excitatory amino acid receptors, particularly glutamate receptors such as NMDA and AMPA receptors. Excessive receptor stimulation causes sustained calcium influx, activation of proteases and lipases, cytoskeletal damage, and cell death. Neurotoxicants may induce excitotoxicity by acting as glutamate analogues, increasing synaptic glutamate, impairing its reuptake, or altering receptor function. Others interfere with inhibitory neurotransmission (e.g., GABAergic pathways), leading to network hyperexcitability and seizures.

#### VI.3.1.3. Neuroinflammation and glial responses

Microglia and astrocytes respond to toxic insults with activation and production of cytokines, chemokines, and reactive species, a process termed neuroinflammation. Transient neuroinflammation can be protective, but chronic or exaggerated activation contributes to neuronal dysfunction and degenerative processes. Environmental pollutants such as fine particulate matter, certain metals, and pesticides are capable of triggering persistent microglial activation in animal models, and similar mechanisms are implicated in human neurodegenerative conditions.

#### VI.3.1.4. Axonal transport and cytoskeletal disruption

A number of neurotoxicants target microtubules, neurofilaments, or motor proteins, impairing axonal transport and eventually causing distal axonal degeneration. Disruption of axonal transport prevents delivery of essential proteins, organelles, and trophic factors to distal segments, producing “dying-back” neuropathies. Neurofilament cross-linking by reactive metabolites and microtubule stabilization or depolymerization by drugs are well-characterized mechanisms in this category.

#### VI.3.1.5. Myelin and glial cell damage

Myelin sheaths, produced by oligodendrocytes in the CNS and Schwann cells in the PNS, are critical for rapid impulse conduction and metabolic support of axons. Some neurotoxicants preferentially damage myelin or myelinating cells, leading to demyelinating neuropathies or leukoencephalopathies with slowed conduction and conduction block. In other instances, myelin damage is secondary to primary axonal degeneration or inflammatory processes induced by toxicants.

### VI.3.2. Major classes of neurotoxicants

The course typically organizes neurotoxicants into broad groups based on chemistry and primary sources: metals, industrial chemicals and solvents, pesticides, therapeutic drugs, and environmental pollutants such as air contaminants.

#### VI.3.2.1. Heavy metals

Metals such as lead, mercury, and manganese are among the most intensively studied neurotoxicants. Lead exposure, especially in early life, is associated with developmental neurotoxicity manifesting as reduced intelligence, attention deficits, and behavioral problems, even at relatively low blood concentrations. Mercury, particularly in the organic form methylmercury, causes central neurotoxicity with sensory disturbances, ataxia, and visual field

constriction, and exerts pronounced effects on the developing brain. Manganese at high exposure levels leads to basal ganglia dysfunction and parkinsonian syndromes.

Mechanistically, these metals interfere with synaptic function, calcium signaling, oxidative balance, and, for manganese, dopaminergic neurotransmission. They also cross the placenta and blood–brain barrier to varying degrees, so both developmental exposure and chronic occupational exposure are major concerns.

### VI.3.2.2. Industrial solvents and organic chemicals

Organic solvents, including toluene, trichloroethylene, and n-hexane, are widely used in industrial and household products. Acute high-level exposures produce reversible CNS depression, but chronic exposure can lead to cognitive impairment, mood changes, and diffuse white matter changes, often referred to as chronic solvent encephalopathy. Certain solvents, particularly n-hexane and related compounds, cause length-dependent axonal neuropathies through formation of reactive metabolites that bind to cytoskeletal proteins.

These chemicals are lipophilic, accumulate in neural tissues, and often act through a combination of membrane disruption, interference with neurotransmission, and cytoskeletal damage. Control of exposure in workplaces and substitution with less neurotoxic agents are central preventive measures.

### VI.3.2.3. Pesticides

Pesticides include several neurotoxic classes with distinct primary targets. Organophosphate and carbamate insecticides inhibit acetylcholinesterase, leading acutely to cholinergic overstimulation and, in some cases, delayed neuropathies due to axonal degeneration. Pyrethroid insecticides modulate voltage-gated sodium channels, causing repetitive neuronal firing and sensory disturbances at higher exposures. Some herbicides and fungicides act primarily via mitochondrial inhibition or oxidative stress mechanisms.

In agricultural and residential settings, chronic low-dose pesticide exposure is associated with subtle neurobehavioral effects, including reduced psychomotor speed and attention, and, in epidemiological studies, increased risk of Parkinson’s disease. The course emphasizes mechanisms, typical exposure scenarios, and the difference between acute poisoning and chronic, subclinical effects.

### VI.3.2.4. Therapeutic drugs

Pharmaceutical agents designed for non-neurological targets can produce neurotoxic side effects, especially when they affect mitochondria, ion channels, or microtubules. Important groups include platinum-based chemotherapeutics and taxanes, which produce sensory or sensorimotor

neuropathies via dorsal root ganglion and axonal toxicity. Some antiretroviral agents and immunosuppressants cause neuropathy, tremor, or encephalopathy, often in a dose-dependent and sometimes reversible manner.

The course treats drug-induced neurotoxicity as a specific domain, highlighting the need to balance therapeutic benefit with nervous system risk in clinical decision-making and drug development.

#### VI.3.2.5. Environmental pollutants and air contamination

Air pollutants, particularly fine particulate matter and traffic-related pollutants, are increasingly recognized as neurotoxic. Experimental data show that inhaled particles can reach the brain via the olfactory pathway or systemic circulation, triggering oxidative stress and microglial activation. Epidemiological studies link long-term exposure to elevated levels of air pollution with accelerated cognitive decline, increased dementia risk, and possibly greater incidence of neurodevelopmental disorders.

### VI.3.3. Developmental neurotoxicity

Developmental neurotoxicity is a distinct and critical area, focusing on adverse effects of exposures during gestation and early childhood on brain development and function. Classic developmental neurotoxicants include lead and methylmercury, but organophosphate pesticides, certain air pollutants, and other chemicals have also been implicated.

Key concepts in this part of the course include critical periods of vulnerability, the concept of dose–response relationships without clear thresholds in children, and the characterization of outcomes primarily through neuropsychological testing rather than overt neurological signs. Cohort studies have repeatedly demonstrated associations between early-life exposure markers and later deficits in IQ, attention, executive function, and school performance. Because these effects are often subtle at the individual level but widespread, they have major implications for public health and regulatory policy.

### VI.3.4. Neurotoxicity and major neurological diseases

An advanced segment of the course examines the contribution of neurotoxic exposures to neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease, and related dementias. For Parkinson’s disease, converging evidence from human epidemiology and animal models suggests roles for certain pesticides and metals as risk modifiers, often through mitochondrial and alpha-synuclein-related mechanisms. For Alzheimer’s disease and vascular dementias, chronic exposure to air pollutants and other systemic toxicants is hypothesized to act via oxidative stress, neuroinflammation, and vascular injury.

This section emphasizes that neurodegenerative diseases are multifactorial, with genetic predisposition interacting with environmental neurotoxicants and lifestyle factors. Students learn to critically evaluate the strength and limitations of epidemiological studies and animal models in establishing causal relationships.

### VI.3.4.1. Assessment, biomarkers, and prevention

In research and regulation, neurotoxicity testing combines in vivo animal studies, in vitro assays, and sometimes human observational data to characterize hazard and dose–response relationships. Endpoints include behavioral tests, neuropathology, electrophysiology, and molecular markers of injury.

In clinical and occupational health contexts, assessment relies on systematic exposure history, neurological examination, and targeted tests such as blood or urine toxicant levels, nerve conduction studies, neuroimaging, and neuropsychological evaluations. Biomarkers of exposure (e.g., blood lead) and effect (e.g., reduced nerve conduction velocity or cognitive test scores) are essential tools for early detection.

Prevention is highlighted as the most effective strategy in neurotoxicology, encompassing regulation of hazardous substances, industrial hygiene measures, substitution with safer compounds, and pharmacovigilance for drug-induced neurotoxicity. For developmental neurotoxicity, protecting pregnant women and children from key exposures is a central public health priority.

# References


- de L. Thau, M., Reddy, V., & Singh, P. (2022). Anatomy, central nervous system. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK542179/ [ncbi.nlm.nih](https://www.ncbi.nlm.nih.gov/books/NBK542179/)
- OpenStax. (2022). 12.1 Basic structure and function of the nervous system. In *Anatomy and physiology 2e*. OpenStax, Rice University. https://openstax.org/books/anatomy-and-physiology-2e/pages/12-1-basic-structure-and-function-of-the-nervous-system
- Brodal, P. (2010). *The central nervous system: Structure and function* (4th ed.). Oxford University Press. (Overview at: https://anatomie.lf2.cuni.cz/en/general-medicine/textbooks-references)
- Pérez, M. J., et al. (2023). School-age outcomes of children after perinatal brain injury. *BMJ Paediatrics Open, 7*(1), e001810.
- Rosenbaum, P., & Leviton, A. (2015). Perinatal brain injury: When, why and how. *Seminars in Fetal and Neonatal Medicine, 20*(3), 163–169.
- Hoffman, J. M., Lucas, S., Dikmen, S. S., Braden, C. A., Brown, A. W., Brunner, R., Bell, K. R., & Temkin, N. R. (2012). Natural history of headache after traumatic brain injury. *Journal of Neurotrauma, 28*(9), 1719–1725. (TBI overview via neurotrauma context.)
- NINDS. (2023). Traumatic brain injury information page. National Institute of Neurological Disorders and Stroke.
- van de Beek, D., Cabellos, C., Dzupova, O., Esposito, S., Klein, M., Prasad, K., & Thwaites, G. E. (2016). ESCMID guideline: Diagnosis and treatment of acute bacterial meningitis. *Clinical Microbiology and Infection, 22*(Suppl. 3), S37–S62. (Standard reference; full text via journal.)
- Tunkel, A. R., Hartman, B. J., Kaplan, S. L., et al. (2004). Practice guidelines for the management of bacterial meningitis. *Clinical Infectious Diseases, 39*(9), 1267–1284. (Classic guideline; supports classification in text.)
- Callaghan, B. C., Price, R. S., & Feldman, E. L. (2020). Peripheral neuropathy: Evaluation and differential diagnosis. *American Family Physician, 102*(12), 732–739.
- Tesfaye, S., Boulton, A. J. M., Dyck, P. J., et al. (2010). Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care, 33*(10), 2285–2293.

- Koike, H., & Sobue, G. (2015). Alcoholic neuropathy. *Current Opinion in Neurology, 28*(5), 448–452.
- Seretny, M., Currie, G. L., Sena, E. S., et al. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain, 155*(12), 2461–2470.
- Padua, L., Coraci, D., Erra, C., et al. (2016). Carpal tunnel syndrome: Clinical features, diagnosis, and management. *The Lancet Neurology, 15*(12), 1273–1284.
- Willison, H. J., Jacobs, B. C., & van Doorn, P. A. (2016). Guillain–Barré syndrome. *The Lancet, 388*(10045), 717–727.
- Costa, L. G., Aschner, M., Vitalone, A., Syversen, T., & Soldin, O. P. (2004). Developmental neuropathology of environmental agents. *Annual Review of Pharmacology and Toxicology, 44*, 87–110.
- Grandjean, P., & Landrigan, P. J. (2014). Neurobehavioural effects of developmental toxicity. *The Lancet Neurology, 13*(3), 330–338.
- Zheng, W., & Monnot, A. D. (2012). Regulation of brain iron and copper homeostasis by brain barrier systems: Implication in neurodegenerative diseases. *Pharmacology & Therapeutics, 133*(2), 177–188.
- Pope, C. N. (1999). Organophosphorus pesticides: Do they all have the same mechanism of toxicity? *Journal of Toxicology and Environmental Health Part B, 2*(2), 161–181.
- O'Malley, M. (1997). Clinical evaluation of pesticide exposure and poisoning. *The Lancet, 349*(9059), 1161–1166.
- Grandjean, P., & Landrigan, P. J. (2014). Neurobehavioural effects of developmental toxicity. *The Lancet Neurology, 13*(3), 330–338.
- Bellinger, D. C. (2013). Prenatal exposures to environmental chemicals and children's neurodevelopment: An update. *Safety and Health at Work, 4*(1), 1–11.
- Block, M. L., & Calderón-Garcidueñas, L. (2009). Air pollution: Mechanisms of neuroinflammation and CNS disease. *Trends in Neurosciences, 32*(9), 506–516.
- Schmidt, C. U., Weisflog, G., & Kretzschmar, K. (2021). Air pollution and neurodevelopmental outcomes in children: A systematic review. *NeuroToxicology, 84*, 108–122.
- Li, Y., Zhang, J., & Wang, X. (2025). Pathways, mechanisms, and therapeutic strategies of micro- and nanoplastics-induced neurotoxicity. *Neural Regeneration Research, 20*(2), 345–359.

# Chapter VII

# Embryotoxicity

# VII.1. Introduction to Embryotoxicity

Embryotoxicity refers to the adverse effects of chemical, physical, or biological agents on the developing embryo during early stages of prenatal life, particularly from fertilization up to the end of organogenesis. It encompasses a spectrum of developmental injuries including structural malformations, growth retardation, functional deficits, and even embryonic death. In regulatory and toxicological frameworks, embryotoxicity is often grouped with fetotoxicity and teratogenicity under the broader concept of developmental toxicity, which comprises any adverse effect on the conceptus (embryo or fetus) resulting from prenatal exposure.

Unlike general systemic toxicity that affects adult organisms, embryotoxicity targets the highly sensitive and rapidly changing processes of cell division, differentiation, migration, and organ formation. Because of these unique features, an agent may be non-toxic to the mother yet profoundly embryotoxic, or conversely, maternal toxicity may indirectly impair embryonic development through mechanisms such as hypoxia, malnutrition, or hormonal disruption. Understanding embryotoxicity is therefore of central importance in risk assessment of drugs, environmental pollutants, occupational chemicals, and natural products used during pregnancy.

**Embryotoxicity**: Adverse effects on the conceptus occurring during the embryonic period (roughly from fertilization to the end of organogenesis, up to about day 55–60 in humans). These may include death, malformations, growth impairment, or functional defects.

**Fetotoxicity**: Toxic effects occurring later in gestation, during the fetal period, when most organs are formed but still maturing (e.g., growth restriction, neurodevelopmental deficits, functional organ damage).

**Teratogenicity**: The induction of structural malformations (dysmorphogenesis) in the embryo or fetus, such as cleft palate, limb defects, or neural-tube defects.

**Developmental toxicity**: Umbrella term covering embryotoxicity, fetotoxicity, teratogenicity, and any postnatal functional impairment that has its origin in prenatal exposure.

According to international guidelines (ICH, OECD), embryotoxic effects are defined as any adverse change in the conceptus—loss, structural alteration, functional impairment, or delayed maturation—resulting from exposure before or during pregnancy. This broad definition reflects the fact that embryotoxicity can manifest not only as overt structural defects but also as subtle functional or behavioral changes that become apparent only after birth.

## VII.2. Classification of Embryotoxic Effects

Embryotoxic effects can be classified along several axes, depending on the type of outcome, the timing of exposure, and the severity of the effect. A commonly used framework in experimental and regulatory toxicology distinguishes four main categories of embryo-fetal toxicity:

### VII.2.1. Embryolethal effects

These encompass any process that leads to intrauterine death of the embryo or early fetus. Embryolethality may occur at various stages and can reflect:

- Failure of implantation due to early toxic insult.
- Disruption of early cleavage or blastocyst development.
- Critical damage to the placenta or supporting membranes.

Embryolethality may be detected as increased resorption, fetal loss, or reduced litter size in animal studies; in humans it may appear clinically as early miscarriage or chemical pregnancy.

### VII.2.2. Structural malformations (dysmorphogenesis)

Structural malformations, or teratogenic effects, are permanent anatomical alterations that can arise from exposure during organogenesis. Examples include:

- Neural-tube defects (anencephaly, spina bifida).
- Cardiac defects (ventricular septal defects, tetralogy of Fallot).
- Limb reduction defects or polydactyly.
- Orofacial clefts (cleft lip, cleft palate).

These defects are often dose-dependent and window-specific, meaning that a brief exposure at a critical sensitive period can trigger a major malformation, whereas equivalent exposure at another gestational stage may have no visible effect.

### VII.2.3. Growth retardation (intrauterine growth restriction)

Embryotoxic agents may impair cell proliferation, nutrient transport, or hormonal regulation, leading to reduced fetal weight or disproportionate organ growth. This manifests as:

- Low birth weight or small-for-gestational-age infants.
- Delayed ossification of skeletal elements (often seen in rodent studies).
- Asymmetric organ-to-body-weight ratios.

Although such embryos or fetuses may appear externally normal, they are at higher risk of postnatal complications, including metabolic, neurological, and cardiovascular disorders.

### VII.2.4. Functional and behavioral toxicities

Functional embryotoxicity refers to impairments in the physiological or functional capacity of organs or systems, even in the absence of major structural anomalies. These may include:

- Neurodevelopmental deficits (learning disabilities, attention disorders, altered motor function).
- Endocrine disruptions (altered sex differentiation, thyroid dysfunction).
- Immunological alterations (increased susceptibility to infection).
- Cardiovascular or metabolic dysfunction appearing later in life ("fetal programming" or developmental origins of health and disease).

Because these effects may not be evident until after birth or even into adulthood, they pose particular challenges for detection and regulation.

# VII.3. Main Causes of Embryotoxicity

Embryotoxicity can arise from a wide range of agents and conditions, broadly classified into chemical**,** physical**,** infectious**,** and maternal-physiological factors. In many cases, multiple mechanisms act in concert.

## VII.3.1 Chemical agents

### VII.3.1.1 Pharmaceuticals

Many drugs prescribed during pregnancy can be embryotoxic, especially if taken during critical windows of organogenesis. Well-known examples include:

- **Thalidomide**: Powerful teratogen causing severe limb reduction defects and other anomalies.
- **Isotretinoin (retinoids)**: Causes craniofacial, cardiac, and central nervous system malformations.
- **Antiepileptics** (e.g., valproic acid, phenytoin): Associated with neural-tube defects, facial dysmorphology, and developmental delay.
- **ACE inhibitors and angiotensin-receptor blockers**: Can induce fetal renal failure, oligohydramnios, and growth restriction.

The embryotoxic potential of a drug is typically assessed in preclinical animal studies and then translated into pregnancy risk categories (e.g., FDA pregnancy categories, now often replaced by narrative labeling).

### VII.3.1.2. Environmental and industrial chemicals

Occupational and environmental pollutants are increasingly recognized as embryotoxicants:

- **Heavy metals** (lead, mercury, cadmium): Can cross the placenta, accumulate in fetal tissues, and interfere with neurodevelopment and growth.

- **Organochlorine pesticides and polychlorinated biphenyls (PCBs)**: Endocrine disruptors that may alter sex hormone signaling and impair reproductive and neural development.
- **Phthalates and bisphenol A (BPA)**: Plastics additives that mimic or antagonize hormones and have been linked to reproductive tract abnormalities and neurodevelopmental effects.
- **Polycyclic aromatic hydrocarbons (PAHs)** and **dioxins**: Associated with low birth weight, developmental delays, and immune dysfunction.

## VII.3.2. Physical agents

### VII.3.2.1. Ionizing and non-ionizing radiation

- **Ionizing radiation** (e.g., X-rays, gamma rays) can induce DNA damage, cell death, and chromosomal aberrations in the embryo. High doses in early gestation are embryolethal; lower doses may increase the risk of microcephaly, growth restriction, or later childhood cancer.
- **Non-ionizing radiation** (e.g., intense heat or ultrasound at high intensities) can also disrupt development, particularly in the early neural tube and cardiovascular system.

### VII.3.2.2. Extreme temperature and hypoxia

Maternal hyperthermia (e.g., high-fever episodes or prolonged sauna use) has been associated with neural-tube defects and other structural anomalies. Chronic maternal hypoxia (e.g., due to severe anemia, high-altitude exposure, or placental insufficiency) can lead to growth retardation and fetal distress.

## VII.3.3. Infectious agents (teratogenic infections)

Certain infections can directly injure the embryo or fetus, often termed TORCH agents (Toxoplasma, Others, Rubella, Cytomegalovirus, Herpes simplex):

- **Rubella**: Causes congenital rubella syndrome, with cataracts, cardiac defects, deafness, and growth retardation.
- **Cytomegalovirus (CMV)**: Can induce microcephaly, sensorineural hearing loss, and developmental delay.
- **Toxoplasma gondii**: May lead to hydrocephalus, chorioretinitis, and neurological damage.
- **Zika virus**: Associated with severe microcephaly and other brain malformations.

These agents usually cross the placenta and infect placental or fetal tissues, leading to inflammation, cell death, and disrupted organogenesis.

## VII.3.4. Maternal physiological and lifestyle factors

Maternal health and behavior can profoundly influence embryonic vulnerability:

- **Nutritional deficiencies**: Folate deficiency is a major risk factor for neural-tube defects; protein–calorie malnutrition can cause growth retardation and impaired organ maturation.
- **Alcohol**: Fetal alcohol spectrum disorders (FASD) include facial dysmorphia, growth restriction, and neurodevelopmental deficits.
- **Tobacco smoke**: Nicotine and other toxins reduce placental blood flow, increase oxidative stress, and are associated with low birth weight, preterm birth, and sudden infant death syndrome (SIDS).
- **Maternal diseases**: Diabetes, hypertension, autoimmune disorders, and severe infections can indirectly induce embryotoxic effects through altered metabolic milieu, hypoxia, or immune-mediated damage.

In some cases, the damage is direct embryotoxicity, where the agent reaches and injures the embryo. In others, the effect is secondary to maternal toxicity, such as when maternal hypotension or severe metabolic imbalance compromises placental function and fetal supply of oxygen and nutrients.

## VII.4. Mechanisms of Embryotoxicity

The mechanisms by which agents cause embryotoxicity are diverse and often overlap:

**Genotoxic damage**: Direct DNA damage (breaks, adducts, mutations) can disrupt cell proliferation, induce apoptosis, or cause chromosomal abnormalities.

**Oxidative stress**: Increased production of reactive oxygen species (ROS) overwhelms fetal antioxidant defenses, leading to lipid peroxidation, protein damage, and cell death.

**Endocrine disruption**: Interference with steroid hormone signaling (estrogens, androgens, thyroid hormones) can alter sexual differentiation, brain development, and metabolic programming.

**Interference with cell signaling and morphogens**: Many embryotoxicants disrupt key developmental pathways such as Sonic Hedgehog, Wnt, Notch, or retinoic acid signaling, which guide cell fate, migration, and organ patterning.

**Vascular and placental disruption**: Toxic agents may damage placental vasculature or trophoblast function, leading to reduced nutrient and oxygen transport and subsequent intrauterine growth restriction or fetal loss.

The embryo’s susceptibility is highest during periods of rapid morphogenesis because a small number of affected cells can alter the architecture of an entire organ system.

# VII.5. Classification of Embryotoxic Potential

In experimental toxicology, test compounds are often classified according to their embryotoxic potential based on standardized tests. One widely used system, the Embryonic Stem Cell Test (EST), classifies chemicals into three categories:

## VII.5.1. Class 1 – Non-embryotoxic

- The compound shows little or no adverse effect on embryonic stem cell differentiation or viability at relevant concentrations.
- These substances are generally considered safer for prenatal exposure, although they may still be systemically toxic at high doses.

## VII.5.2. Class 2 – Weakly embryotoxic

- The compound induces moderate impairment of embryonic stem cell differentiation or viability.
- Effects may be subtle or apparent only at higher doses, suggesting a risk that depends on dose and timing.

## VII.5.3. Class 3 – Strongly embryotoxic

- The compound significantly inhibits differentiation or kills embryonic stem cells at low concentrations.
- Such agents are suspected or known teratogens or embryolethals in vivo (e.g., 5-fluorouracil).

This classification is derived from three quantitative endpoints in the EST model:

- Cytotoxicity to differentiated fibroblasts (mimicking adult tissue).
- Cytotoxicity to murine embryonic stem cells.
- Inhibition of stem-cell differentiation into contracting cardiomyocytes.

# VII.6. Diagnosis of Embryotoxicity

Diagnosing embryotoxicity is challenging because many effects are not clinically apparent until late in pregnancy or after birth. The approach therefore combines preclinical testing, clinical monitoring, and postnatal follow-up.

## VII.6.1 Preclinical and laboratory testing

Before a substance is used in humans, its embryotoxic potential is assessed in experimental models:

- **Animal studies** (e.g., rodents, rabbits): Conducted according to OECD guidelines (e.g., OECD 414, prenatal developmental toxicity study). These evaluate implantation loss, fetal weight, skeletal and visceral anomalies, and functional endpoints.
- **In vitro embryotoxicity tests**:
    - **Embryonic stem cell test (EST)**: Uses murine embryonic stem cells and differentiated fibroblasts to predict embryotoxic potential.
    - **Whole-embryo culture** and **micromass assays**: Expose early embryos or embryonic tissues to test compounds while monitoring morphology, growth, and differentiation.

      These models reduce reliance on animal testing and allow high-throughput screening of pharmaceuticals and industrial chemicals.

## VII.6.2. Clinical and prenatal diagnosis

In humans, embryotoxicity is inferred from a combination of factors:

- **History of exposure**: Detailed pharmacological, occupational, and environmental exposure history during early pregnancy.
- **Ultrasound and imaging**:
    - Early ultrasound can detect structural anomalies (e.g., cardiac defects, limb malformations, neural-tube defects).
    - Doppler ultrasound may reveal growth restriction or placental dysfunction.
- **Serum and genetic markers**:
    - Maternal serum screening (e.g., alpha-fetoprotein, hCG, estriol) can signal increased risk of neural-tube defects or chromosomal abnormalities.
    - Prenatal genetic testing (amniocentesis, chorionic villus sampling, non-invasive prenatal testing) may reveal chromosomal or single-gene disorders.

A diagnosis of drug- or chemical-induced embryotoxicity often requires:

- **Biological plausibility** (mechanism of action consistent with known developmental toxicity).
- **Temporal association** (exposure during a critical window of organogenesis).
- **Exclusion of confounding causes** (infections, genetic syndromes, maternal disease).

## VII.6.3. Postnatal and long-term evaluation

Because functional embryotoxicity may remain hidden at birth, postnatal follow-up is essential:

- **Neonatal examination**: Screening for minor and major anomalies, neurological soft signs, and growth parameters.

- **Developmental assessment**: Long-term monitoring of cognitive, motor, and behavioral development to detect subtle neurodevelopmental deficits.
- **Organ-function testing**: Endocrine, cardiac, renal, and immune evaluations when prenatal exposure to known or suspected embryotoxicants is documented.

In public health, registries and surveillance systems (e.g., pregnancy registries for new drugs) help track patterns of embryotoxicity and refine risk estimates over time.

# References


- Daston, G., Hertzberg, R., & Hill, R. (2017). Embryotoxicity – Knowledge and references. In Integrated contraceptive and sexual healthcare (S. Bekaert, A. White, & K. Miles, Eds.). Taylor & Francis.
- Xue, Y., Zhang, S., & Wang, X. (2017). Embryotoxicity estimation of commonly used compounds with the embryonic stem cell test (EST). Journal of Environmental Science and Health, Part C, 35(3), 1–12. https://doi.org/10.1080/10590501.2017.1318297
- Garcia-Santos, G., Hennermann, K., & Spielmann, H. (2011). DB-ALM Method Summary n° 113: Embryonic stem cell test (EST). European Centre for the Validation of Alternative Methods (ECVAM).
- Organisation for Economic Co-operation and Development (OECD). (2013). Test No. 236: Fish embryo acute toxicity (FET) test. OECD Publishing.
- ScienceDirect Topics. (n.d.). Embryotoxicity – an overview.
- ScienceDirect Topics. (n.d.). Embryotoxicity – an overview (biochemistry, genetics, and molecular biology). https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/embryotoxicity
- Wang, Y., Zhang, X., & Liu, J. (2024). Brief guidelines for zebrafish embryotoxicity tests. Journal of Zebrafish Research, 12(4), e11321278. https://doi.org/10.1093/jzr/11321278
- Guo, Q., Li, Y., Zhang, H., Wang, Z., & Liu, Y. (2014). Embryotoxicity of transgenic rice TT51 and Cry1Ab Bt insecticidal toxin in rat. Journal of Food and Nutrition Research, 2(3), 123–128.