[Date]

PHYSIOLOGY II

2nd. stage

LECT. 1

By Assistance Lecturer
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Gastrointestinal tract:

The alimentary tract provides the body with a continual supply of water, electrolytes, vitamins, and nutrients. To achieve this requires

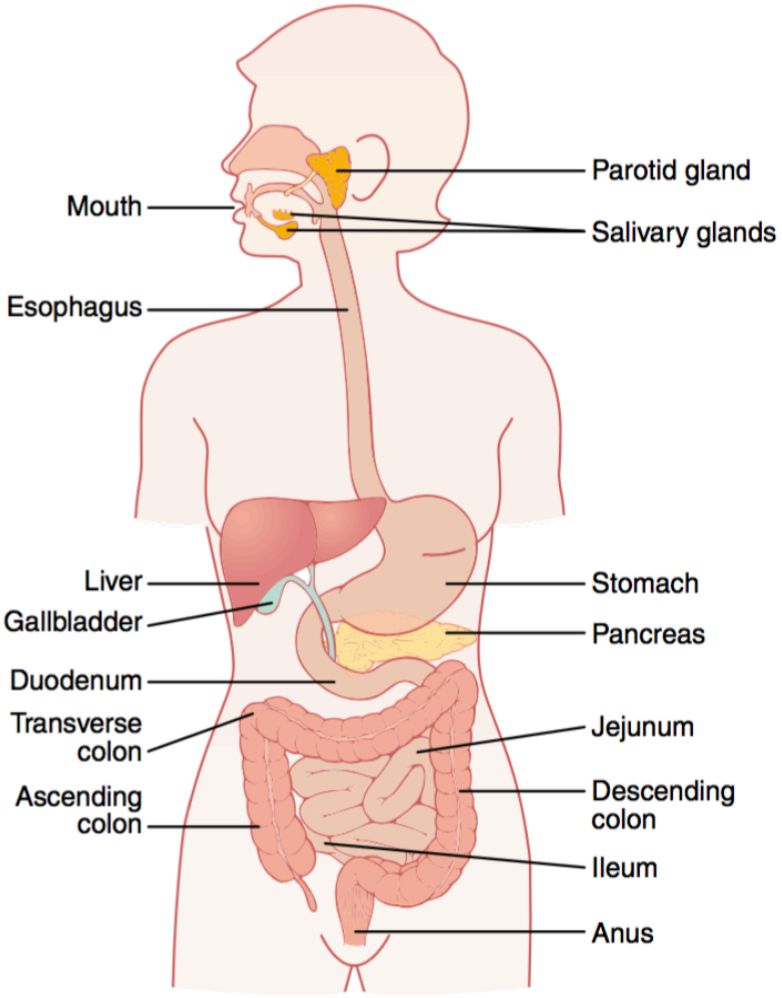
(1) movement of food through the alimentary tract;

(2) secretion of digestive juices and digestion of the food;

(3) absorption of water, various electrolytes, vitamins, and digestive products;

(4) circulation of blood through the gastrointestinal organs to carry away the absorbed substances; and

(5) control of all these functions by local, nervous, and hormonal systems



Each part is adapted to its specific functions: some to simple passage of food, such as the esophagus; others to temporary storage of food, such as the stomach; and others to digestion and absorption, such as the small intestine.

The adult gastrointestinal tract is a tube approximately 9 m (30 feet) in length, running through the body from mouth to anus. The lumen of the tract is continuous with the external environment, which means that its contents are technically outside the body. This fact is relevant to understanding some of the tract's properties. For example, the large intestine is colonized by billions of bacteria, most of which are harmless and even beneficial in this location. However, if the same bacteria enter the internal environment, as may happen, for example, if a portion of the large intestine is perforated, they may cause a severe infection.

Most food enters the gastrointestinal tract as large particles containing macromolecules, such as proteins and polysaccharides, which are unable to cross the intestinal epithelium. Before ingested food can be absorbed, therefore, it must be dissolved and broken down into small molecules. (Small nutrients such as vitamins and minerals do not need to be broken down and can cross the epithelium intact.) This dissolving and breaking-down process is called digestion and is accomplished by the action of hydrochloric acid in the stomach, bile from the liver, and a variety of digestive enzymes released by the system's exocrine glands. Each of these substances is released into the lumen of the GI tract through the process of secretion. In addition, some digestive enzymes are located on the luminal membranes of the intestinal epithelium. The molecules produced by digestion, along with water and small nutrients that do not require digestion, then move from the lumen of the GI tract across a layer of epithelial cells and enter the blood or lymph. This process is called absorption.

While digestion, secretion, and absorption are taking place, contractions of smooth muscles in the GI tract wall serve two functions:

A-They mix the luminal contents with the various secretions, and

B- they move the contents through the tract from mouth to anus.

These contractions are referred to as the motility of the GI tract. In some cases, muscular movements travel in a wave- like fashion in one direction along the length of a part of the tract, a process called peristalsis. The functions of the digestive system can be described in terms of these four major processes— (digestion, secretion, absorption, and motility) (Figure 2)—and the mechanisms controlling them.

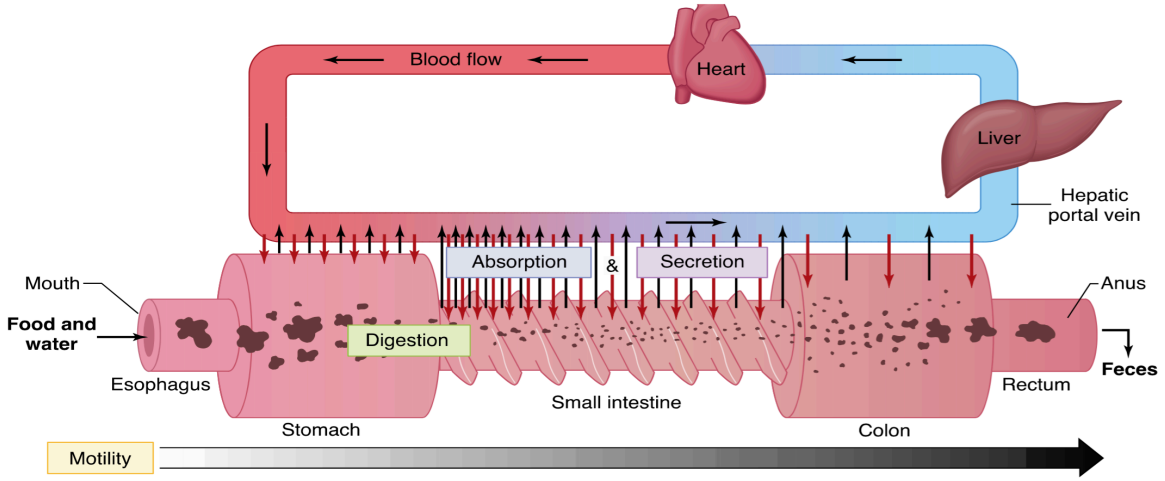


Figure 2: Four major processes the gastrointestinal tract carries out: digestion, secretion, absorption, and motility. Outward- pointing (black) arrows indicate absorption of the products of digestion, water, minerals, and vitamins into the blood. Inward-pointing (red) arrows represent the secretion of ions, enzymes, and bile salts into the GI tract. The length and density of the arrows indicate the relative importance of each segment of the tract; the small intestine is where most absorption and secretion occurs. The feces represent a fifth function of the GI tract: elimination. The wavy configuration of the small intestine represents muscular contractions (motility) throughout the tract.

Small amounts of certain metabolic end products are excreted via the GI tract, primarily by way of the bile. Elimination is representing a minor function of the GI tract in healthy individuals. In fact, the lungs and kidneys are usually responsible for the elimination of most of the body's waste products. The material known as feces leaves the system at the end of the GI tract. Feces consist almost entirely of bacteria and ingested material that was neither digested nor absorbed, that is, material that was never actually absorbed into the internal environment.

A typical cross section of the intestinal wall, including the following layers from outer surface inward:

(1) the *serosa,*

(2) A *longitudinal smooth muscle layer,*

(3) a *circular smooth muscle layer,*

(4) the *submucosa,* and

(5) the *mucosa.*

In addition, sparse bundles of smooth muscle fibers, the *mucosal muscle,* lie in the deeper layers of the mucosa. The motor functions of the gut are performed by the different layers of smooth muscle. Fig.3

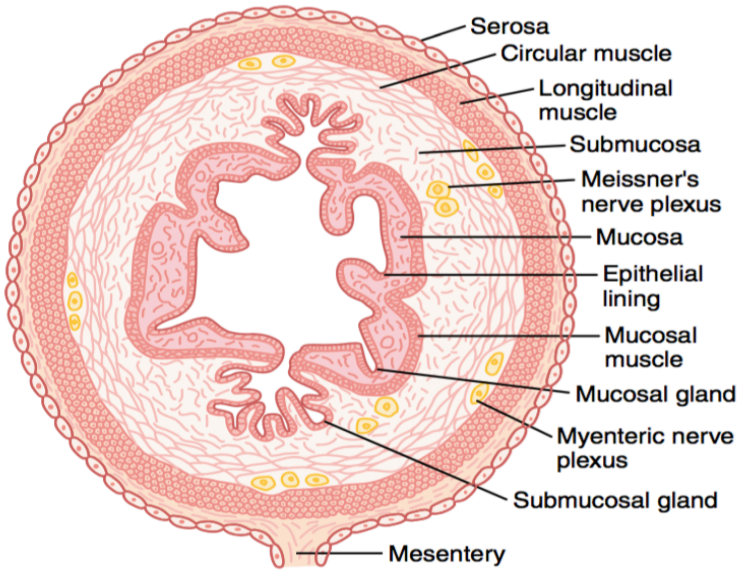


Figure 3 Typical cross section of the gut.

The individual smooth muscle fibers in the gastrointestinal tract are 200 to 500 micrometers in length and 2 to 10 micrometers in diameter, and they are arranged in bundles of as many as 1000 parallel fibers. In the longitudinal muscle layer, the bundles extend longitudinally down the intestinal tract; in the circular muscle layer, they extend around the gut. **So**, the gastrointestinal smooth muscle functions as a **Syncytium**. Within each bundle, the muscle fibers are electrically connected with one another through large numbers of *gap junctions* that allow low-resistance movement of ions from one muscle cell to the next. Therefore, electrical signals that initiate muscle contractions can travel readily from one fiber to the next within each bundle but more rapidly along the length of the bundle than sideways. Each bundle of smooth muscle fibers is partly separated from the next by loose connective tissue, but the muscle bundles fuse with one another at many points, so in reality each muscle layer represents a branching latticework of smooth muscle bundles. Therefore, each muscle layer functions as a *syncytium;* that is, when an action potential is elicited anywhere within the muscle mass, it generally travels in all directions in the muscle.

General Functions of the Gastrointestinal

Using Table 1 as a guide, this section briefly surveys the gastrointestinal functions.

Digestion begins with chewing in the mouth where large pieces of food are broken up into smaller particles that we can swallow. Saliva secreted by three pairs of exocrine salivary glands located in the head (Figure 1), drains into the mouth through a series of short ducts. Saliva, which contains mucus, moistens and lubricates the food particles before swallowing. It also contains the enzyme amylase, which partially digests polysaccharides (complex sugars) described later. A third function of saliva is to dissolve some of the food molecules. Only in

the dissolved state can these molecules react with chemoreceptors in the mouth, giving rise to the sensation of taste. Finally, saliva has antibacterial properties.

Table 1: *Functions of the Gastrointestinal Organs*

Organ	Exocrine Secretions	Functions Related to Digestion and Absorption
Mouth and pharynx		Chewing begins; initiation of swallowing reflex
Salivary glands	Salt and water	Moisten and dissolve food
	Mucus	Lubrication
	Amylase	Polysaccharide-digesting enzyme
Esophagus		Move food to stomach by peristaltic waves
	Mucus	Lubrication
Stomach		Store, mix, dissolve, and continue digestion of food; regulate emptying of dissolved food into small intestine
	HCl	Solubilization of food particles; kill microbes; activation of pepsinogen to pepsin
	Pepsin	Begin the process of protein digestion in the stomach
	Mucus	Lubricate and protect epithelial surface
Pancreas		Secretion of enzymes and bicarbonate; also has nondigestive endocrine functions
	Enzymes	Digest carbohydrates, fats, proteins, and nucleic acids
	Bicarbonate	Neutralize HCl entering small intestine from stomach
Liver		Secretion of bile
	Bile salts	Solubilize water-insoluble fats
	Bicarbonate	Neutralize HCl entering small intestine from stomach
	Organic waste products and trace metals	Elimination in feces
Gallbladder		Store and concentrate bile between meals
Small intestine		Digestion and absorption of most substances; mixing and propulsion of contents
	Enzymes	Digestion of macromolecules
	Salt and water	Maintain fluidity of luminal contents
	Mucus	Lubrication and protection
Large intestine		Storage and concentration of undigested matter; absorption of salt and water; mixing and propulsion of contents; defecation
	Mucus	Lubrication

The next segments of the tract, the pharynx and esophagus, do not contribute to digestion but provide the pathway for ingested materials to reach the stomach. The muscles in the walls of these segments control swallowing.

The stomach is a saclike organ located between the esophagus and the small intestine. Its functions are to store, dissolve, and partially digest the macromolecules in food and to regulate the rate at which the contents of the stomach empty into the small intestine. The acidic environment in the gastric (adjective for “stomach”) lumen alters the ionization of polar molecules, leading to denaturation of protein.

Polysaccharides and fat are major food components that are not dissolved to a significant extent by acid. The low pH also kills most of the bacteria that enter along with food. This process is not completely effective, and some bacteria survive to colonize and multiply in the gastrointestinal tract, particularly the large intestine.

The digestive actions of the stomach reduce food particles to a solution known as chyme, which contains molecular fragments of proteins and polysaccharides; droplets of fat; and salt, water, and various other small molecules ingested in the food. Virtually none of these molecules, except water, can cross the epithelium of the gastric wall, and thus little absorption of organic nutrients occurs in the stomach.

Most absorption and digestion occur in the next section of the tract, the small intestine, a tube about 2.4 cm in diameter and 3 m in length, which leads from the stomach to the large intestine. Hydrolytic enzymes in the small intestine break down molecules of intact or partially digested carbohydrates, fats, proteins, and nucleic acids into monosaccharides, fatty acids, amino acids, and nucleotides. Some of these enzymes are on the luminal surface of the intestinal lining cells, whereas others are secreted by the pancreas and enter the intestinal lumen. The products of digestion are absorbed across the epithelial cells and enter the blood and/or lymph. Vitamins, minerals, and water, which do not require enzymatic digestion, are also absorbed in the small intestine.

The small intestine is divided into three segments: An initial short segment, the duodenum, is followed by the jejunum and then by the longest segment, the ileum. Normally, most of the chyme entering from the stomach is digested and absorbed in the first quarter of the small intestine in the duodenum and jejunum. Therefore, the small intestine has a very large reserve for the absorption of most nutrients; removal of portions of the small intestine as a treatment for disease does not necessarily result in nutritional deficiencies, depending on which part of the intestine is removed.

In the small intestine, monosaccharides and amino acids are absorbed by specific transporter-mediated processes in the plasma membranes of the intestinal epithelial cells, whereas fatty acids enter these cells primarily by diffusion. Most mineral ions are actively absorbed by transporters, and water diffuses passively down osmotic gradients.

The motility of the small intestine: (1) mixes the luminal contents with the various secretions, (2) brings the contents into contact with the epithelial surface where absorption takes place, and (3) slowly advances the luminal material toward the large intestine, the next segment of the alimentary canal.

Because most substances are absorbed in the small intestine, only a small amount of water, salts, and undigested material passes on to the large intestine. The large intestine temporarily

stores the undigested material (some of which is metabolized by bacteria) and concentrates it by absorbing salts and water. Contractions of the rectum, the final segment of the large intestine, and relaxation of associated sphincter muscles expel the feces in a process called defecation.

Two major organs—the pancreas and liver—secrete substances that flow via ducts into the duodenum. The pancreas, an elongated gland located behind the stomach, has both endocrine and exocrine functions, but only the latter are directly involved in gastrointestinal function.

The exocrine portion of the pancreas secretes digestive enzymes and fluid rich in + HCO3. The high acidity of the chyme coming from the stomach would inactivate the + pancreatic enzymes in the small intestine if the acid were not neutralized by the HCO3 in the pancreatic fluid.

The liver, a large organ located in the upper-right portion of the abdomen, has a variety of functions. We will be concerned in our lectures primarily with the liver's exocrine functions that are directly related to the secretion of bile. Bile contains HCO3+, cholesterol, phospholipids, bile pigments, a number of organic wastes, and—most important—a group of substances collectively termed bile salts. The HCO3+, like that from the pancreas, helps neutralize acid from the stomach, whereas the bile salts solubilize dietary fat. These fats would otherwise be insoluble in water, and their solubilization increases the rates at which they are digested and absorbed.

Bile is secreted by the liver into small ducts that join to form the common hepatic duct. Between meals, secreted bile is stored in the gallbladder, a small sac underneath the liver that branches from the common hepatic duct. The gallbladder concentrates the organic molecules in bile by absorbing some salts and water. During a meal, the smooth muscles in the gallbladder wall contract, causing a concentrated bile solution to be injected into the duodenum via the common bile duct an extension of the common hepatic duct.

Bile is secreted in two stages by the liver:

(1) The initial portion is secreted by the principal functional cells of the liver, the hepatocytes; this initial secretion contains large amounts of bile acids, cholesterol, and other organic constituents. It is secreted into minute bile canaliculi that originate between the hepatic cells.

(2) Next, the bile flows in the canaliculi toward the interlobular septa, where, finally reaching the hepatic duct and common bile duct. From these the bile either empties directly into the duodenum or is diverted for minutes up to several hours through the cystic duct into the gallbladder, shown in Figure 3.

In its course through the bile ducts, a second portion of liver secretion is added to the initial bile. This additional secretion is a watery solution of sodium and bicarbonate ions secreted by secretory epithelial cells that line the ductules and ducts. This second secretion sometimes increases the total quantity of bile by as much as an additional 100%. The second secretion is

stimulated especially by *secretin*, which causes release of additional quantities of bicarbonate ions to supplement the bicarbonate ions in pancreatic secretion (for neutralizing acid that empties into the duodenum from the stomach)

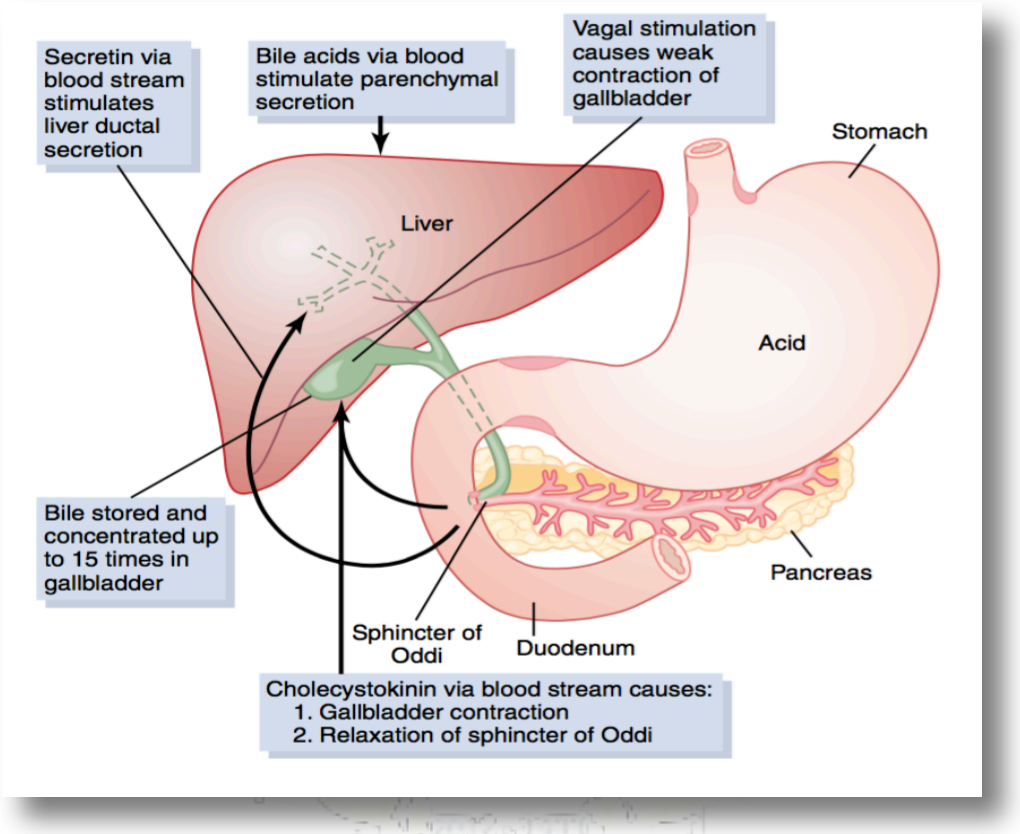


Fig.3 Liver secretion and gallbladder emptying.

Neural Control of Gastrointestinal Function—Enteric Nervous System

The gastrointestinal tract has a nervous system all its own called the *enteric nervous system*. It lies entirely in the wall of the gut, beginning in the esophagus and extending all the way to the anus.

The enteric nervous system is composed mainly of two plexuses:

(1) an outer plexus lying between the longitudinal and circular muscle layers, called the ***myenteric plexus*** or ***Auerbach's plexus***, and

(2) an inner plexus, called the ***submucosal plexus*** or ***Meissner's plexus***, that lies in the submucosa

The myenteric plexus controls mainly the gastrointestinal movements, and the submucosal plexus controls mainly gastrointestinal secretion and local blood flow.

Types of Neurotransmitters Secreted by Enteric Neurons

In an attempt to understand better the multiple functions of the gastrointestinal enteric nervous system, research workers the world over have identified a dozen or more different neurotransmitter substances that are released by the nerve endings of different types of enteric neurons. Two of them with which we are already familiar are

(1) *acetylcholine*

(2) *norepinephrine.*

(3) *adenosine triphosphate,*

(4) *serotonin,*

(5) *dopamine,*

(6) *cholecystokinin,*

(7) *substance P,*

(8) *vasoactive intestinal polypeptide,*

(9) *somatostatin,*

(10) *leuenkephalin,*

(11) *metenkephalin,* and

(12) *bombesin*.

Autonomic Control of the Gastrointestinal Tract

A- The parasympathetic supply to the gut is divided into *cranial* and *sacral divisions,* except for a few parasympathetic fibers to the mouth and pharyngeal regions of the alimentary tract, the *cranial parasympathetic* nerve fibers are almost entirely in the *vagus nerves.* These fibers provide extensive innervation to the esophagus, stomach, and pancreas and somewhat less to the intestines down through the first half of the large intestine the *sacral parasympathetic* originate in the second, third, and fourth sacral segments of the spinal cord and pass through the *pelvic nerves* to the distal half of the large intestine and all the way to the anus The sigmoidal, rectal, and anal regions are considerably better supplied with parasympathetic fibers than are the other intestinal areas. **So**, parasympathetic stimulation increases activity of the enteric nervous system**.**

B- In general, stimulation of the sympathetic nervous system *inhibits* activity of the gastrointestinal tract, causing many effects opposite to those of the parasympathetic system. It exerts its effects in two ways:

(1) to a slight extent by direct effect of secreted norepinephrine to inhibit intestinal tract smooth muscle (except the mucosal muscle, which it excites) and

(2) to a major extent by an inhibitory effect of norepinephrine on the neurons of the entire enteric nervous system. Strong stimulation of the sympathetic system can inhibit motor movements of the gut so greatly that this can literally block movement of food through the GIT. This occur due to The sympathetic nerve endings secrete mainly *norepinephrine* but also small amounts of *epinephrine.* **So**, sympathetic stimulation usually inhibits GIT activity.

Hormonal Control of Gastrointestinal Motility

The gastrointestinal hormones are released into the portal circulation and exert physiological actions on target cells with specific receptors for the hormone. The effects of the hormones persist even after all nervous connections between the site of release and the site of action have been severed.

1- *Gastrin* is secreted by the "G" cells of the *antrum of the stomach* in response to stimuli associated with ingestion of a meal, such as distention of the stomach, the products of proteins, and *gastrin releasing peptide,* which is released by the nerves of the gastric mucosa during vagal stimulation. The primary actions of gastrin are (A) *stimulation of gastric acid secretion* and (B) *stimulation of growth of the gastric mucosa.*

2- *Cholecystokinin* (CCK) is secreted by "I" cells in the *mucosa of the duodenum and jejunum* mainly in response to digestive products of fat, fatty acids, and monoglycerides in the intestinal contents. This hormone strongly contracts the gallbladder, expelling bile into the small intestine, where the bile in turn plays important roles in emulsifying fatty substances, and allowing them to be digested and absorbed. CCK also inhibits stomach contraction moderately. Therefore, at the same time that this hormone causes emptying of the gallbladder, it also slows the emptying of food from the stomach to give adequate time for digestion of the fats in the upper intestinal tract. CCK also inhibits appetite to prevent overeating during meals by stimulating sensory afferent nerve fibers in the duodenum these fibers, in turn, send signals by way of the vagus nerve to inhibit feeding centers in the brain.

3- *Secretin* was the first gastrointestinal hormone discovered and is secreted by the "S" cells in the *mucosa of the duodenum* in response to acidic gastric juice emptying into the duodenum from the pylorus of the stomach. Secretin has a mild effect on motility of the gastrointestinal tract and acts to promote pancreatic secretion of bicarbonate, which in turn helps to neutralize the acid in the small intestine.

4- *Gastric inhibitory peptide* (GIP) is secreted by the *mucosa of the upper small intestine,* mainly in response to fatty acids and amino acids but to a lesser extent in response to carbohydrate. It has a mild effect in decreasing motor activity of the stomach and therefore slows emptying of gastric contents into the duodenum when the upper small intestine is already overloaded with food products. GIP, at blood levels even lower than those needed to inhibit gastric motility, also stimulates insulin secretion and for this reason is also known as *glucose- dependent insulinotropic peptide.*

5- *Motilin* is secreted by the stomach and *upper duodenum* during fasting, and the only known function of this hormone is to *increase gastrointestinal motility*. Motilin is released cyclically and stimulates waves of gastrointestinal motility called *interdigestive myoelectric complexes* that move through the stomach and small intestine every 90 minutes in a fasted person. Motilin secretion is inhibited after ingestion by mechanisms that are not fully understood.

Hormone	Stimuli for Secretion	Site of Secretion	Actions
Gastrin	Protein Distention Nerve *(Acid inhibits release)*	G cells of the antrum, duodenum, and jejunum	Stimulates Gastric acid secretion Mucosal growth
Cholecystokinin	Protein Fat Acid	I cells of the duodenum, jejunum, and ileum	Stimulates Pancreatic enzyme secretion Pancreatic bicarbonate secretion Gallbladder contraction Growth of exocrine pancreas Inhibits Gastric emptying
Secretin	Acid Fat	S cells of the duodenum, jejunum, and ileum	Stimulates Pepsin secretion Pancreatic bicarbonate secretion Biliary bicarbonate secretion Growth of exocrine pancreas Inhibits Gastric acid secretion
Gastric inhibitory peptide	Protein Fat Carbohydrate	K cells of the duodenum and jejunum	Stimulates Insulin release Inhibits Gastric acid secretion
Motilin	Fat Acid Nerve	M cells of the duodenum and jejunum	Stimulates Gastric motility Intestinal motility

Table. 2

PHISOLOGY II

2nd. stage

LECT. 2

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DIGESTION

The major foods on which the body lives (with the exception of small quantities of substances such as vitamins and minerals) can be classified as *carbohydrates, fats,* and *proteins.*

They generally cannot be absorbed in their natural forms through the gastrointestinal mucosa and, for this reason, are useless as nutrients without preliminary digestion. Almost all the carbohydrates of the diet are either large *polysaccharides* or *disaccharides,* which are combinations of *monosaccharides* bound to one another by *condensation.* This means that a hydrogen ion (H^+) has been removed from one of the monosaccharides, and a hydroxyl ion (^-OH) has been removed from the next one. The two monosaccharides then combine with each other at these sites of removal, and the hydrogen and hydroxyl ions combine to form water (H_2O).

When carbohydrates are digested, the above process is reversed and the carbohydrates are converted into monosaccharides. Specific enzymes in the digestive juices of the gastrointestinal tract return the hydrogen and hydroxyl ions from water to the polysaccharides and thereby separate the monosaccharides from each other.

$$R''\text{-}R' + H_2O \longrightarrow R''OH + R'H$$

Digestion of Carbohydrates

Carbohydrate Foods of the Diet. Only three major sources of carbohydrates exist in the normal human diet. They are

1. *sucrose,* which is the disaccharide known popularly as cane sugar;
2. *lactose,* which is a disaccharide found in milk; and
3. *starches,* which are large polysaccharides present in almost all non-animal foods, particularly in potatoes and different types of grains.

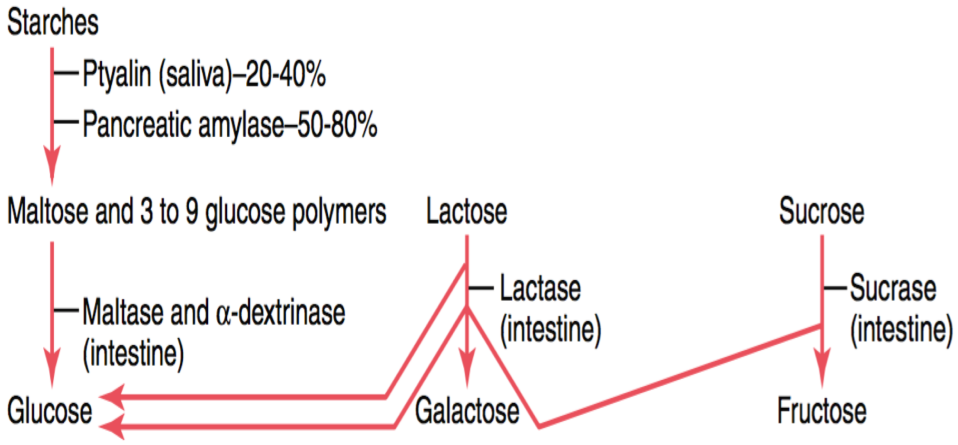
Other carbohydrates ingested to a slight extent are *amylose, glycogen, alcohol, lactic acid, pyruvic acid, pectins, dextrins,* and minor quantities of *carbohydrate derivatives in meats.*

The diet also contains a large amount of cellulose, which is a carbohydrate. However, no enzymes capable of hydrolyzing cellulose are secreted in the human digestive tract. Consequently, cellulose cannot be considered a food for humans.

When food is chewed, it is mixed with saliva, which contains the digestive enzyme *ptyalin* (an amylase) secreted mainly by the parotid glands. This enzyme hydrolyzes starch into the disaccharide *maltose* and other small polymers of glucose that contain three to nine glucose molecules. However, the food remains in the mouth only a short time, so probably not more than 5% of all the starches will have become hydrolyzed by the time the food is swallowed. Starch digestion sometimes continues in the body and fundus of the stomach for as long as 1 hour before the food becomes mixed with the stomach secretions. Then activity of the salivary amylase is blocked by acid of the gastric secretions because the amylase is essentially non-active as an enzyme once the pH of the medium falls below about 4.0. in spite of that, on the average, before food and its accompanying saliva do become completely mixed with the gastric secretions, as much as (30 - 40 %) of the starches will have been hydrolyzed mainly to form *maltose,* this process occurs in the Mouth and Stomach.

Digestion of carbohydrates.

Fig. 1



Digestion of Proteins:

Pepsin, the important peptic enzyme of the stomach, is most active at a pH of 2.0 to 3.0 and is inactive at a pH above about 5.0. Consequently, for this enzyme to cause digestion of protein, the stomach juices must be acidic the gastric glands secrete a large quantity of Hcl. This Hcl is secreted by the parietal (oxyntic) cells ((1) *mucous neck cells,* (2) *peptic* cells, & (3) *parietal* (or *oxyntic*) *cells*) in the glands at a pH of about 0.8, but by the time it is mixed with the stomach contents and with secretions from the non-oxyntic glandular cells of the stomach, the pH then averages around 2.0 to 3.0, a highly favorable range of acidity for pepsin activity.

One of the important features of pepsin digestion is its ability to digest the protein *collagen,* an albuminoid type of protein that is affected little by other digestive enzymes. Collagen is a major constituent of the intercellular connective tissue of meats; therefore, for the digestive enzymes of the digestive tract to penetrate meats and digest the other meat proteins, it is necessary that the collagen fibers be digested. Consequently, in persons who lack pepsin in the stomach juices, the ingested meats are less well penetrated by the other digestive enzymes and, therefore, may be poorly digested.

pepsin only initiates the process of protein digestion, usually providing only (10 - 20 %) of the total protein digestion to convert the protein to proteoses, peptones, and a few polypeptides. This splitting of proteins occurs as a result of hydrolysis at the peptide linkages between amino acids

Most Protein Digestion Results from Actions of Pancreatic Proteolytic Enzymes, and the digestion occurs in the upper small intestine, in the duodenum and jejunum, under the influence of proteolytic enzymes from pancreatic secretion. Immediately on entering the small intestine from the stomach, the partial breakdown products of the protein foods are attacked by major proteolytic pancreatic enzymes: *trypsin, chymotrypsin, carboxypolypeptidase,* and *proelastase (Fig. 2).* Both trypsin and chymotrypsin split protein molecules into small polypeptides; carboxypolypeptidase then cleaves individual amino acids from the carboxyl ends of the polypeptides. Proelastase, in turn, is converted into elastase, which then digests elastin fibers that partially hold meats together. Only a small % of the proteins are digested all the way to their constituent amino acids by the pancreatic juices. Most remain as dipeptides and tripeptides.

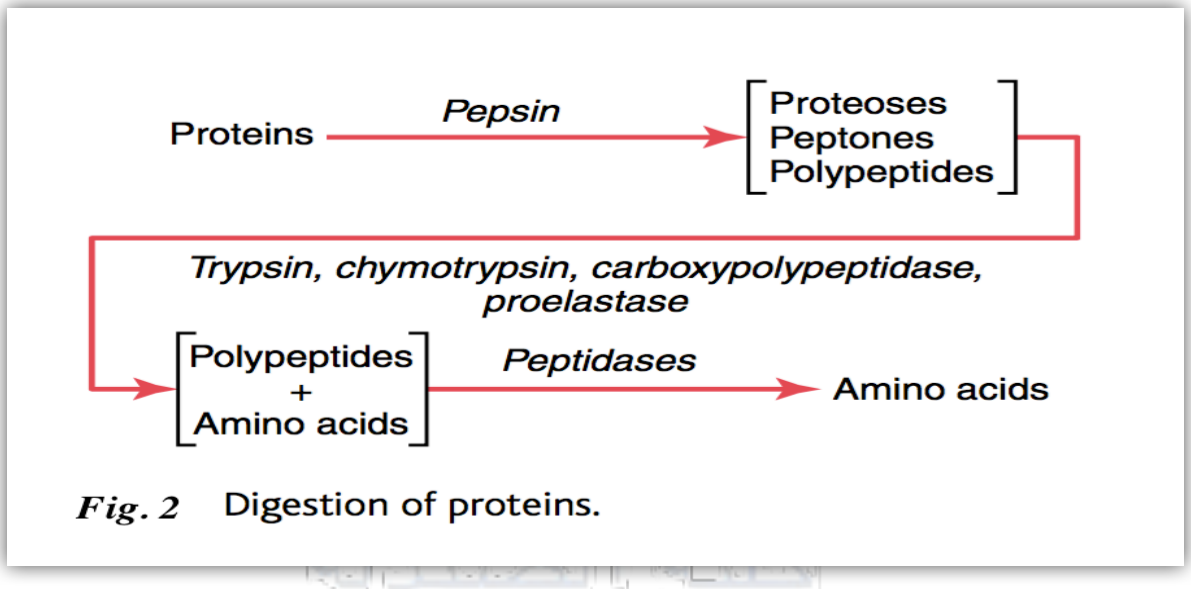


Fig. 2 Digestion of proteins.

The last digestive stage of the proteins in the intestinal lumen is achieved by the enterocytes that line the villi of the small intestine, mainly in the duodenum and jejunum. These cells have a *brush border* that consists of hundreds of *microvilli* projecting from the surface of each cell. In the membrane of each of these microvilli are multiple *peptidases* that protrude through the membranes to the exterior, where they come in contact with the intestinal fluids.

Two types of peptidase enzymes are especially important, *aminopolypeptidase* and several *dipeptidases*. They succeed in splitting the remaining larger polypeptides into tripeptides and dipeptides and a few into amino acids. Both the amino acids plus the dipeptides and tripeptides are easily transported through the microvillar membrane to the interior of the enterocyte.

Finally, inside the cytosol of the enterocyte are multiple other peptidases that are specific for the remaining types of linkages between amino acids. Within minutes, virtually all the last dipeptides and tripeptides are digested to the final stage to form single amino acids; these then pass on through to the other side of the enterocyte and thence into the blood.

More than 99 % of the final protein digestive products that are absorbed are individual amino acids, with only rare absorption of peptides and very, very rare absorption of whole protein molecules.

Digestion of fat:

The most abundant fats of the diet are the neutral fats, also known as *triglycerides,* each molecule of which is composed of a glycerol nucleus and three fatty acid side chains (Fig. 3), neutral fat is a major constituent in food of animal origin but much, much less so in food of plant origin.

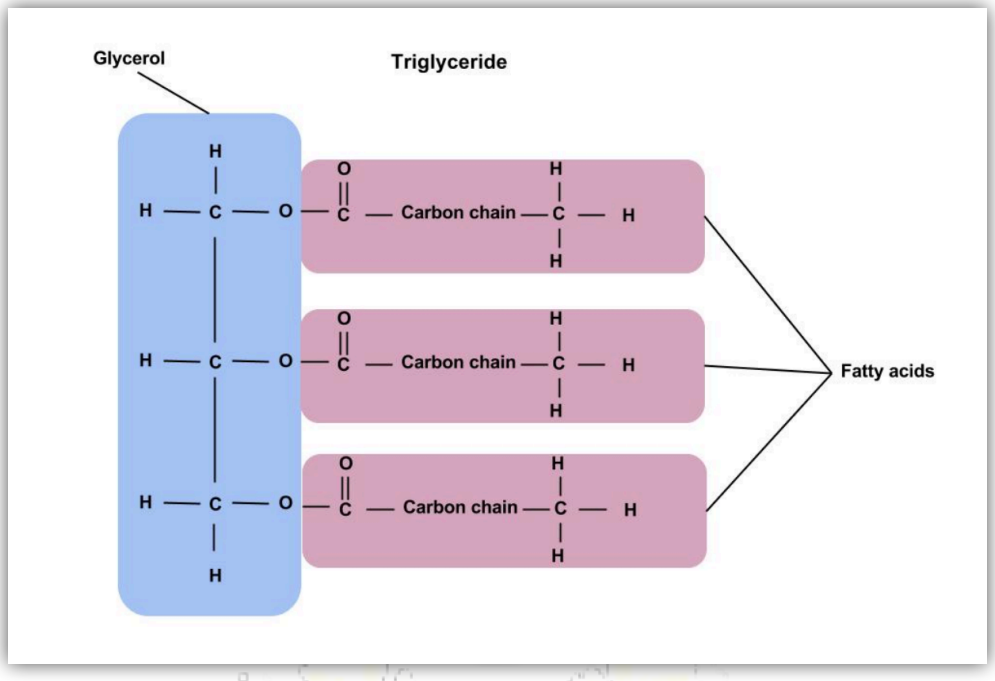


fig. 3 Triglyceride structure

In the usual diet are also small quantities of phospholipids, cholesterol, and cholesterol esters. The phospholipids and cholesterol esters contain fatty acid and therefore can be considered **fats**. Cholesterol, however, is a sterol compound that contains no fatty acid, but it does exhibit some of the physical and chemical characteristics of fats; plus, it is derived from fats and is metabolized similarly to fats. Therefore, cholesterol is considered, from a dietary point of view, a fat.

Digestion of Fats in the Intestine.

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

The First Step in Fat Digestion Is Emulsification by Bile Acids and Lecithin (*derived from several sources, including* ***egg yolks***, ***soybeans***, ***sunflower***, ***canola***, ***corn*** *and others is synthesis by organelles called* ***lamellar bodies***). The first step in fat digestion

is physically to break the fat globules into small sizes so that the water-soluble digestive enzymes can act on the globule surfaces. This process is called *emulsification of the fat,* and it begins by agitation in the stomach to mix the fat with the products of stomach digestion.
Then, most of the emulsification occurs in the duodenum under the influence of *bile,* the secretion from the liver that does not contain any digestive enzymes. However, bile does contain a large quantity of bile salts, as well as the phospholipid *lecithin.* Both of these, but especially the lecithin, are extremely important for emulsification of the fat. The polar parts (the points where ionization occurs in water) of the bile salts and lecithin molecules are highly soluble in water, whereas most of the remaining portions of their molecules are highly soluble in fat. Therefore, the fat-soluble portions of these liver secretions dissolve in the surface layer of the fat globules, with the polar portions projecting. The polar projections, in turn, are soluble in the surrounding watery fluids, which greatly decreases the interfacial tension of the fat and makes it soluble as well.

When the interfacial tension of a globule of non-miscible fluid is low, this non-miscible fluid, on agitation, can be broken up into many tiny particles far more easily than it can when the interfacial tension is great. Consequently, a major function of the bile salts and lecithin, especially the lecithin, in the bile is to make the fat globules readily fragmentable by agitation with the water in the small bowel. This action is the same as that of many detergents that are widely used in household cleaners for removing grease.

Each time the diameters of the fat globules are significantly decreased as a result of agitation in the small intestine, the total surface area of the fat increases many fold. Because the average diameter of the fat particles in the intestine after emulsification has occurred is > 1 micrometer, this represents an increase of as much as 1000-fold in total surface areas of the fats caused by the emulsification process.

The lipase enzymes are water-soluble compounds and can attack the fat globules only on their surfaces. Consequently, this detergent function of bile salts and lecithin is very important for digestion of fats. The most important enzyme for digestion of the triglycerides is *pancreatic lipase,* present in enormous quantities in pancreatic juice, enough to digest within 1 minute all triglycerides that it can reach. In addition, the enterocytes of the small intestine contain additional lipase, known as *enteric lipase,* but this is usually not needed.

Most of the triglycerides of the diet are split by pancreatic lipase into *free fatty acids* and *2-monoglycerides,* as shown in Figure 3.

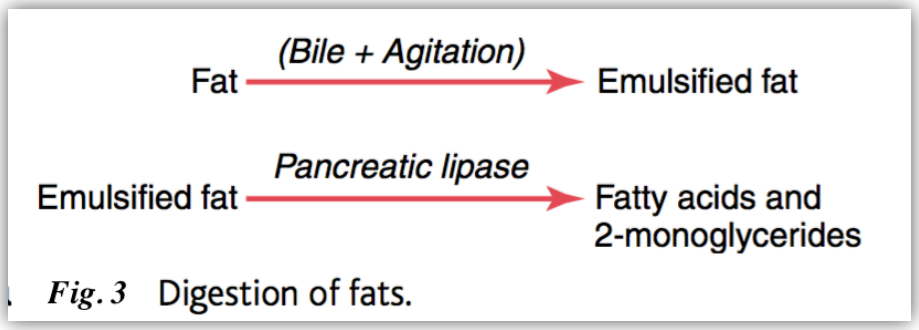


Fig. 3 Digestion of fats.

The hydrolysis of triglycerides is a highly reversible process; therefore, accumulation of monoglycerides and free fatty acids in the vicinity of digesting fats quickly blocks further digestion. But the bile salts play the additional important role of removing the monoglycerides and free fatty acids from the vicinity of the digesting fat globules almost as rapidly as these end products of digestion are formed. This occurs in the following way.

Bile salts, when in high enough concentration in water, have the propensity to form *micelles,* which are small spherical, cylindrical globules 3 - 6 nanometers in diameter composed of 20 - 40 molecules of bile salt. These develop because each bile salt molecule is composed of a sterol nucleus that is highly fat-soluble and a polar group that is highly water-soluble. The sterol nucleus encompasses the fat digestate, forming a small fat globule in the middle of a resulting micelle, with polar groups of bile salts projecting outward to cover the surface of the micelle. Because these polar groups are negatively charged, they allow the entire micelle globule to dissolve in the water of the digestive fluids and to remain in stable solution until the fat is absorbed into the blood.

The bile salt micelles also act as a transport medium to carry the monoglycerides and free fatty acids, both of which would otherwise be relatively insoluble, to the brush borders of the intestinal epithelial cells. There the monoglycerides and free fatty acids are absorbed into the blood, but the bile salts themselves are released back into the chyme to be used again and again for this "**ferrying**" process.

Digestion of Cholesterol Esters and Phospholipids. Most cholesterol in the diet is in the form of cholesterol esters, which are combinations of free cholesterol and one molecule of fatty acid. Phospholipids also contain fatty acid within their molecules. Both the cholesterol esters and the phospholipids are hydrolyzed by two other lipases in the pancreatic secretion that free the fatty acids—the enzyme *cholesterol ester hydrolase* to hydrolyze the cholesterol ester, and *phospholipase* A_2 to hydrolyze the phospholipid.

The bile salt micelles play the same role in "ferrying" free cholesterol and phospholipid molecule digestates that they play in "ferrying" monoglycerides and

free fatty acids. Indeed, essentially no cholesterol is absorbed without this function of the micelles.

[Date]

PHISOLOGY II

2nd. stage

LECT. 3

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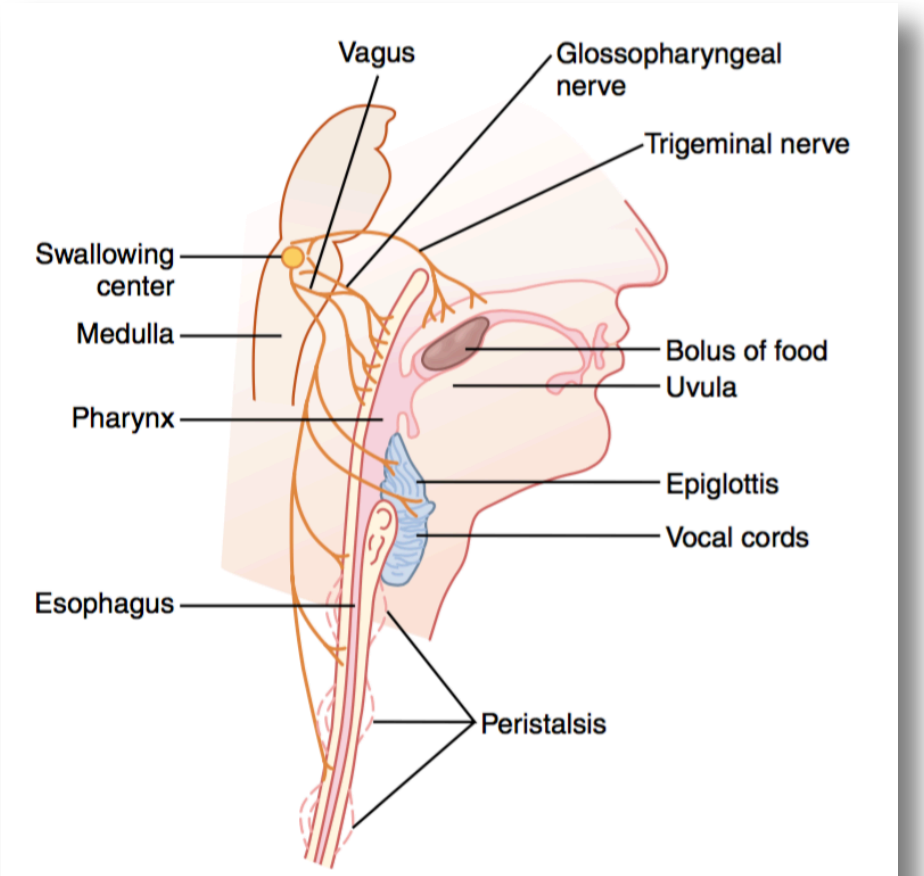

Figure (-1 Swallowing mechanism.

Ingestion of Food

The amount of food that a person ingests is determined principally by intrinsic desire for food called *hunger*. The type of food that a person preferentially seeks is determined by *appetite*. These mechanisms are extremely important for maintaining an adequate nutritional supply for the body

Mastication (Chewing)

The teeth are admirably designed for chewing. The anterior teeth (incisors) provide a strong cutting action and the posterior teeth (molars) a grinding action. All the jaw muscles working together can close the teeth with a force as great as 55 pounds on the incisors and 200 pounds on the molars. Most of the muscles of chewing are innervated by the motor branch of the fifth cranial nerve, and the chewing process is controlled by nuclei in the brain stem. Stimulation of specific reticular areas in the brain stem taste centers will cause rhythmical chewing

movements. Also, stimulation of areas in the hypothalamus, amygdala, and even the cerebral cortex near the sensory areas for taste and smell can often cause chewing.

Chewing is important for digestion of all foods Digestive enzymes act only on the surfaces of food particles; therefore, the rate of digestion is absolutely dependent on the total surface area exposed to the digestive secretions. In addition, grinding the food to a very fine particulate consistency prevents excoriation of the gastrointestinal tract and increases the ease with which food is emptied from the stomach into the small intestine, then into all succeeding segments of the gut.

Swallowing (Deglutition)

Swallowing is a complicated mechanism, principally because the pharynx subserves respiration and swallowing. The pharynx is converted for only a few seconds at a time into a tract for propulsion of food.

In general, swallowing can be divided into

(1) a *voluntary stage,* which initiates the swallowing process;

(2) a *pharyngeal stage,* which is involuntary and constitutes passage of food through the pharynx into the esophagus; and

(3) an *esophageal stage,* another involuntary phase that transports food from the pharynx to the stomach.

(1) Voluntary Stage of Swallowing. When the food is ready for swallowing, it is "voluntarily" squeezed or rolled posteriorly into the pharynx by pressure of the tongue upward and backward against the palate, as shown in Figure 1. From here on, swallowing becomes entirely— or almost entirely—automatic and ordinarily cannot be stopped

(2) Pharyngeal Stage of Swallowing. As the bolus of food enters the posterior mouth and pharynx, it stimulates *epithelial swallowing receptor areas* all around the opening of the pharynx

(3) Esophageal Stage of Swallowing. The esophagus functions primarily to conduct food rapidly from the pharynx to the stomach, and its movements are organized specifically for this function.

The esophagus normally exhibits two types of peristaltic movements: *primary peristalsis* and *secondary peristalsis.* Primary peristalsis is simply continuation

of the peristaltic wave that begins in the pharynx and spreads into the esophagus during the pharyngeal stage of swallowing

secondary peristaltic waves result from distention of the esophagus itself by the retained food; these waves continue until all the food has emptied into the stomach. The secondary peristaltic waves are initiated partly by intrinsic neural circuits in the myenteric nervous system and partly by reflexes that begin in the pharynx and are then transmitted upward through vagal afferent fibers to the medulla and back again to the esophagus through glossopharyngeal and vagal efferent nerve fibers.

The first third of esophagus controlled by skeletal nerve impulses from the glossopharyngeal and vagus nerves and the other controlled by portion of the esophagus is also strongly controlled by the vagus nerves acting through connections with the esophageal myenteric nervous system.

Function of the Lower Esophageal Sphincter (Gastroesophageal Sphincter). At the lower end of the esophagus, extending upward about 3 centimeters above its juncture with the stomach, the esophageal circular muscle functions as a broad *lower esophageal sphincter,* also called the *gastroesophageal sphincter*.

Nervous Initiation of the Pharyngeal Stage of Swallowing. The most sensitive tactile areas of the posterior mouth and pharynx for initiating the pharyngeal stage of swallowing lie in a ring around the pharyngeal opening, with greatest sensitivity on the tonsillar pillars. Impulses are transmitted from these areas through the sensory portions of the trigeminal and glossopharyngeal nerves into the medulla oblongata, either into or closely associated with the tractus solitarius, which receives essentially all sensory impulses from the mouth.

The successive stages of the swallowing process are then automatically initiated in orderly sequence by neuronal areas of the reticular substance of the medulla and lower portion of the pons. The areas in the medulla and lower pons that control swallowing are collectively called the deglutition or swallowing center.

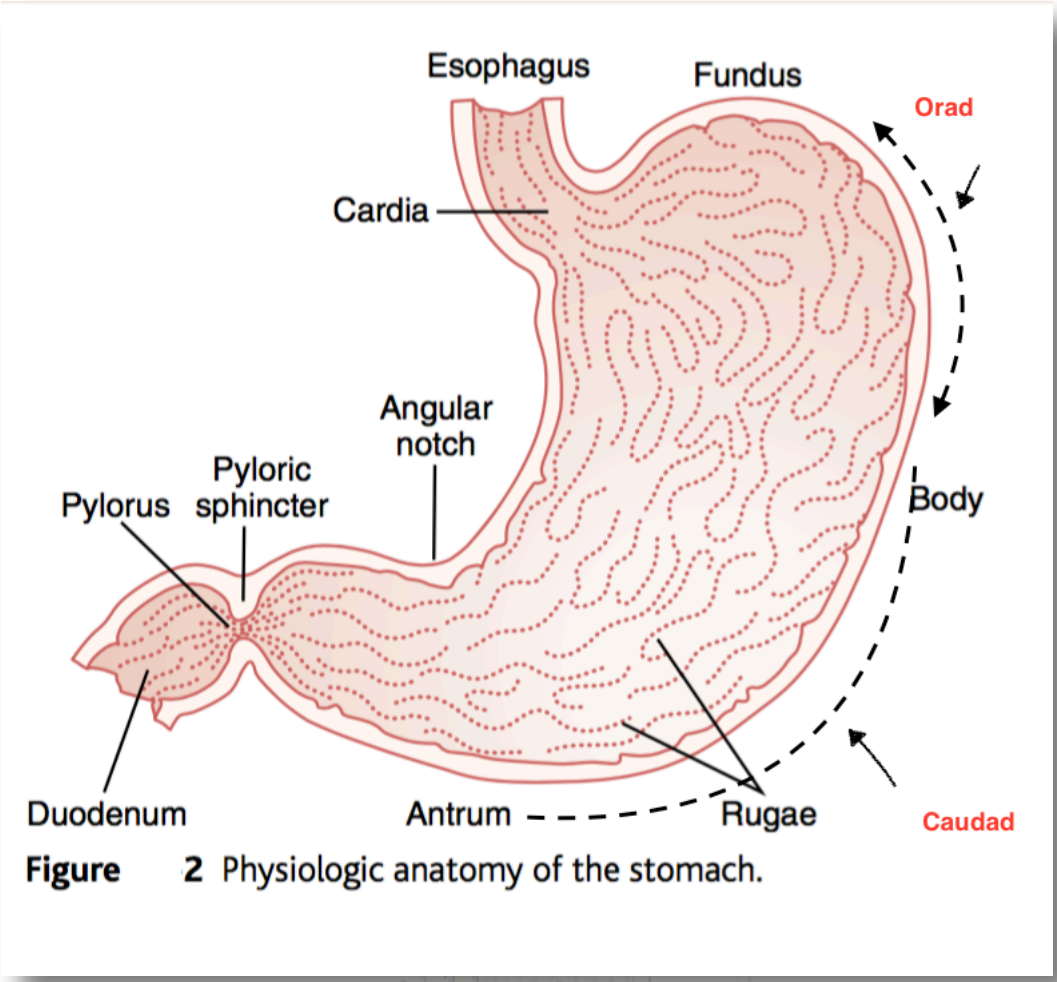

Figure 2 Physiologic anatomy of the stomach.

Stomach

The epithelial layer lining the stomach invaginate into the mucosa, forming many tubular glands. Glands in the thin-walled upper portions of the body of the stomach (Figure 2) secrete mucus, hydrochloric acid, and the enzyme precursor pepsinogen. The uppermost part of the body of the stomach is called the fundus and is functionally part of the body. The lower portion of the stomach, the antrum, has a much thicker layer of smooth muscle and is responsible for mixing and grinding the stomach contents. The glands in this region secrete little acid but contain the endocrine cells that secrete the hormone gastrin.

Anatomically, the stomach is usually divided into two major parts: (1) the *body* and (2) the *antrum*. Physiologically, it is more appropriately divided into (1) the "*orad*" portion, comprising about the first two thirds of the body, and (2) the "*caudad*" portion, comprising the remainder of the body plus the antrum

Motor Functions of the Stomach

The motor functions of the stomach are threefold:

(1) storage of large quantities of food until the food can be processed in the stomach, duodenum, and lower intestinal tract;

(2) mixing of this food with gastric secretions until it forms a semifluid mixture called *chyme;* and

(3) slow emptying of the chyme from the stomach into the small intestine at a rate suitable for proper digestion and absorption by the small intestine.

The cells at the opening of the glands secrete mucus. Lining the walls of the glands are parietal cells (also known as oxyntic cells), which secrete acid and intrinsic factor, and chief cells, which secrete pepsinogen. The unique invaginations of the luminal membrane of parietal cells shown in Figure 3 are called canaliculi (singular, canaliculus); these increase the surface area of the parietal cells thereby maximizing secretion into the lumen of the stomach.

Each of the three major exocrine secretions of the stomach (mucus, acid, and pepsinogen) is secreted by a different cell type. The gastric glands in the antrum also contain enteroendocrine cells, which secrete gastrin. In addition, enterochromaffin-like (ECL) cells, which release the paracrine agent histamine, and endocrine cells called D cells, which secrete the peptide somatostatin, are scattered throughout the tubular glands or in surrounding tissue; both of these substances play roles in regulating acid secretion by the stomach.

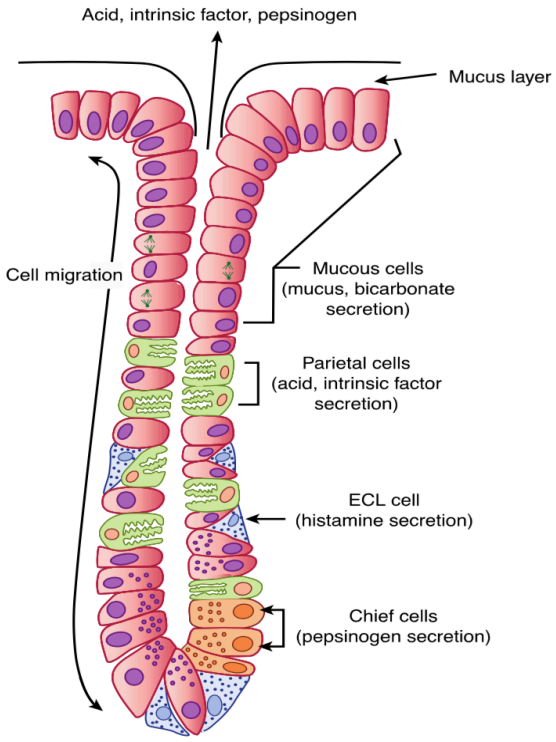

Figure 3 *A gastric gland in the stomach. The unique invaginations of the luminal membranes of parietal cells are called canaliculi and greatly increase the surface area for secretion.*

HCl Production and Secretion

The stomach secretes about 2 L of hydrochloric acid per day. The concentration of H+ in the lumen of the stomach may reach >150 mM, which is 1 to 3 million times greater than the con- centration in the blood. This requires an efficient production mechanism to generate large numbers of hydrogen ions. The origin of the hydrogen ions is CO2 in the parietal cell. The

enzyme carbonic anhydrase catalyzes the reaction between CO2 with water to produce carbonic acid, which dissociates to H+ and HCO3-. Primary H+/K+-ATPases in the luminal membrane of the parietal cells pump these hydrogen ions into the lumen of the stomach (Figure 4). This primary active transporter also pumps K+ into the cell, which then leaks back into the lumen through K+ channels. As H+ is secreted into the lumen, HCO3- is secreted on the opposite side of the cell into the blood in exchange for Cl-. In this way, production and secretion of H^- are coupled. Increased acid secretion, stimulated by factors described later, results from the transfer of H^+/K^+-ATPase proteins from the membranes of intracellular vesicles to the plasma membrane by fusion of these

vesicles with the membrane, thereby increasing the number of pump proteins in the plasma membrane.

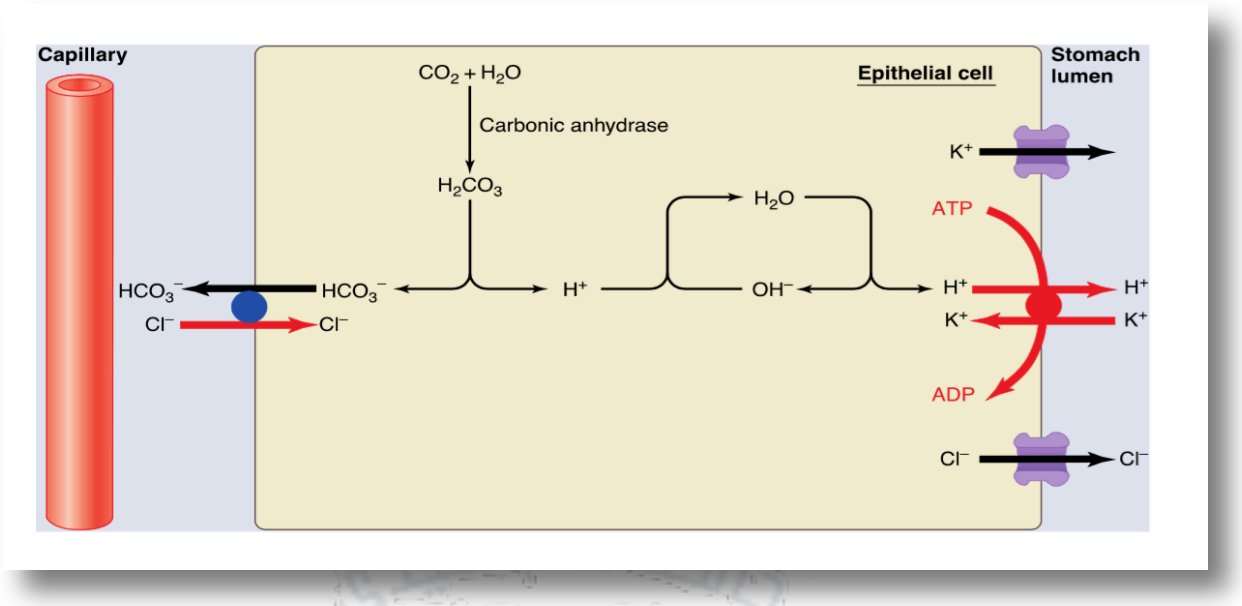

Figure 4: Secretion of hydrochloric acid by parietal cells

Hunger Contractions. Besides the peristaltic con- tractions that occur when food is present in the stomach, another type of intense contractions, called *hunger con- tractions,* often occurs *when the stomach has been empty* for several hours or more. They are rhythmical peristaltic contractions in the *body* of the stomach. When the successive contractions become extremely strong, they often fuse to cause a continuing tetanic contraction that some- times lasts for 2 to 3 minutes. It most occurs intense in young, healthy people who have high degrees of gastrointestinal tonus; they are also greatly increased by the person's having lower than normal levels of blood sugar. The person sometimes experiences mild pain in the pit of the stomach, called *hunger pangs.*

Gastric Factors That Promote Emptying

1- **Gastric Food Volume:** Increased food volume in the stomach pro- motes increased emptying from the stomach.
2- **The Hormone *Gastrin:*** when person feed meat will cause secretion of highly acidic gastric juice by the stomach glands Gastrin also has mild to moderate stimulatory effects on motor functions in the body of the stomach. The types of factors that are continually monitored in the duodenum and that can initiate enterogastric inhibitory reflexes include the

following:

a. The degree of distention of the duodenum

b. The presence of any degree of irritation of the duodenal mucosa

c. The degree of acidity of the duodenal chyme

d. The degree of osmolality of the chyme

e. The presence of certain breakdown products in the chyme, especially breakdown products of proteins and, perhaps to a lesser extent, of fats

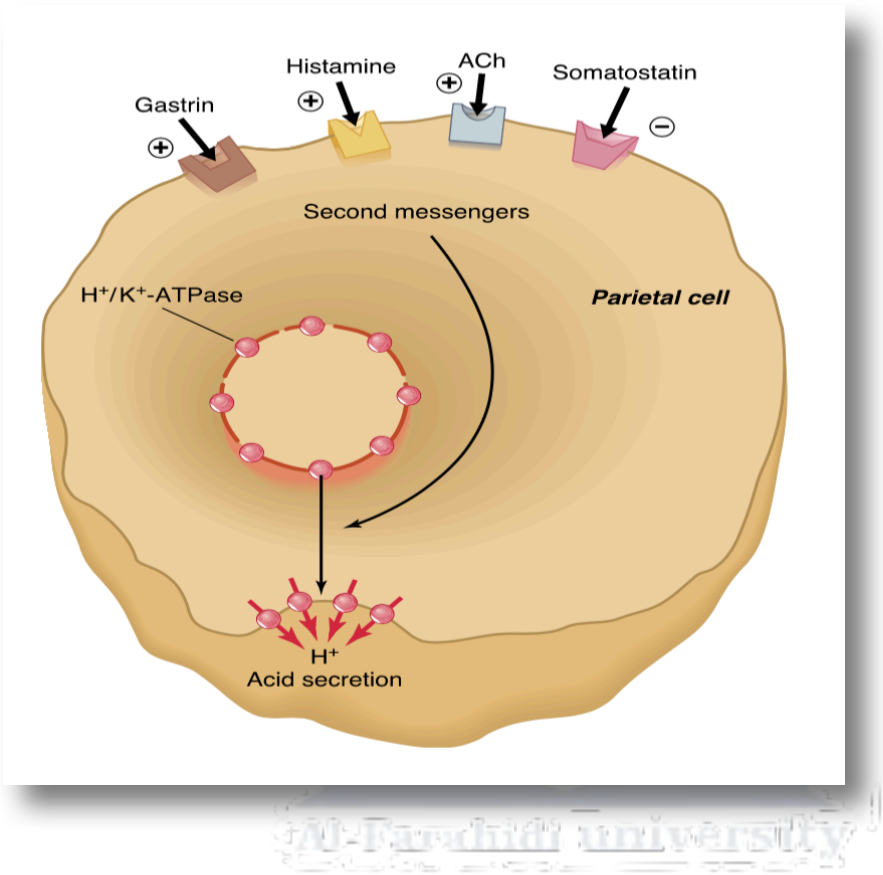

***Figure 5**: The four neurohumoral inputs to parietal cells that regulate acid secretion by generating second messengers. These second messengers control the transfer of the H^+/K^+-ATPase pumps in cytoplasmic vesicle membranes to the plasma membrane. Not shown are the effects of peptides and amino acids on acid secretion.*

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PHISOLOGY II

2nd. stage

LECT. 4

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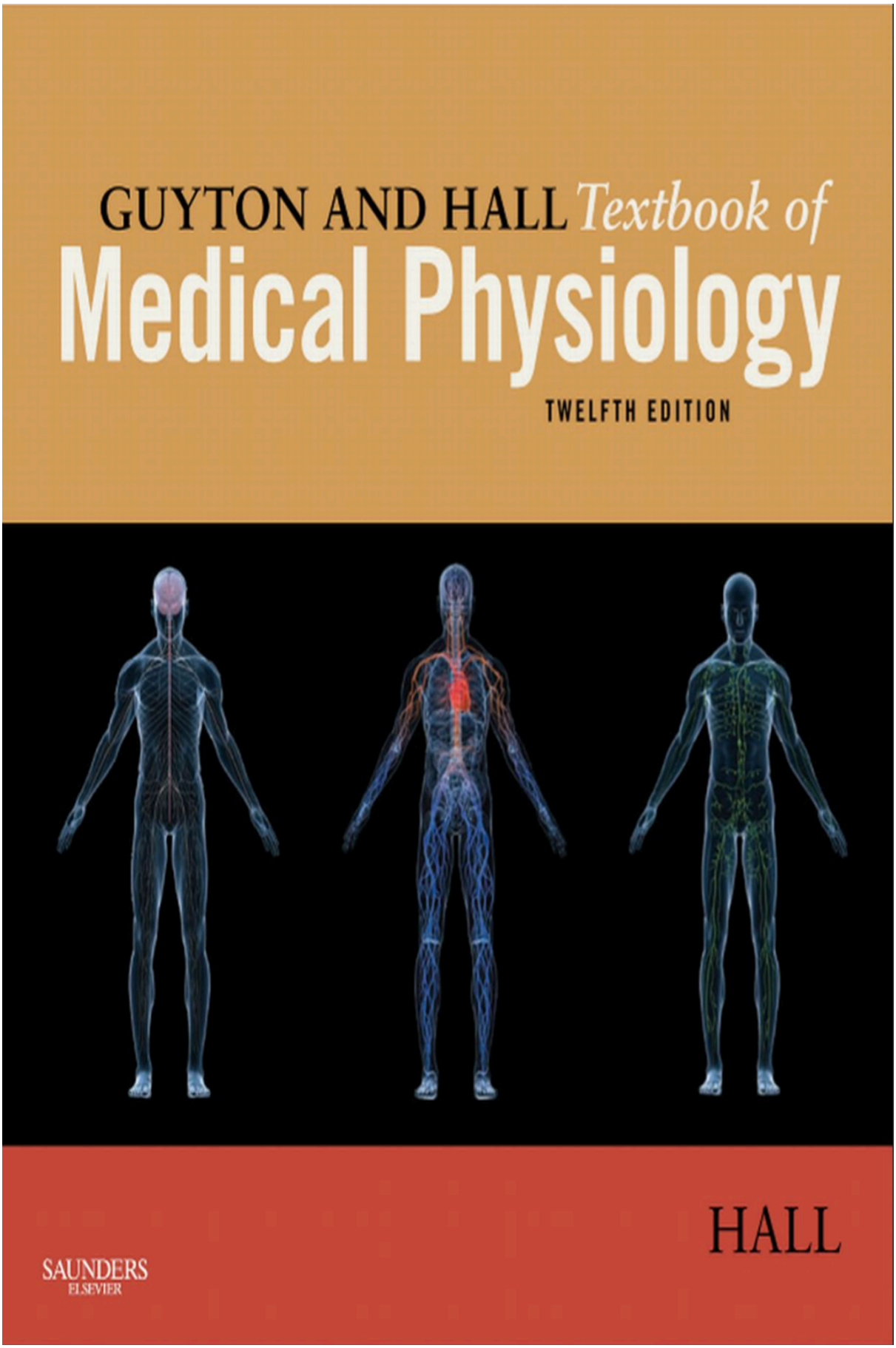
GUYTON AND HALL Textbook of
Medical Physiology
TWELFTH EDITION
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Absorption in the Small Intestine

Absorption from the small intestine each day consists of several hundred grams of carbohydrates, 100 or more grams of fat, 50 to 100 grams of amino acids, 50 to 100 grams of ions, and 7 to 8 liters of water. The absorptive *capacity* of the normal small intestine is far greater than this: as much as several kilograms of carbohydrates per day, 500 grams of fat per day, 500 to 700 grams of proteins per day, and 20 or more liters of water per day

Absorption of Water by Osmosis

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

Sodium Is Actively Transported (*requires energy*) Through the Intestinal Membrane. Sodium also plays an important role in helping to absorb sugars and amino acids (*At the same time they also provide secondary active absorption of glucose and amino acids, powered by the active* Na^+-K^+ *ATPase pump on the basolateral membrane*). (20–30) grams of sodium are secreted in the intestinal secretions each day. In addition, the average person eats 5 to 8 grams of sodium each day. Therefore, to prevent net loss of sodium into the feces, the intestines must absorb 25 to 35 grams of sodium each day, which is equal to about 1/7 of all the sodium present in the body. Normally the intestine less than 0.5 % of intestinal sodium is lost in feces each day because its rapidly absorbed through intestinal mucosa.

In case of severe diarrhea, the body lose extremely amount of sodium to lethal levels within hours. As the concentration of sodium in chyme about equal to that in chyme, the sodium moves down this steep electro- chemical gradient from the chyme through the brush border of the epithelial cell into the epithelial cell cytoplasm.

Sodium is also co-transported through the brush border membrane by several specific carrier proteins, including:

(1) sodium-glucose co-transporter,

(2) sodium- amino acid co-transporters, and

(3) sodium-hydrogen exchanger.

Aldosterone Greatly Enhances Sodium Absorption. When a person becomes dehydrated, large amounts of aldosterone almost always are secreted by the cortices of the adrenal glands. Within 1 to 3 hours this aldosterone causes increased activation of the enzyme and transport mechanisms for all aspects of sodium absorption by the intestinal epithelium. And the increased sodium absorption in turn causes secondary increases in absorption of chloride ions, water, and some other substances. This effect of aldosterone is especially important in the colon because it allows virtually no loss of sodium chloride in the feces and also little water loss. Thus, the function of aldosterone in the intestinal tract is the same as that achieved by aldosterone in the renal tubules, which also serves to conserve sodium chloride and water in the body when a person becomes dehydrated

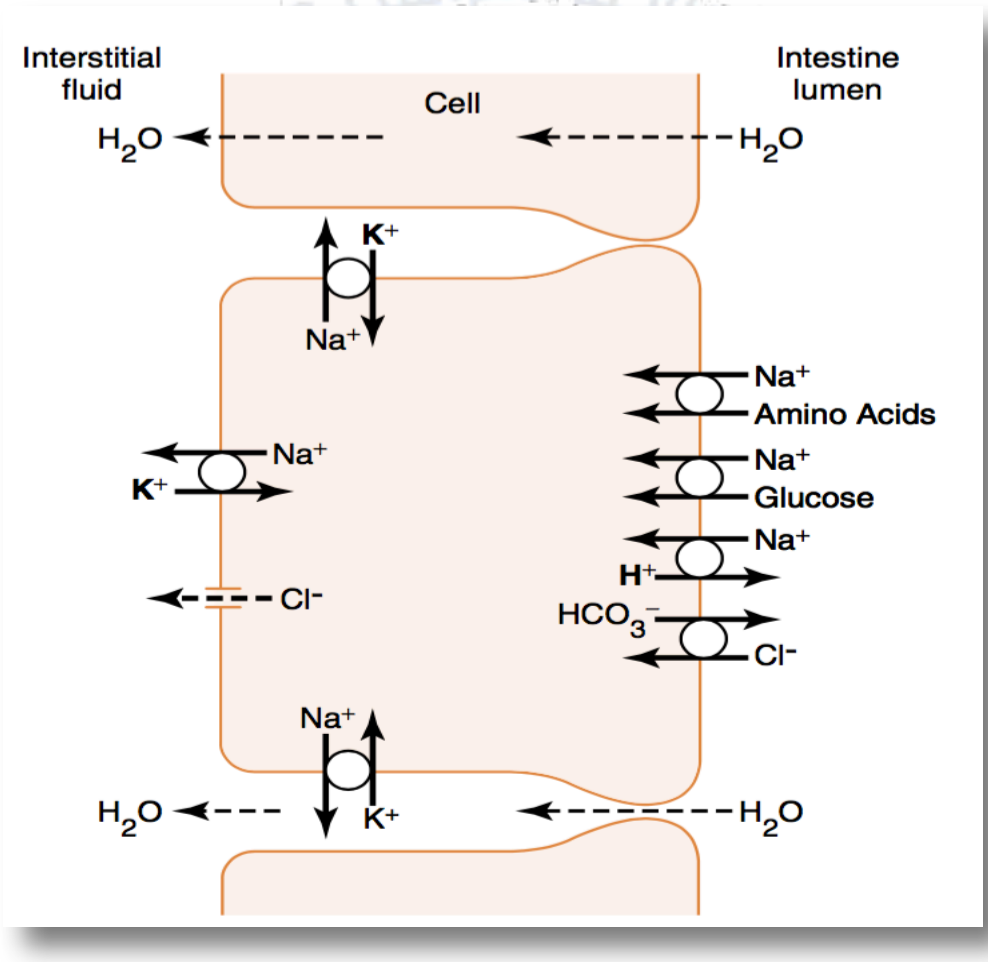

Figure 1

Absorption of Chloride Ions in the Small Intestine. In the upper part of the small intestine, chloride ion absorption is rapid and occurs mainly by diffusion (i.e., absorption of sodium ions through the epithelium creates electronegativity in the chyme and electropositivity in the paracellular spaces between the epithelial cells). Then chloride ions move along this electrical gradient to "follow" the sodium ions. Chloride is also absorbed across the brush border membrane of parts of the ileum and large intestine by a brush border membrane chloride- bicarbonate exchanger; chloride exits the cell on the basolateral membrane through chloride channels

Absorption of **Bicarbonate Ions** in the Duodenum and Jejunum. Often large quantities of bicarbonate ions must be reabsorbed from the upper small intestine because large amounts of bicarbonate ions have been secreted into the duodenum in both pancreatic secretion and bile.

The bicarbonate ion is absorbed in an indirect way as follows: When sodium ions are absorbed, moderate amounts of hydrogen ions are secreted into the lumen of the gut in exchange for some of the sodium. These hydrogen ions in turn combine with the bicarbonate ions to form carbonic acid (H_2CO_3), which then dissociates to form water and carbon dioxide. The water remains as part of the chyme in the intestines, but the carbon dioxide is readily absorbed into the blood and subsequently expired through the lungs. Thus, this is so-called "active absorption of bicarbonate ions.

Secretion of Bicarbonate Ions in the Ileum and Large Intestine—Simultaneous Absorption of Chloride Ions

The epithelial cells on the surfaces of the villi in the ileum, as well as on all surfaces of the large intestine, have a special capability of secreting bicarbonate ions in exchange for absorption of chloride ions. This is important because it provides alkaline bicarbonate ions that neutralize acid products formed by bacteria in the large intestine.

One important factor controlling calcium absorption is *parathyroid hormone* secreted by the parathyroid glands, and another is *vitamin D*. Parathyroid hormone activates vitamin D, and the activated vitamin D in turn greatly enhances calcium absorption

Iron ions are also actively absorbed from the small intestine. The principles of iron absorption and regulation of its absorption in proportion to the body's need for iron, especially for the formation of hemoglobin

Potassium, magnesium, phosphate, and probably *still other ions* can also be actively absorbed through the intestinal mucosa

Absorption of Nutrients

Carbohydrates Are Mainly Absorbed as Monosaccharides

Essentially all the carbohydrates in the food are absorbed in the form of monosaccharides (80% of carbohydrate calories absorbed is *glucose)*; only a small fraction is absorbed as disaccharides (20% is composed almost entirely of *galactose*- milk- and *fructose*- cane sugar -*),* and almost none as larger carbohydrate compounds

Glucose Is Transported by a Sodium Co-Transport Mechanism

In the absence of sodium transport through the intestinal membrane, virtually no glucose can be absorbed. The reason is that glucose absorption occurs in a co-transport mode with active transport of sodium

There are two **stages** in the transport of sodium through the intestinal membrane.

First is active transport of sodium ions through the basolateral membranes of the intestinal epithelial cells into the blood, thereby depleting sodium inside the epithelial cells.

Second, decrease of sodium inside the cells causes sodium from the intestinal lumen to move through the brush border of the epithelial cells to the cell interiors by a process of *secondary active transport*.

Intestinal glucose also combines simultaneously with the same transport protein and then both the sodium ion and glucose molecule are transported together to the interior of the cell. So the low concentration of sodium inside the cells will lead to pull the sodium inside the cells concomitant with glucose. At this moment in the epithelial cell, other transport proteins and enzymes cause facilitated diffusion of glucose through the cells' basolateral membrane into the paracellular space and into the blood.

Absorption of Other Monosaccharides

Galactose is transported by almost exactly the same mechanism as glucose. fructose transport does not occur by the sodium co-transport mechanism. Instead, fructose is trans- ported by facilitated diffusion all the way through the intestinal epithelium but not coupled with sodium transport. Much of the fructose, on entering the cell, becomes phosphorylated, then converted to glucose, and finally transported in the form of glucose the rest of the way into the blood

Absorption of Proteins as Dipeptides, Tripeptides, or Amino Acids

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

Absorption of Fats

monoglycerides and free fatty acids, are dissolved in the central lipid portions of *bile micelles.* Because the molecular dimensions of these micelles are only 3 to 6 nanometers in diameter, and because of their highly charged exterior, they are soluble in chyme. the monoglycerides and free fatty acids are carried to the surfaces of the microvilli of the intestinal cell brush border and then penetrate into the recesses among the moving, agitating microvilli. both the monoglycerides and fatty acids diffuse immediately out of the micelles and into the interior of the epithelial cells, which is possible because the lipids are also soluble in the epithelial cell membrane.

[Date]

PHISOLOGY II

2nd. stage

LECT. 5

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The multiple activities of the cells, tissues, and organs of the body are coordinated by the interplay of several types of chemical messenger systems:

1. *Neurotransmitters* are released by axon terminals of neurons into the synaptic junctions and act locally to control nerve cell functions.

2. *Endocrine hormones* are released by glands or specialized cells into the circulating blood and influence the function of target cells at another location in the body.

3. *Neuroendocrine hormones* are secreted by neurons into the circulating blood and influence the function of target cells at another location in the body.

4. *Paracrins* are secreted by cells into the extra cellular fluid and affect neighboring target cells of a different type.

5. *Autocrines* are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them.

6. *Cytokines* are peptides secreted by cells into the extracellular fluid and can function as autocrines, paracrines, or endocrine hormones. Examples of cytokines include the *interleukins* and other *lymphokines* that are secreted by helper cells and act on other cells of the immune system. Cytokine hormones (e.g., *leptin*) produced by adipocytes are sometimes called *adipokines*.

Chemical Structure and Synthesis of Hormones

Three general classes of hormones exist:

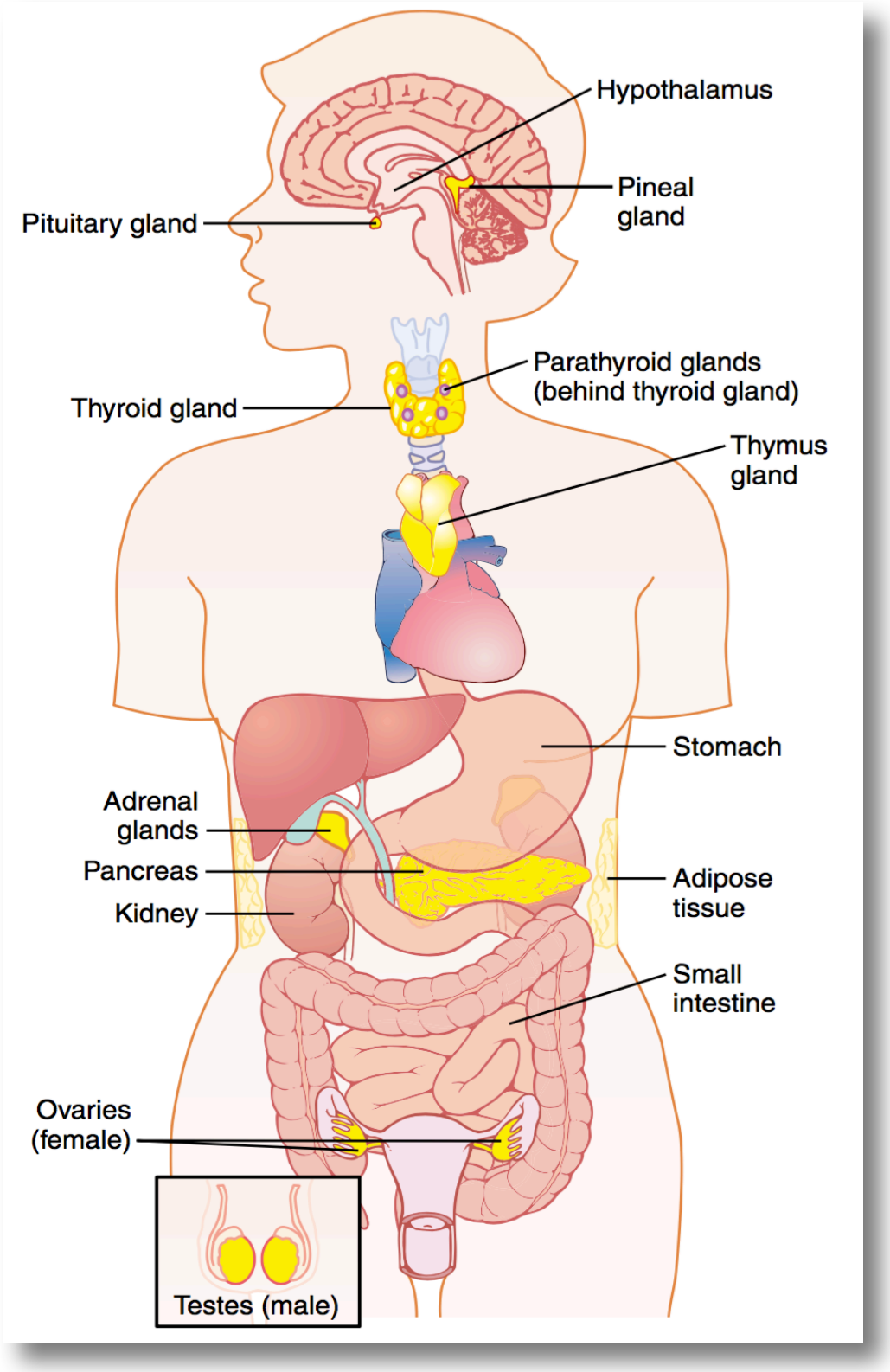
1. *Proteins and polypeptides,* including hormones secreted by the anterior and posterior pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland (parathyroid hormone), and many others

2. *Steroids* secreted by the adrenal cortex (cortisol and aldosterone), the ovaries (estrogen and progesterone), the testes (testosterone), and the placenta (estrogen and progesterone).

3. *Derivatives of the amino acid tyrosine,* secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae (epinephrine and norepinephrine). There are no known polysaccharides or nucleic acid hormones.

- Polypeptide and Protein Hormones Are Stored in Secretory Vesicles Until Needed. Most of the hormones in the body are polypeptides and proteins. These hormones range in size from small peptides with as few as 3 amino acids to

proteins with almost 200 amino acids. In general, polypeptides with 100 or more amino acids are called *proteins,* and those with fewer than 100 amino acids are referred to as *peptides*



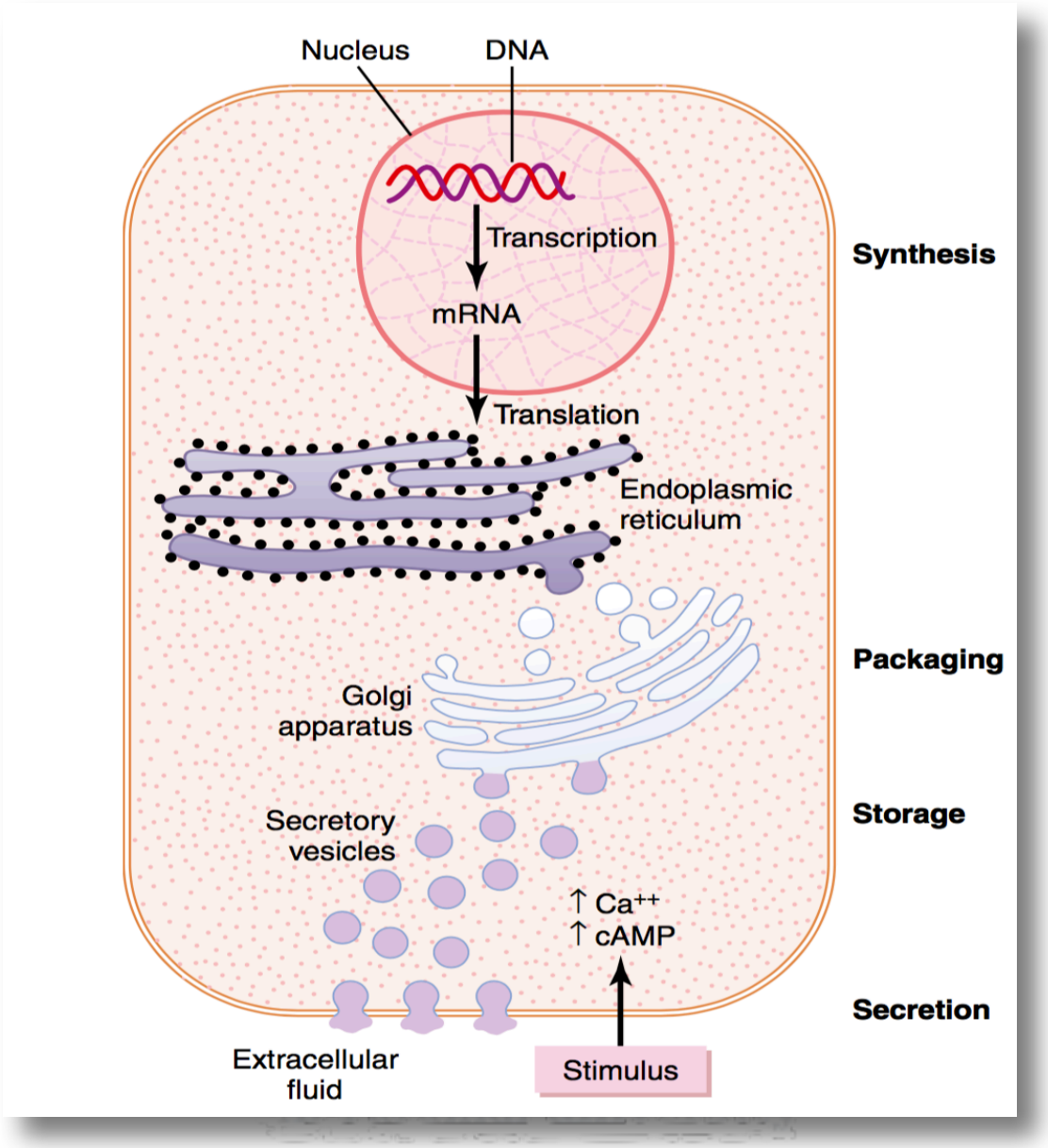
Protein and peptide hormones are synthesized on the rough end of the endoplasmic reticulum of the different endocrine cells. They are usually synthesized first as larger proteins that are not biologically active *(preprohormones)* and are cleaved to form smaller *prohormones* in the endoplasmic reticulum. These are then transferred to the Golgi apparatus for packaging into secretory vesicles. In this process, enzymes in the vesicles cleave the prohormones to produce smaller, biologically active hormones and inactive fragments. The vesicles are stored within the cytoplasm, and many are bound to the cell membrane until their secretion is needed. Secretion of the hormones occurs when the secretory vesicles fuse with the cell membrane and the granular contents are extruded into the interstitial fluid or directly into the blood stream by *exocytosis*.

An increase in cytosolic calcium concentration caused by depolarization of the plasma membrane and/or stimulation of an endocrine cell surface receptor causes increased cyclic adenosine monophosphate (cAMP) and subsequently activation of protein kinases that initiate secretion of the hormone. The peptide hormones are water soluble, allowing them to enter the circulatory system easily, where they are carried to their target tissues

Steroid Hormones Are Usually Synthesized from Cholesterol and Are Not Stored. They are lipid soluble. Because the steroids are highly lipid soluble, once they are synthesized, they simply diffuse across the cell membrane and enter the interstitial fluid and then the blood.

Amine Hormones Are Derived from Tyrosine. The two groups of hormones derived from tyrosine, the *thyroid* and the *adrenal medullary hormones*, are formed by the actions of enzymes in the cytoplasmic compartments of the glandular cells. The thyroid hormones are synthesized and stored in the thyroid gland and incorporated into macromolecules of the protein *thyroglobulin,* which is stored in large follicles within the thyroid gland. After entering the blood, most of the thyroid hormones combine with plasma proteins, especially *thyroxine-binding globulin,* which slowly releases the hormones to the target tissues

Epinephrine and norepinephrine are formed in the adrenal medulla, which normally secretes about four times more epinephrine than norepinephrine. Catecholamines are taken up into preformed vesicles and stored until secreted.



Onset of Hormone Secretion After a Stimulus, and Duration of Action of Different Hormones. Some hormones, such as norepinephrine and epinephrine, are secreted within seconds after the gland is stimulated, and they may develop full action within another few seconds to minutes; the actions of other hormones, such as thyroxine or growth hormone, may require months for full effect.

Concentrations of Hormones in the Circulating Blood, and Hormonal Secretion Rates. The concentrations of hormones required to control most metabolic and endocrine functions are incredibly small.

Feedback Control of Hormone Secretion

Negative feedback prevents over activity of hormone systems. Although the plasma concentrations of many hormones fluctuate in response to various stimuli that occur throughout the day, all hormones studied thus far appear to be closely controlled. In most instances, this control is exerted through *negative feed- back mechanisms* that ensure a proper level of hormone activity at the target tissue, the hormone (or one of its products) has a negative feedback effect to prevent over-secretion of the hormone or over activity at the target tissue. The controlled variable is sometimes not the secretory rate of the hormone itself but the degree of activity of the target tissue

Surges of Hormones Can Occur with Positive Feedback. In a few instances, positive feedback occurs when the biological action of the hormone causes additional secretion of the hormone

One example of this is the surge of *luteinizing hormone* (LH) that occurs as a result of the stimulatory effect of estrogen on the anterior pituitary before ovulation. The secreted LH then acts on the ovaries to stimulate additional secretion of estrogen, which in turn causes more secretion of LH.

Transport of Hormones in the Blood

Water-soluble hormones (peptides and catecholamines) are dissolved in the plasma and transported from their sites of synthesis to target tissues, where they diffuse out of the capillaries, into the interstitial fluid, and ultimately to target cells. *Steroid and thyroid hormones,* in contrast, circulate in the blood mainly bound to plasma proteins. Usually less than 10 percent of steroid or thyroid hormones in the plasma exist free in solution.

"Clearance" of Hormones from the Blood

Two factors can increase or decrease the concentration of a hormone in the blood. One of these is the rate of hormone secretion into the blood. The second is the rate of removal of the hormone from the blood, which is called the *metabolic clearance rate.* This is usually expressed in terms of the number of milliliters of plasma cleared of the hormone per minute.

- To calculate this clearance rate, one measures

(1) the rate of disappearance of the hormone from the plasma (e.g., nanograms per minute) and

(2) the plasma concentration of the hormone (e.g., nanograms per milliliter of plasma). Then, the metabolic clearance rate is calculated by the following

formula:

$$\text{Metabolic clearance rate} = \frac{\text{Rate of disappearance of hormone from the plasma}}{\text{Concentration of hormone}}$$

Hormones are “cleared” from the plasma in several ways, including

(1) metabolic destruction by the tissues,

(2) binding with the tissues,

(3) excretion by the liver into the bile, and

(4) excretion by the kidneys into the urine.

Mechanisms of Action of Hormones:

The first step of a hormone’s action is to bind to specific *receptors* at the target cell. When the hormone combines with its receptor, this usually initiates a cascade of reactions in the cell. Hormonal receptors are large proteins, and each cell that is to be stimulated usually has some 2000 to 100,000 receptors.

The locations for the different types of hormone receptors are generally the following:

1. *In or on the surface of the cell membrane.* The membrane receptors are specific mostly for the protein, peptide, and catecholamine hormones.

2. *In the cell cytoplasm.* The primary receptors for the different steroid hormones are found mainly in the cytoplasm.

3. *In the cell nucleus.* The receptors for the thyroid hormones are found in the nucleus and are believed to be located in direct association with one or more of the chromosomes.

[Date]

PHISOLOGY II

2nd. stage

LECT. 6

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Pituitary Gland

The Pituitary Gland has two distinct parts (the Anterior and Posterior Lobes) the pituitary gland (Figure 1), also called the ***hypophysis,*** is a small gland about 1 cm in diameter and (0.5 - 1) gm in weight that lies in the ***sella turcica,*** a bony cavity at the base of the brain, and is **connected** to the hypothalamus by the *pituitary* (or *hypophysial*) stalk. **Physiologically**, the pituitary gland is divisible into two distinct portions: the *anterior pituitary,* also known as the ***adenohypophysis,*** and the *posterior pituitary,* also known as the ***neurohypophysis***

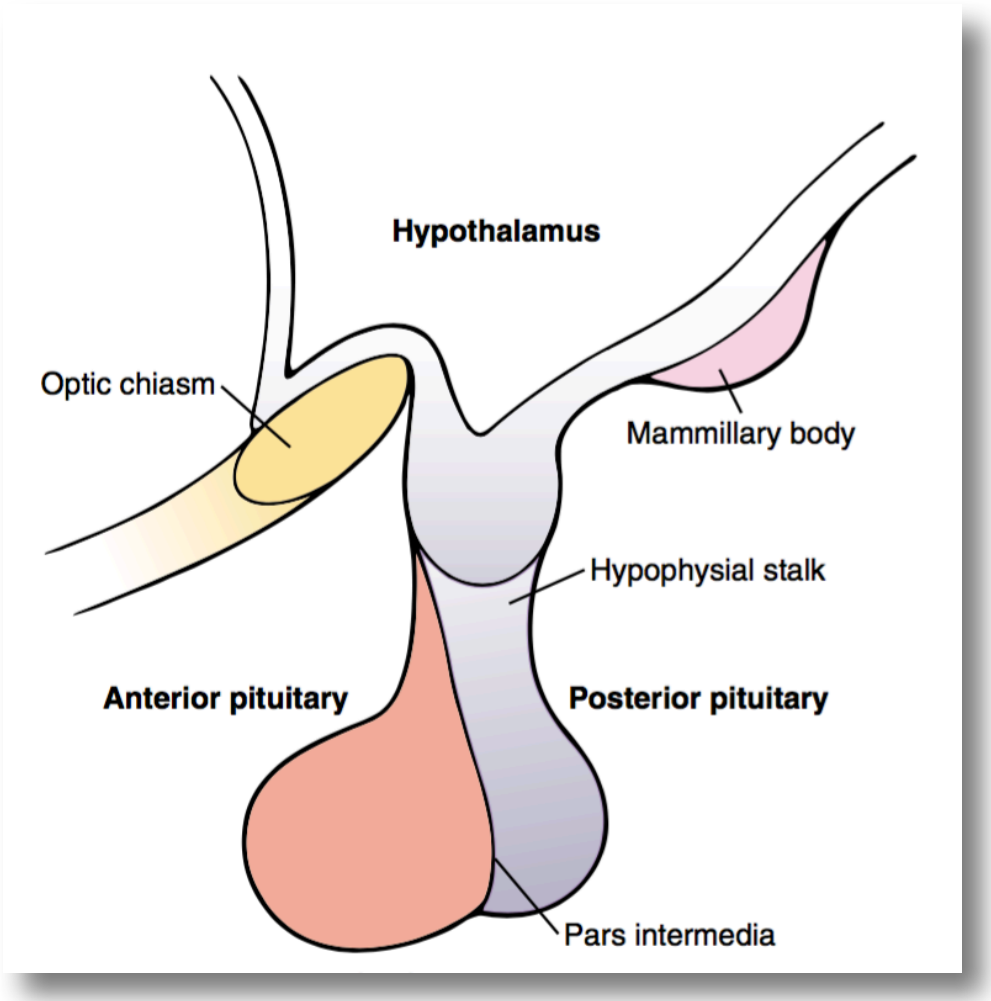


Figure 1

Between these is a small, relatively avascular zone called the pars intermedia, which is much less developed in the human being but is larger and much more functional in some lower animals.

Embryologically, the two portions of the pituitary originate from different sources—the anterior pituitary from Rathke's pouch (*hypophyseal diverticulum*), which is an embryonic invagination of the pharyngeal epithelium, and the posterior pituitary from a neural tissue outgrowth from the hypothalamus. The origin of the anterior pituitary from the pharyngeal epithelium explains the epithelioid nature of its cells, and the origin of the posterior pituitary from neural tissue explains the presence of large numbers of glial-type cells *(astrocytes, oligodendrocytes, and microglial cells)* in this gland.

Six important peptide hormones plus several hormones of lesser importance are secreted by the anterior pituitary, and **two** important peptide hormones are secreted by the posterior pituitary. The hormones of the anterior pituitary play major roles in the control of **metabolic** functions throughout the body, as shown in Figure 2.

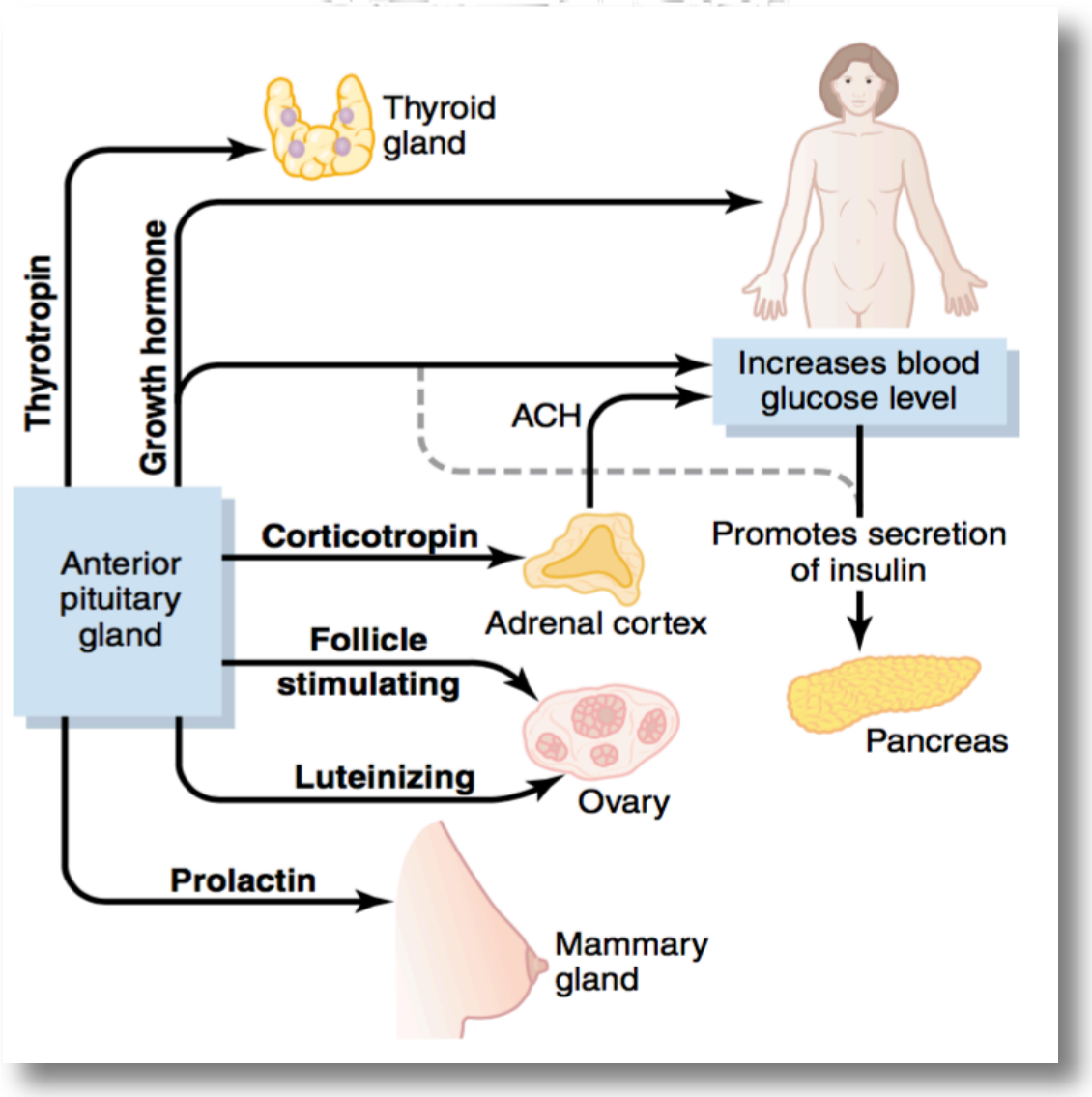


Figure 2

- *Growth hormone* promotes growth of the entire body by affecting protein formation, cell multiplication, and cell differentiation.
- *Adrenocorticotropin (corticotropin)* controls the secretion of some of the adrenocortical hormones, which affect the metabolism of glucose, proteins, and fats.
- *Thyroid-stimulating hormone (TSH) (thyrotropin)* controls the rate of secretion of thyroxine (T4) and triiodothyronine (T3) by the thyroid gland, and these hormones control the rates of most intracellular chemical reactions in the body.
- *Prolactin* promotes mammary gland development and milk production.
- *Two separate gonadotropic hormones, follicle-stimulating hormone (FSH)* and *luteinizing hormone (LH),* control growth of the ovaries and testes, as well as their hormonal and reproductive activities.

The two hormones secreted by the posterior pituitary play other roles.

- *Antidiuretic hormone (ADH)* (also called *vasopressin*) controls the rate of water excretion into the urine, thus helping to control the concentration of water in the body fluids.
- *Oxytocin* helps express milk from the glands of the breast to the nipples during suckling and helps in the delivery of the baby at the end of gestation.

Anterior Pituitary Gland Contains Several Different Cell Types That Synthesize and Secrete Hormones as shown in Table 1

Cell	Hormone	Chemistry	Physiological Action
Somatotropes	Growth hormone (GH; somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of IGF-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH; corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH; thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids) Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production

Table 1

The summary of these cell types, the hormones they produce, and their physiological actions. These five cell types are:

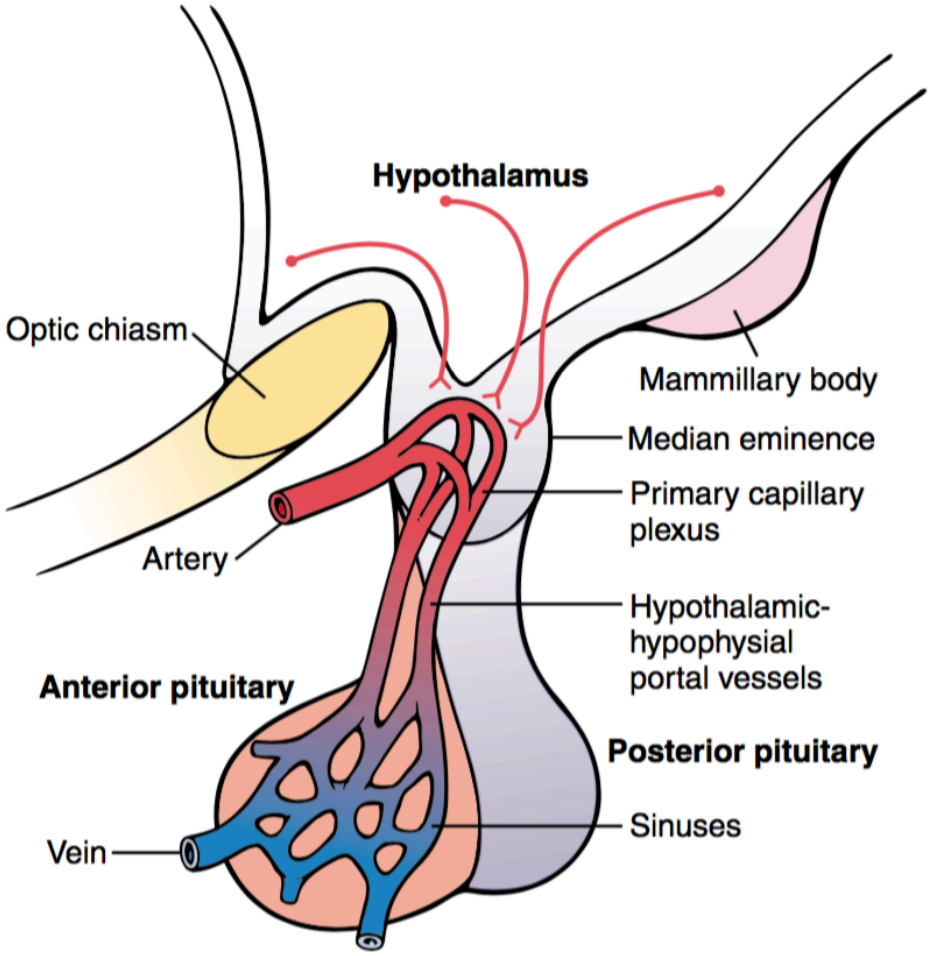
1. *Somatotropes* (30-40) % human growth hormone (hGH)
2. *Corticotropes* (20%) adrenocorticotropin (ACTH)
3. *Thyrotropes* (3-5) % thyroid-stimulating hormone (TSH)
4. *Gonadotropes* (3-5) % gonadotropic hormones, which include both luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
5. *Lactotropes* (3-5) % prolactin (PRL)

Posterior pituitary hormones are synthesized by cell bodies in the hypothalamus. The bodies of the cells that secrete the *posterior* pituitary hormones are not located in the pituitary gland itself but are large neurons, called ***magnocellular neurons***, located in the *supraoptic* and *paraventricular nuclei* of the hypothalamus. The hormones are then transported in the axoplasm of the neurons' nerve fibers passing from the hypothalamus to the posterior pituitary gland.

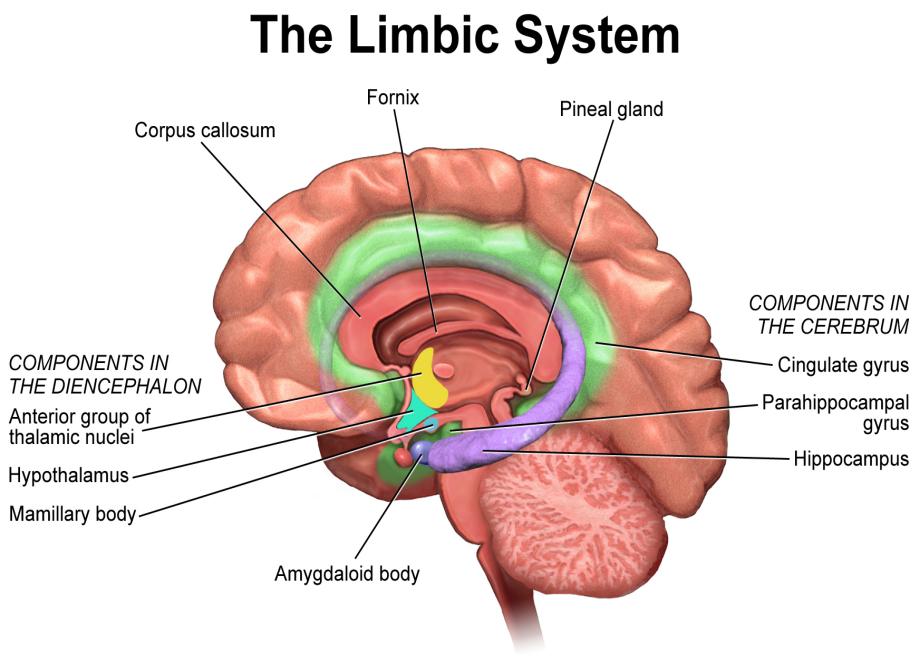
Hypothalamus Controls Pituitary Secretion:

All secretion by the pituitary is controlled by either hormonal or nervous signals from the hypothalamus. If we change the position of pituitary gland away from the hypothalamus, its rates of secretion of the different hormones fall to very low level (except for prolactin).

Secretion from the **posterior** pituitary is controlled by nerve signals that originate in the **hypothalamus** and terminate in the posterior pituitary. In contrast, secretion by the anterior pituitary is controlled by hormones called hypothalamic releasing and hypothalamic inhibitory hormones (or factors) secreted within the hypothalamus and then conducted to the anterior pituitary through minute blood vessels called hypothalamic-hypophysial portal vessels. In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion



The hypothalamus receives signals from many sources in the nervous system. Thus, when a person is exposed to pain, and a person experiences some powerful depressing or exciting thought, a portion of the pain signal is transmitted into the hypothalamus. Olfactory stimuli denoting pleasant or unpleasant smells transmit strong signal components directly and through the amygdaloid nuclei into the hypothalamus. Even the concentrations of nutrients, electrolytes, water, and various hormones in the blood excite or inhibit various portions of the hypothalamus. Thus, the hypothalamus is a collecting center for information concerning the internal well-being of the body, and **much** of this information is used to control secretions of the many globally important pituitary hormones.



The major hypothalamic releasing and inhibitory hormones are the following (Table 2):

7. *Thyrotropin-releasing hormone* (TRH), which causes release of thyroid-stimulating hormone (TSH).

8. *Corticotropin-releasing hormone* (CRH), which causes release of adrenocorticotropin (ACTH).

9. *Growth hormone–releasing hormone* (GHRH), which causes release of growth hormone, and *growth hormone inhibitory hormone* (GHIH), also called *somatostatin,* which inhibits release of growth hormone.

10. *Gonadotropin-releasing hormone* (GnRH), which causes release of the two gonadotropic hormones, *luteinizing hormone* (LH) and *follicle-stimulating hormone* (FSH).

11. *Prolactin inhibitory hormone* (PIH), which causes inhibition of *prolactin* secretion.

Hormone	Structure	Primary Action on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Peptide of 3 amino acids	Stimulates secretion of TSH by thyrotropes
Gonadotropin-releasing hormone (GnRH)	Single chain of 10 amino acids	Stimulates secretion of FSH and LH by gonadotropes
Corticotropin-releasing hormone (CRH)	Single chain of 41 amino acids	Stimulates secretion of ACTH by corticotropes
Growth hormone-releasing hormone (GHRH)	Single chain of 44 amino acids	Stimulates secretion of growth hormone by somatotropes
Growth hormone inhibitory hormone (somatostatin)	Single chain of 14 amino acids	Inhibits secretion of growth hormone by somatotropes
Prolactin-inhibiting hormone (PIH)	Dopamine (a catecholamine)	Inhibits synthesis and secretion of prolactin by lactotropes

Table 2

[Date]

PHISOLOGY II

2nd. stage

LECT. 7

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Thyroid Metabolic Hormones

The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea, is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults. The thyroid secretes two major hormones, *thyroxine* and *triiodothyronine,* commonly called T_4 and T_3 , respectively. Both of these hormones profoundly increase the metabolic rate of the body.

Complete lack of thyroid secretion usually causes the basal metabolic rate to fall 40 to 50 percent below normal, and extreme excesses of thyroid secretion can increase the basal metabolic rate to 60 to 100 percent above normal. Thyroid secretion is controlled primarily by *thyroid-stimulating hormone* (TSH) secreted by the anterior pituitary gland. It also secretes *calcitonin,* an important hormone for calcium metabolism

Synthesis and Secretion of the Thyroid Metabolic Hormones

About 93 % of the metabolically active hormones secreted by the thyroid gland is *thyroxine*, and 7 % *triiodothyronine.* Almost all the thyroxine is eventually converted to triiodothyronine in the tissues, so both are functionally important. Both of these hormones have the same functionally action, but they differ in rapidity and intensity of action. Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine.

Physiologic Anatomy of the Thyroid Gland

The thyroid gland is composed, as shown in Figure (1), of large numbers of closed *follicles* (100 to 300 micrometers in diameter) filled with a secretory substance called *colloid* and lined with *cuboidal epithelial cells* that secrete into the interior of the follicles. The major constituent of colloid is the large glycoprotein *thyroglobulin,* which contains the thyroid hormones. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can function in the body.

The thyroid gland has a blood flow about five times the weight of the gland each minute, which is a blood supply as great as that of any other area of the body, with the possible exception of the adrenal cortex. To form normal quantities of thyroxine, thyroid gland need about 50 mg of ingested iodine (iodides) are required *each year,* or about 1 mg/week. Iodides ingested orally are absorbed

from the gastrointestinal tract into the blood in about the same manner as chlorides.

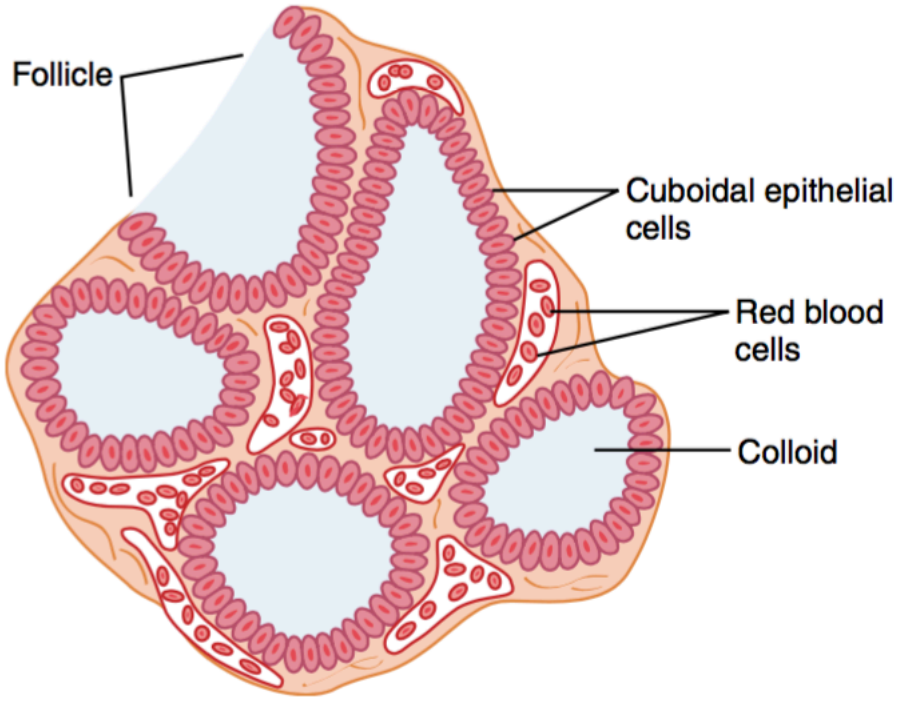


Figure (1) Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.

Normally, most of the iodides are rapidly excreted by the kidneys, but only 1/5 of the iodides pick up by the gland to synthesis thyroid hormones.

Iodide trapping:

Is the process of concentrating the iodide in the cell, in which the first stage in the formation of thyroid hormones, shown in figure 2, is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal mem- brane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is achieved by the action of a *sodium-iodide symporter* (NIS), which co-transports one iodide ion along with two sodium ions across the basolateral (plasma) membrane into the cell. The transport of iodide is active in which it exchanges with Na^+ by Na^+-K^+ ATPase. Normal gland pump concentrates the iodide to about 30 times its concentration in the blood, while

maximum action of the gland can rise to as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH; TSH stimulates and hypophysectomy greatly diminishes the activity of the iodide pump in thyroid cells.

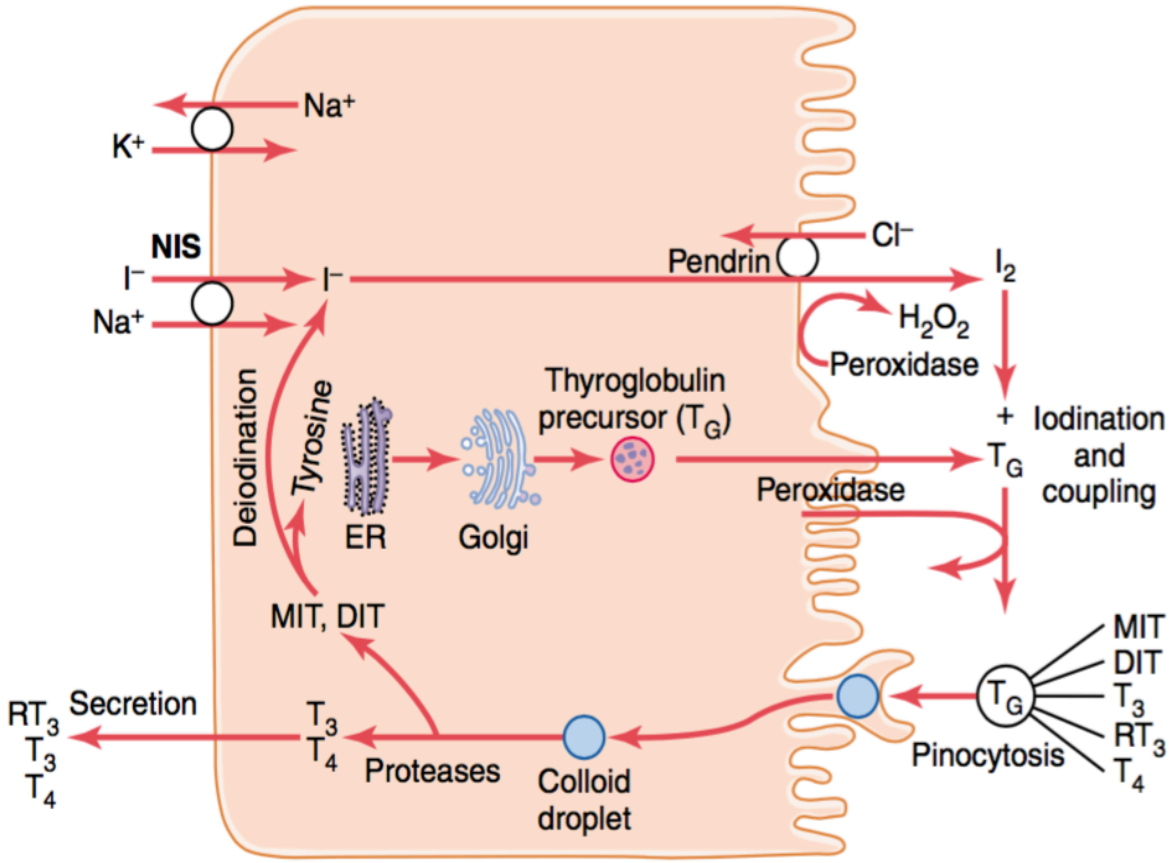
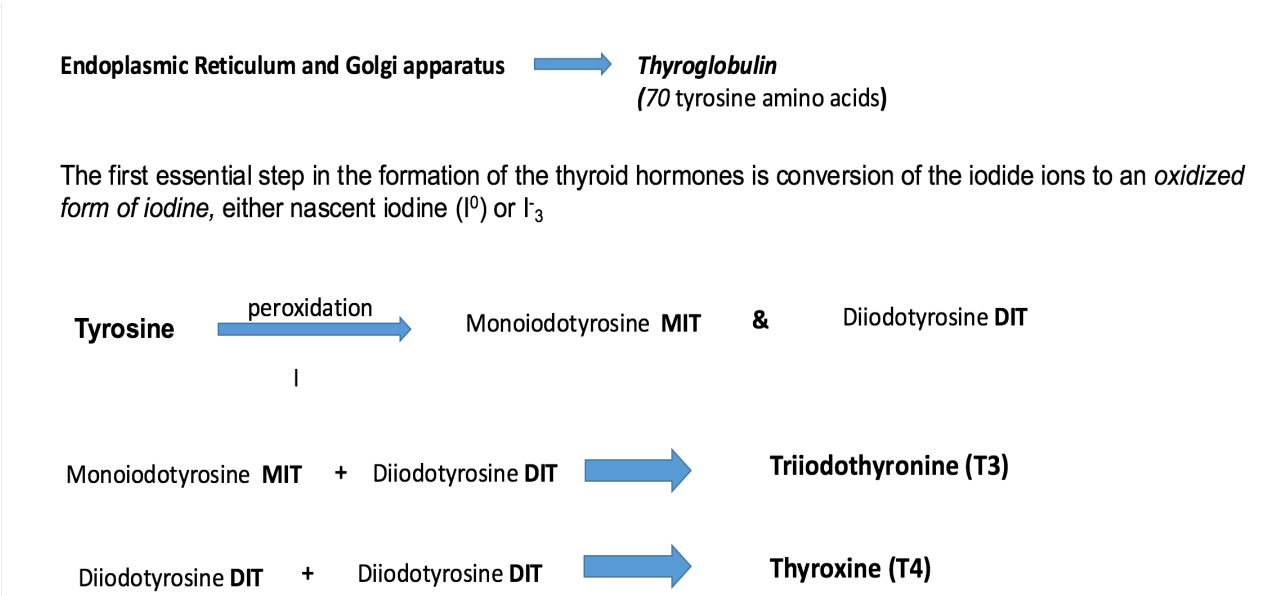


Figure (2): Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. DIT, diiodotyrosine; MIT, monoiodotyrosine; NIS, sodium-iodide symporter; RT_3, reverse triiodothyronine; T_3, triiodothyronine; T_4, thyroxine; T_G, thyroglobulin.



The binding of iodine with the thyroglobulin molecule is called *organification* of the thyroglobulin.

The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months.

Releasing of thyroid hormones:

Thyroglobulin itself is not released into the circulating blood in measurable amounts; instead, thyroxine and triiodothyronine must first be cleaved from the thyroglobulin molecule, and then these free hormones are released. This process occurs as follows: The apical surface of the thyroid cells sends out pseudopod extensions that close around small portions of the colloid to form ***pinocytic vesicles*** that enter the apex of the thyroid cell. Then *lysosomes* in the cell cytoplasm immediately fuse with these vesicles to form digestive vesicles containing digestive enzymes from the lysosomes mixed with the colloid. Multiple *proteases* among the enzymes digest the thyroglobulin molecules and

release thyroxine and triiodothyronine in free form. These then diffuse through the base of the thyroid cell into the surrounding capillaries. Thus, the thyroid hormones are released into the blood. The results of MIT & DIT are not secreted into blood but cleaved to tyrosine & iodine. Instead, their iodine is cleaved from them by a *deiodinase enzyme* that makes virtually all this iodine available again for recycling within the gland for forming additional thyroid hormones. T4 lose I^- to form T_3 by the action of deiodinase enzyme

Daily Rate of Secretion of Thyroxine and Triiodothyronine

About 93 % of the thyroid hormone released from the thyroid gland is normally thyroxine and only 7 % is triiodothyronine. during the ensuing few days, about one half of the thyroxine is slowly deiodinated to form additional triiodothyronine.

Thyroxine and Triiodothyronine Are Bound to Plasma Proteins

On entering the blood, more than 99 % of the thyroxine and triiodothyronine combines immediately with several of the plasma proteins, all of which are synthesized by the liver. They combine mainly with *thyroxine-binding globulin* and much less so with *thyroxine-binding prealbumin* and *albumin*.

Thyroxine and Triiodothyronine Are Released Slowly to Tissue Cells. Because of high affinity of the plasma-binding proteins for the thyroid hormones, these substances—in particular, thyroxine—are released to the tissue cells slowly. Half the thyroxine in the blood is released to the tissue cells about every 6 days, whereas half the triiodothyronine—because of its lower affinity— is released to the cells in about 1 day. On entering the tissue cells, both thyroxine and triiodothyronine again bind with intracellular proteins, the thyroxine binding more strongly than the triiodothyronine. Therefore, they are again stored, but this time in the target cells themselves, and they are used slowly over a period of days or weeks

Physiological Functions of the Thyroid Hormones

Thyroid Hormones Increase the Transcription of Large Numbers of Genes
The general effect of thyroid hormone is to activate nuclear transcription of large numbers of genes figure (3) Therefore, in virtually all cells of the body, great numbers of protein enzymes, structural proteins, transport proteins, and other substances are synthesized. The net result is generalized increase in functional

activity throughout the body.

Intracellular thyroid hormone receptors have a high affinity for triiodothyronine. Consequently, more than 90 percent of the thyroid hormone molecules that bind with the receptors is triiodothyronine. The thyroid hormone receptors are either attached to the DNA genetic strands or located in proximity to them. The thyroid hormone receptor usually forms a heterodimer with *retinoid X receptor* (RXR) at specific *thyroid hormone response elements* on the DNA. On binding with thyroid hormone, the receptors become activated and initiate the transcription process. Then large numbers of different types of messenger RNA are formed followed within another few minutes or hours by RNA translation on the cytoplasmic ribosomes to form hundreds of new intracellular proteins. It is believed that most of the actions of thyroid hormone result from the subsequent enzymatic and other functions of these new proteins. Thyroid hormones also appear to have *nongenomic* cellular effects that are independent of their effects on gene transcription. The site of nongenomic thyroid hormone action appears to be the plasma membrane, cytoplasm, and perhaps some cell organelles such as mitochondria. Nongenomic actions of thyroid hormone include the regulation of ion channels and oxidative phosphorylation and appear to involve the activation of intracellular secondary messengers such as cyclic AMP or protein kinase signaling cascades.

1. **Thyroid Hormones Increase Cellular Metabolic Activity**
   The thyroid hormones increase the metabolic activities of almost all the tissues of the body. The basal metabolic rate can increase to 60 to 100 percent above normal when large quantities of the hormones are secreted. The rate of utilization of foods for energy is greatly accelerated.
2. **Thyroid Hormones Increase Active Transport of Ions through Cell Membranes**. One of the enzymes that increases its activity in response to thyroid hormone is *Na-K-ATPase*. This in turn increases the rate of transport of both sodium and potassium ions through the cell membranes of some tissues Because this process uses energy and increases the amount of heat produced in the body, it has been suggested that this might be one of the mechanisms by which thyroid hormone increases the body's metabolic rate.
3. **Effect of Thyroid Hormone on Growth** Thyroid hormone has both general and specific effects on growth. the effect of thyroid hormone on growth is manifest mainly in growing children. In those who are

hypothyroid, the rate of growth is greatly retarded

4. **Effects of Thyroid Hormone on Specific Bodily Mechanisms**

A. Stimulation of carbohydrate metabolism.

B. Effect on plasma and liver fats

C. Increased requirement for vitamins.

D. Increased basal metabolic rate.

E. Decreased body weight.

F. Increased respiration**.**

G. Increased gastrointestinal motility.

H. Excitatory effects on the central nervous system.

I. Effect on the Function of the Muscles.

J. Muscle Tremor

K. Effect on Sleep, it is difficult to sleep.

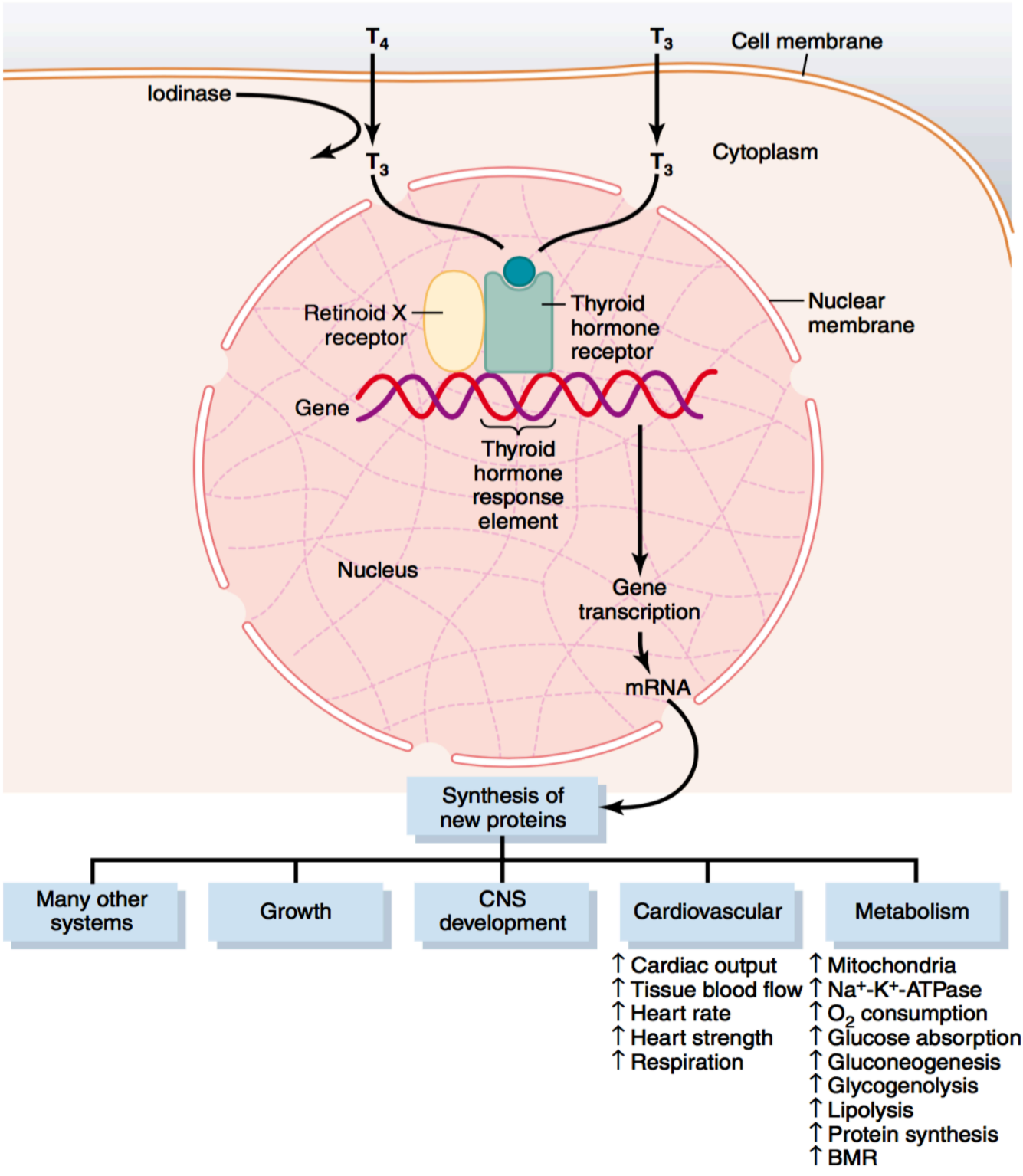

T4
T3
Cell membrane
Iodinase
T3
T3
Cytoplasm
Retinoid X receptor
Thyroid hormone receptor
Nuclear membrane
Gene
Thyroid hormone response element
Nucleus
Gene transcription
mRNA
Synthesis of new proteins
Many other systems
Growth
CNS development
Cardiovascular
Metabolism
↑ Cardiac output
↑ Tissue blood flow
↑ Heart rate
↑ Heart strength
↑ Respiration
↑ Mitochondria
↑ Na+-K+-ATPase
↑ O2 consumption
↑ Glucose absorption
↑ Gluconeogenesis
↑ Glycogenolysis
↑ Lipolysis
↑ Protein synthesis
↑ BMR

figure (3)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