FIFTH EDITION

TEXTBOOK OF MEDICAL PHYSIOLOGY

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trone, but such a hormone has never yet been identified as a specific entity. On the other hand, another hormone, *secretin*, which is released from the duodenum in response to certain foods (as will be discussed in detail in the following chapter) does have an important inhibitory effect on stomach contractions. Unfortunately, fats play a relatively minor role in the extraction of secretin from the mucosa of the duodenum.

For the present, therefore, it is difficult to account for the effect of fat in the duodenum in reducing stomach emptying, even though this effect is important to the process of fat digestion and fat absorption.

Role of Pyloric Sphincter Contraction in Stomach Emptying. Ordinarily, the degree of contraction of the pyloric sphincter is not very great, and the contraction that does occur is usually blocked as the pyloric pump peristaltic wave approaches the pylorus. However, many of the same duodenal factors that inhibit gastric contraction can simultaneously increase the degree of contraction of the pyloric sphincter, this factor adding to the diminished stomach emptying and therefore enhancing control over the emptying process. For instance, the presence of excess acid or excess irritation in the duodenal bulb promotes a moderate degree of pyloric contraction.

Effect of Fluidity of the Stomach Chyme on Emptying. Obviously, the more liquid the stomach chyme the greater will be the ease of emptying. Therefore, pure fluids ingested into the stomach have rapid passage into the duodenum, while more solid foods must await mixing with the gastric secretions as well as beginning fluidization of the solids by the process of stomach digestion.

Summary. Emptying of the stomach is controlled to a moderate degree by stomach factors, such as the degree of filling in the stomach and the activity of stomach peristalsis. Probably the more important control of stomach emptying, however, resides in feedback signals from the duodenum, including especially the enterogastric reflex and to a less extent hormonal feedback. These two feedback signals work together to slow the rate of emptying when (a) too much fluid is already in the small intestine or (b) the chyme is excessively acid, contains too much protein or fat, is hypotonic or hypertonic, or is irritating. In this way the rate of stomach emptying is limited to that amount of chyme that the small intestine can process.

MOVEMENTS OF THE SMALL INTESTINE

The movements of the small intestine, as elsewhere in the gastrointestinal tract, can be divided into the *mixing contractions* and the *propulsive contractions*. However, to a great extent this separation is artificial because essentially all movements of the small intestine cause at least some degree of both mixing and propulsion. Yet, the usual classification of these processes is the following:

MIXING CONTRACTIONS (SEGMENTATION CONTRACTIONS)

When a portion of the small intestine becomes distended with chyme, this elicits localized concentric contractions spaced at intervals along the intestine. These rhythmic contractions proceed at a rate of 11 to 12 per minute in the duodenum and at progressively slower rates down to approximately 7 per minute in the terminal ileum. The longitudinal length of each one of the contractions is only about 1 cm. so that each set of contractions causes "segmentation" of the small intestine, as illustrated in Figure 63–7, dividing the intestine at times into regularly spaced segments that have the appearance of a chain of sausages. As one set of segmentation contractions relaxes a new set begins, but the contractions this time occur at new points between the previous contractions. Therefore, the segmentation contractions "chop" the chyme many times a minute, in this way promoting progressive mixing of the solid food particles with the secretions of the small intestine.

These mixing movements are dependent mainly on the myenteric plexus of the gut,

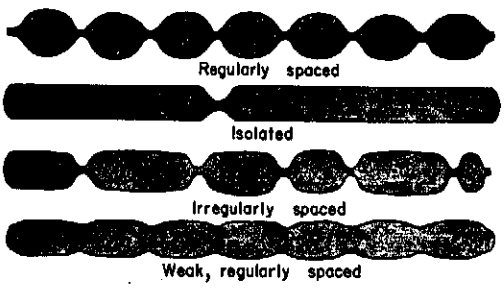
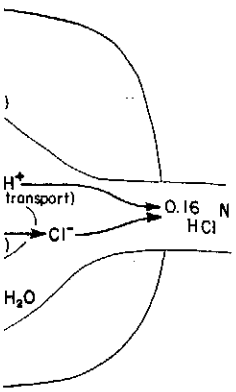


Figure 63–7. Segmentation movements of the small intestine.



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once pepsinogen is secreted and comes in contact with previously formed pepsin in the presence of hydrochloric acid, it is immediately activated to form active pepsin. In this process, the pepsinogen molecule having a molecular weight of 42,500 is split to the pepsin molecule having a molecular weight of 35,000.

Pepsin is an active proteolytic enzyme in a highly acid medium (optimum pH = 2.0), but above a pH of about 5 it has little proteolytic activity and soon becomes completely inactivated. Therefore, hydrochloric acid secretion is equally as necessary as pepsin secretion for protein digestion in the stomach.

Secretion of Other Enzymes. Small quantities of other enzymes are also secreted in the stomach juices, including *gastric lipase* and *gastric amylase*. Gastric lipase is of little quantitative importance and is actually a *tributyrase*, for its principal activity is on tributyrin, which is butterfat; it has almost no lipolytic activity on the other fats. Gastric amylase plays a very minor role in digestion of starches.

Secretion of Mucus in the Stomach. The pyloric and cardiac glands are structurally similar to the gastric glands, but contain almost no chief and parietal cells. Instead, they contain almost entirely mucous cells that are identical with the mucous neck cells of the gastric glands. All these cells secrete a thin mucus, which protects the stomach wall from digestion by the gastric enzymes.

In addition, the surface of the stomach mucosa between glands has a continuous layer of mucous cells that secrete large quantities of a far more *viscid and alkaline mucus* that coats the mucosa with a mucous gel layer over 1 mm. thick, thus providing a major shell of protection for the stomach wall as well as contributing to lubrication of food transport. Even the slightest irritation of the mucosa directly stimulates the mucous cells to secrete copious quantities of this thick, viscid mucus.

REGULATION OF GASTRIC SECRETION BY NERVOUS AND HORMONAL MECHANISMS

Gastric secretion is regulated by both nervous and hormonal mechanisms, nervous regulation being effected through the parasympathetic fibers of the vagus nerves as well as through local myenteric plexus reflexes and hormonal regulation taking place by means of the hormone *gastrin*. Thus, regulation of gastric secretion is different from the regulation of salivary secretion, which is effected entirely by nervous mechanisms.

Vagal Stimulation of Gastric Secretion

Nervous signals to cause gastric secretion originate in the dorsal motor nuclei of the vagi and pass via the vagus nerves to the myenteric plexus of the stomach and thence to the gastric glands. In response, these glands secrete vast quantities of both pepsin and acid, but with a higher proportion of pepsin than in gastric juice elicited in other ways. Also, vagal signals to the pyloric glands, the cardiac glands, and the mucous neck cells of the gastric glands cause some increase in secretion of mucus as well.

Still another effect of vagal stimulation is to cause the antral part of the stomach mucosa to secrete the hormone gastrin. As will be explained in the following paragraphs, this hormone then acts on the gastric glands to cause additional flow of highly acid gastric juice. Thus, vagal stimulation excites stomach secretion both directly by stimulation of the gastric glands and indirectly through the gastrin mechanism.

Stimulation of Gastric Secretion by Gastrin

When food enters the stomach, it causes the antral portion of the stomach mucosa to secrete the hormone gastrin, a heptadecapeptide. The food causes release of this hormone in two ways: (1) The actual bulk of the food distends the stomach, and this causes the hormone gastrin to be released from the antral mucosa. (2) Certain substances called secretagogues—such as food extractives, partially digested proteins, alcohol (in low concentration), caffeine, and so forth—also cause gastrin to be liberated from the antral mucosa.

Both of these stimuli—the distention and the chemical action of the secretagogues—elicit gastrin release by means of myenteric reflexes. That is, they stimulate sensory nerve fibers in the stomach epithelium which in turn synapse with the myenteric plexus. This then transmits efferent signals to special epithelial "gastrin" cells that have been identified in the gastric mucosa and that secrete the gastrin. Therefore, any factor that blocks this myenteric reflex will also block the formation of gastrin. For instance, anesthetization of the gastric mucosa to block the sensory stimuli will prevent gastrin release; administration of atropine, which blocks the action on the gastrin cells of the acetylcholine released by the myenteric plexus, will also prevent gastrin release.

Gastrin is absorbed into the blood and carried to the gastric glands where it stimulates mainly

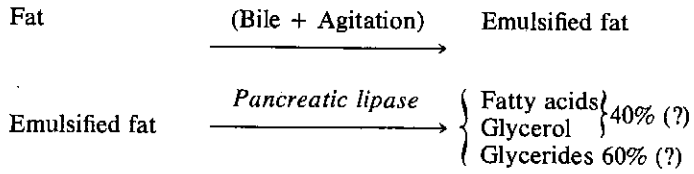


Figure 65–3. Digestion of fats.

Role of Bile Salts in Accelerating Fat Digestion—Formation of Micelles. The hydrolysis of triglycerides is a highly reversible process; therefore, accumulation of monoglycerides and free fatty acids in the vicinity of digesting fats very quickly blocks further digestion. Fortunately, the bile salts play an important role in removing the monosaccharides and the 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 have the propensity to form *micelles*, which are small spherical globules about 25 Angstroms in diameter and composed of 20 to 50 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 nuclei of the 20 to 50 bile salt molecules of the micelle aggregate together to form a small fat globule in the middle of the micelle. This aggregation causes the polar groups to project outward to cover the surface of the micelle. Since these polar groups are negatively charged, they allow the entire micelle globule to become dissolved in the water of the digestive fluids and to remain in stable solution despite the very large size of the micelle.

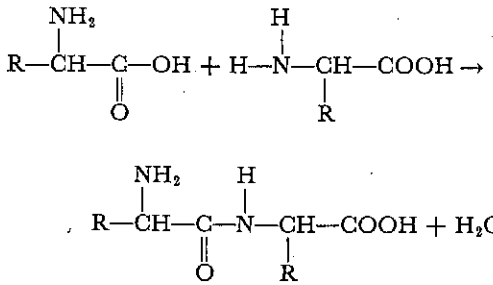
During the triglyceride digestion, as rapidly as the monoglycerides and free fatty acids are formed they become dissolved in the fatty portion of the micelles, which immediately removes these end-products of digestion from the vicinity of the digesting fat globules. Consequently, the digestive process can proceed unabated.

The bile salt micelles also act as a transport medium to carry the monoglycerides and the free fatty acids to the brush borders of the epithelial cells. There the monoglycerides and free fatty acids are absorbed, as will be discussed later. On delivery of these substances to the brush border, the bile salts are again released back into the chyme to be used again and again for this "ferrying" process.

Digestion of Cholesterol Esters. Most of the cholesterol in the diet is in the form of cholesterol esters, which cannot be absorbed in this form, though free cholesterol is readily absorbed. A *cholesterol esterase* in the pancreatic juice hydrolyzes the esters and thus frees the cholesterol. The bile salt micelles play identically the same role in "ferrying" cholesterol as they play in "ferrying" monoglycerides and free fatty acids. Indeed, this role of the bile salt micelles is absolutely essential to the absorption of cholesterol because essentially no cholesterol is absorbed without the presence of bile salts. On the other hand, as much as 60 per cent of the triglycerides can be digested and absorbed even in the absence of bile salts.

DIGESTION OF PROTEINS

The Proteins of the Diet. The dietary proteins are derived almost entirely from meats and vegetables. These proteins in turn are formed of long chains of amino acids bound together by *peptide linkages*. A typical linkage is the following:



The characteristics of each type of protein are determined by the types of amino acids in the protein molecule and by the arrangement of these amino acids. The physical and chemical characteristics of the different proteins will be discussed in Chapter 69.

Digestion of Proteins in the Stomach. Pepsin, the important peptic enzyme of the stomach, is most active at a pH of about 2 and is completely inactive at a pH above approximately 5. Consequently, for this enzyme to cause any digestive action on protein, the stomach juices must be acidic. It will be recalled from Chapter 64 that the gastric glands secrete a large quantity of hydrochloric acid. This hydrochloric acid is secreted by the parietal cells at a pH of about 0.8, but, by the time it is mixed with the stomach contents and with the secretions from the nonparietal glandular cells of the stomach, the pH ranges around 2 to 3, a highly favorable range of acidity for pepsin activity.

Pepsin is capable of digesting essentially all the different types of proteins in the diet. One of the important features of pepsin digestion is its ability to digest collagen, an albuminoid that is affected little by other digestive enzymes. Collagen is a major constituent of the intercellular connective tissue of meats, and for the digestive enzymes of the digestive tract to penetrate meats and digest the cellular proteins it is first necessary that the collagen fibers be digested. Consequently, in persons lacking peptic ac-

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formed as a result of bacterial action, and (3) gases that diffuse from the blood into the gastrointestinal tract.

Most gases in the stomach are nitrogen and oxygen derived from swallowed air, and a large proportion of these are expelled by belching.

Only small amounts of gas are usually present in the small intestine, and these are composed principally of air that passes from the stomach into the intestinal tract. In its transport through the small intestine, only 5 to 15 per cent of the air is absorbed, and a considerable amount of carbon dioxide actually diffuses from the blood into the air to bring it into equilibrium with the carbon dioxide of the tissue fluids.

In the large intestine, the greater proportion of the gases is derived from bacterial action; these gases include especially *carbon dioxide*, *methane*, and *hydrogen*. When the methane and hydrogen become suitably mixed with oxygen from swallowed air, an actual explosive mixture is occasionally formed.

Essentially all the gases in the large intestine are highly diffusible through the intestinal mucosa. Therefore, if the gases remain in the large intestine for many hours the final mixture contains approximately 75 per cent or more of nitrogen and little of the other gases. The reason for this is that nitrogen in the gut cannot easily be absorbed into the blood because of the high P_{N_2} already in the blood, as explained in Chapter 43. However, if the gases are passed on through the colon rapidly, the composition of the expelled flatus may be as little as 20 per cent nitrogen, with the remaining 80 per cent composed mainly of carbon dioxide, methane, and hydrogen.

Certain foods are known to cause greater expulsion of flatus from the large intestine than others—beans, cabbage, onions, cauliflower, corn, and certain highly irritant foods such as vinegar. Some of these foods serve as a suitable medium for gas-forming bacteria, especially because of unabsorbed fermentable types of carbohydrates, but in other instances excess gas results from irritation of the large intestine, which promotes rapid expulsion of the gases before they can be absorbed.

The amount of gases entering or forming in the large intestine each day averages 7 to 10 liters, whereas the average amount expelled is usually only about 0.5 liter. The remainder is absorbed through the intestinal mucosa. Most often, a person expels large quantities of gases not because of excessive bacterial activity but because of excessive motility of the large intestine, the gases being moved on through the large intestine before they can be absorbed.

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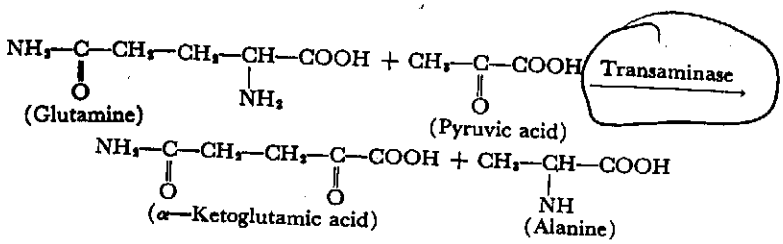


Figure 69–3. Synthesis of alanine from pyruvic acid by transamination.

transaminases, all of which are derivatives of pyridoxine, one of the B vitamins. Without this vitamin, the nonessential amino acids cannot be synthesized, and, therefore, protein formation cannot proceed normally.

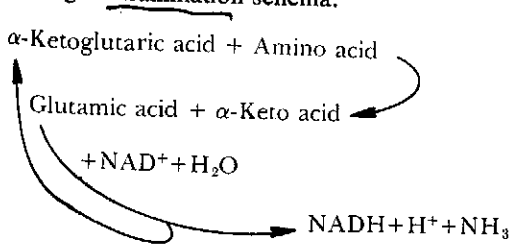
Formation of Proteins from Amino Acids. Once the appropriate amino acids are present in a cell, whole proteins are synthesized rapidly. However, each peptide linkage requires from 500 to 4000 calories of energy, and this must be supplied from ATP in the cell. Protein formation proceeds through two steps: (1) "activation" of each amino acid, during which the amino acid is "energized" by energy derived from ATP, and (2) alignment of the amino acids into the peptide chains, a function that is under control of the genetic system of each individual cell. Both of these processes were discussed in detail in Chapter 3. Indeed, the formation of cellular proteins is the basis of life itself and is so important that the reader would do well to review Chapter 3.

USE OF PROTEINS FOR ENERGY

It was pointed out earlier that there is an upper limit to the amount of protein that can accumulate in each particular type of cell. Once the cells are filled to their limits, any additional amino acids in the body fluids are degraded and used for energy or stored as fat. This degradation occurs almost entirely in the liver, and it begins with the process known as deamination.

Deamination. Deamination means removal of the amino groups from the amino acids. This can occur by several different means, two of which are especially important: (1) transamination, which means transfer of the amino group to some acceptor substance as explained above in relation to the synthesis of amino acids, and (2) oxidative deamination.

The greatest amount of deamination occurs by the following transamination schema:



Note from this schema that the amino group from the amino acid is transferred to α-ketoglutaric acid, which then becomes glutamic acid. The glutamic acid can then transfer the amino group to still other substances or can release it in the form of ammonia. In the process of losing the amino group, the glutamic acid once again becomes α-ketoglutaric acid, so that the cycle can be repeated again and again.

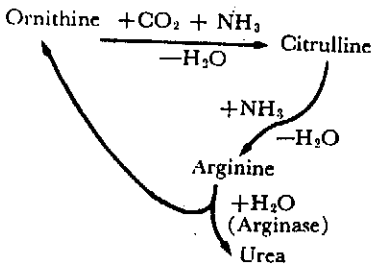
Oxidative deamination occurs to much less extent and is catalyzed by amino acid oxidases. In this process the amino acid is oxidized at the point where the amino radical attaches, which causes the amino radical to be released.

Urea Formation by the Liver. The ammonia released during deamination is removed from the blood almost entirely by conversion into urea, two molecules of ammonia and one molecule of carbon dioxide combining in accordance with the following net reaction:

$$2NH_3 + CO_2 \rightarrow H_2N{-}\underset{\underset{O}{\|}}{C}{-}NH_2 + H_2O$$

Essentially all urea formed in the human body is synthesized in the liver. In the absence of the liver or in serious liver disease, ammonia accumulates in the blood. This in turn is extremely toxic, especially to the brain, often leading to a state called *hepatic coma.*

The stages in the formation of urea are essentially the following:



The reaction begins with the amino acid derivative *ornithine*, which combines with one molecule of carbon dioxide and one molecule of ammonia to form a second substance, *citrulline*. This in turn combines with still another molecule of ammonia to form *arginine*, which then splits into *ornithine* and *urea*. The urea diffuses from the liver cells into the body fluids

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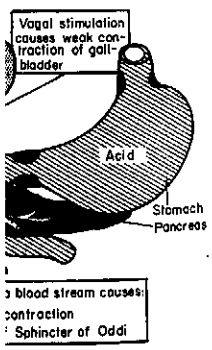


liver secretion and

TABLE 70–1. Composition of Bile

	Liver Bile	*Gallbladder Bile*
Water	97.5 gm. %	92 gm. %
Bile salts	1.1 gm. %	6 gm. %
Bilirubin	0.04 gm. %	0.3 gm. %
Cholesterol	0.1 gm. %	0.3 to 0.9 gm. %
Fatty acids	0.12 gm. %	0.3 to 1.2 gm. %
Lecithin	0.04 gm. %	0.3 gm. %
Na^+	145 mEq./l.	130 mEq./l.
K^+	5 mEq./l.	12 mEq./l.
Ca^+	5 mEq./l.	23 mEq./l.
Cl^-	100 mEq./l.	25 mEq./l.
HCO_3^-	28 mEq./l.	10 mEq./l.

lytes are reabsorbed by the gallbladder mucosa, but essentially all the other constituents, including especially the bile salts and lipid substances such as cholesterol, are not reabsorbed and therefore become highly concentrated in the gallbladder bile.

THE BILE SALTS AND THEIR FUNCTION

The liver cells form about 0.5 gram of *bile salts* daily. The precursor of the bile salts is *cholesterol*, which is either supplied in the diet or synthesized in the liver cells during the course of fat metabolism and then converted to *cholic acid* or *chenodeoxycholic acid* in about equal quantities. These acids then combine principally with glycine and to a lesser extent with taurine to form *glyco-* and *tauro-conjugated acids*. The salts of these acids are secreted in the bile.

The bile salts have two important actions in the intestinal tract. First, they have a detergent action on the fat particles in the food, which decreases the surface tension of the particles and allows the agitation in the intestinal tract to break the fat globules into minute sizes. This is called the *emulsifying* or *detergent function* of bile salts. Second, and even more important than the emulsifying function, bile salts help in the absorption of fatty acids, monoglycerides, cholesterol, and other lipids from the intestinal tract. They do this by forming minute complexes with the fatty acids and monoglycerides; the complexes are called *micelles*, and they are highly soluble because of the electrical charges of the bile salts. The lipids are "ferried" in this form to the mucosa where they are then absorbed; this mechanism was described in detail in Chapter 65. Without the presence of bile salts in the intestinal tract, up to 40 per cent of the lipids are lost into the stools, and the person often develops a metabolic deficit due to this nutrient loss.

Also, when fats are not absorbed adequately, the fat-soluble vitamins are not absorbed satisfactorily. Therefore, in the absence of bile salts, vitamins A, D, E, and K are poorly absorbed. Though large quantities of the first three of these vitamins are usually stored in the body, this is not true of vitamin K. Within only a few days after bile secretion ceases, the person usually develops a deficiency of vitamin K. This in turn results in deficient formation by the liver of several blood coagulation factors—prothrombin, and factors VII, IX, and X—thus resulting in serious impairment of blood coagulation.

Enterohepatic Circulation of Bile Salts. Approximately 94 per cent of the bile salts are reabsorbed by the intestinal mucosa in the distal ileum. They enter the portal blood and pass to the liver. On reaching the liver the bile salts are absorbed from the venous sinusoids into the hepatic cells and then resecreted into the bile. In this way about 94 per cent of all the bile salts are recirculated into the bile, so that on the average these salts make the entire circuit some 18 times before being carried out in the feces. The small quantities of bile salts lost into the feces are replaced by new amounts formed continually by the liver cells. This recirculation of the bile salts is called the *enterohepatic circulation*.

The quantity of bile secreted by the liver each day is highly dependent on the availability of bile salts—the greater the quantity of bile salts in the enterohepatic circulation (usually a total of about 4 gm.), the greater is the rate of bile secretion. When a bile fistula forms so that bile is lost directly from the common bile duct to the exterior, the bile salts cannot be reabsorbed. Therefore, the total quantity of bile salts in the enterohepatic circulation becomes greatly depressed, and concurrently the volume of liver secretion is also depressed.

However, if a bile fistula continues to empty the bile salts to the exterior for several days to several weeks, the liver increases its production of bile salts as much as 10-fold, which increases the rate of bile secretion approximately back to normal. This also demonstrates that the daily rate of bile salt secretion is actively controlled, though the mechanism of this control is unknown.

EXCRETION OF BILIRUBIN IN THE BILE

In addition to secreting substances synthesized by the liver itself, the liver cells also *excrete* a number of substances formed elsewhere in the body. Among the most important of these is *bilirubin*, which is one of the major end-products of hemoglobin decomposition, as was pointed out in Chapter 5.

Briefly, when the red blood cells have lived out their life span, averaging 120 days, and have become too fragile to exist longer in the circulatory system, their cell membranes rupture, and the released hemoglobin is phagocytized by reticuloendothelial cells throughout the body. Here, the hemoglobin is first split into *globin* and *heme*, and the heme ring is opened to give a straight chain of four pyrrole nuclei that is the substrate from which the bile pigments are formed. The first pigment formed is *biliverdin*, but this is rapidly reduced to *free bilirubin*, which is

luteinizing hormone, prolactin, and *melanocyte-stimulating hormone.*

Posterior pituitary hormones: *antidiuretic hormone (vasopressin)* and *oxytocin.*

Adrenocortical hormones: especially *cortisol* and *aldosterone.*

Thyroid hormones: *thyroxine, tri-iodothyronine,* and *calcitonin.*

Pancreatic hormones: *insulin* and *glucagon.*

Ovarian hormones: *estrogens* and *progesterone.*

Testicular hormone: *testosterone.*

Parathyroid hormone: *parathormone.*

Placental hormones: *chorionic gonadotropin, estrogens, progesterone,* and *human placental lactogen.*

Negative Feedback in the Control of Hormonal Secretion. At many points both in this chapter and in the succeeding few chapters we will see that once a hormone accomplishes its physiological function, its rate of secretion is prevented from increasing further and at times is even decreased. This is caused by negative feedback, a phenomenon we have seen to be important in nervous control systems. In general, each gland has a basic tendency to *oversecrete* its particular hormone, but, once the normal physiological effect of the hormone has been achieved, information is transferred either directly or indirectly back to the producing gland to inhibit further secretion. On the other hand, if the gland undersecretes, the physiological effects of the hormone diminish, and the feedback decreases, thus allowing the gland to begin secreting adequate quantities of the hormone once again. In this way, the rate of secretion of each hormone is controlled in accord with the need for the hormone. The specific negative feedback mechanisms are discussed in relation to the different individual hormones.

Chemistry of the Hormones. Chemically, the basic types of hormones are: (1) proteins or derivatives of proteins or amino acids and (2) steroid hormones. For example, the hormones of the pancreas and anterior pituitary are proteins or large polypeptides, while the hormones of the posterior pituitary, thyroid, and adrenal medulla are derivatives of proteins or amino acids. The steroids are secreted by the glands derived from the mesenchymal zone of the embryo, including the adrenal cortex, the ovary, and the testis.

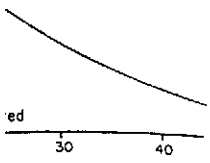
Measurement of Hormone Concentrations

Most hormones are present in the circulating body fluids and tissues in extremely minute quantities, some in concentrations as low as one-millionth of a milligram (one picogram) per milliliter. Therefore, except in a few instances, it has been almost impossible to measure these concentrations by usual chemical means. There are two important methods that have been employed for this purpose: (1) bioassay and (2) radioactive competitive binding methods.

Bioassay. Bioassay means developing an appropriate animal preparation in which one can test the action of the hormone on the animal. For instance, an appropriate bioassay for antidiuretic hormone is to measure the degree of water conservation caused by injecting plasma or a concentrated extract of the plasma from an experimental animal or human being into a test animal and to compare the animal's response with the response to a known quantity of pure antidiuretic hormone. In a similar manner, bioassay for growth hormone is based on stimulation of growth, usually of rats. Bioassays for gonadotropic hormones are based on their effects on the ovaries or other gonadotropic target tissues. By appropriate titration, a reasonable degree of accuracy can be achieved for most hormones but not for all, because appropriate animal models have not been achieved for all hormones.

Competitive Binding Assays—Radioimmunoassay. For measuring extremely low concentrations of hormones, a substance that specifically binds with the hormone is first found. For instance, antibodies can usually be developed that will bind specifically with a given hormone. Then a mixture is made of three different elements: (1) a fluid from the animal to be assayed, (2) the antibody, and (3) an approximate equivalent amount of purified hormone of the type to be measured but that has been tagged with a radioactive isotope. However, one specific condition must be met: There must be too little antibody for all of the hormone from the two separate sources to combine completely. Therefore, the natural hormone and the radioactive hormone *compete for the binding sites* on the antibody; the quantity of each hormone that will bind is proportional to its concentration. After binding is complete, the antibody–hormone complex is separated from the remainder of the solution, and the quantity of radioactive hormone that has bound with the antibody is measured by means of radioactive counting techniques. If a large amount of radioactive hormone has bound, then it is clear that there was only a small amount of natural hormone to compete. Conversely, if only a small amount of radioactive hormone has bound, it is clear that there was a very large amount of natural hormone to compete for the binding sites. Thus, by the use of an appropriate calibration curve, very precise measurements of the quantities of most hormones in body fluids can be achieved. As little as a fraction of a picogram (one-trillionth of a gram) of vasopressin per milliliter of assay fluid has been measured in this way.

Several other competitive binding techniques for assay of minute quantities of hormones have also been employed. One of these is to use—in place of the antibody—the specific carrier globulins of plasma



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Effect of Thyroid Hormones on the Cellular Enzyme Systems. Within a week or so following administration of the thyroid hormones, at least 100 and probably many more intracellular enzymes are increased in quantity. This may result from the direct effect of the thyroid hormones to cause generalized increase in protein synthesis. As an example, one enzyme, α-glycerophosphate dehydrogenase, can be increased to an activity six times its normal level. Since this enzyme is particularly important in the degradation of carbohydrates, its increase could help to explain the rapid utilization of carbohydrates under the influence of thyroxine. Also, the oxidative enzymes and the elements of the electron transport system, both of which are normally found in mitochondria, are greatly increased.

Effect of Thyroid Hormones on Mitochondria. When thyroxine or triiodothyronine is given to an animal, the mitochondria in most cells of the body increase in size and also in number. Furthermore, the total membrane surface of the mitochondria increases almost directly in proportion to the increased metabolic rate of the whole animal. Therefore, it is an obvious deduction that the principal function of thyroxine might be simply to increase the number and activity of mitochondria, and these in turn increase the rate of formation of ATP to energize cellular function. Unfortunately, though, the increase in number and activity of mitochondria could as well be the *result* of increased activity of the cells as be the cause of the increase.

When *extremely* high concentrations of thyroid hormones are administered, the mitochondria swell inordinately, and there is uncoupling of the oxidative phosphorylation process. However, under natural conditions, the concentration of thyroid hormones seems never to become high enough to cause this effect, even in human beings who have thyrotoxicosis.

Effect of Thyroid Hormone to Increase Cellular Cyclic AMP. Thyroid hormones increase cyclic AMP in some—perhaps all—cells of the body, but especially in muscle cells. Therefore, some physiologists believe that the primary action of the thyroid hormones might be simply to activate adenylcyclase, which in turn causes the formation of cyclic AMP. Then the cyclic AMP presumably acts as a *second messenger,* as was explained in the previous chapter, to initiate all or at least many of the intracellular functions of thyroid hormones.

Summary. It is clear that we know many specific events that occur in the cells throughout the body under the influence of the thyroid hormones. But it is equally clear that the basic mechanisms leading to all of these effects are still almost completely unknown.

EFFECTS OF THYROID HORMONE ON METABOLISM OF SPECIFIC DIETARY SUBSTANCES

Effect on Protein Metabolism and on Growth. The rates of both protein anabolism and catabolism are increased by thyroid hormone, which is the expected effect because of the increased enzymatic activities in the cells. Thus, thyroid hormone is necessary for development of structural and other proteins of the body cells and therefore is necessary for growth in the young person.

On the other hand, thyroid hormone causes rapid oxidation of carbohydrates and fats, and, when these "protein sparers" are depleted, proteins must be utilized for energy. As a result, a negative nitrogen balance then ensues. Thyroid hormone also has a specific effect on the tissues to "mobilize" protein and thereby release amino acids into the extracellular fluids. In addition to making these amino acids available for energy purposes, this effect also increases the rate of gluconeogenesis.

Effect on Bone Growth and Calcium Metabolism. Thyroid hormone increases the growth of bone in the same way that it increases growth of all other tissues of the body. This probably results from the effect of thyroid hormone to increase protein formation. On the other hand, thyroid hormone also causes rapid closure of the epiphyses. Therefore, a young person under the influence of thyroid hormone grows rapidly at first but then stops growing at a much younger age than his normal counterpart. Consequently, his final height may actually be less than normal.

Thyroid hormone also increases osteoclastic activity in the bones. When the concentration of the hormone is marked, the osteoclastic activity causes the bones to become porous, and greater than normal quantities of calcium and phosphate are emptied into the urine and excreted into the gastrointestinal tract. This same effect occurs when the rate of metabolism is increased as a result of fever, which indicates that the loss of calcium and phosphate from the bones following thyroid hormone administration could result simply from the increased rate of metabolism.

Effect on Carbohydrate Metabolism. Thyroid hormone stimulates almost all aspects of carbohydrate metabolism, including rapid uptake of glucose by the cells, enhanced glycolysis, enhanced gluconeogenesis, increased rate of absorption from the gastrointestinal tract, and even increased insulin se-

cretion with its resultant secondary effects on carbohydrate metabolism. All of these effects probably result from the overall increase in enzymes caused by thyroid hormone.

Effect on Fat Metabolism. Essentially all aspects of fat metabolism are also enhanced under the influence of thyroid hormone. However, since fats are the major source of long-term energy supplies, the fat stores of the body are depleted to a greater extent than are most of the other tissue elements; in particular, lipids are mobilized from the fat tissue, which increases the free fatty acid concentration in the plasma, and thyroid hormone also greatly accelerates the oxidation of free fatty acids by the cells.

Effect on Blood and Liver Fats. Increased thyroid hormone *decreases* the quantity of cholesterol, phospholipids, and triglycerides in the blood, even though it *increases* the free fatty acids. On the other hand, decreased thyroid secretion greatly increases the concentrations of cholesterol, phospholipids, and triglycerides and almost always causes excessive deposition of fat in the liver. The large increase in circulating blood lipids in prolonged hypothyroidism is always associated with severe arteriosclerosis, which was discussed in Chapter 68.

The cause of the reduced blood cholesterol induced by thyroid hormone is enhancement of its excretion into the gut and its conversion to bile acids by the liver.

Effect on Vitamin Metabolism. Because thyroid hormone increases the quantities of many of the different enzymes and because vitamins are essential parts of some of the enzymes or coenzymes, thyroid hormone causes increased need for vitamins. Therefore, a relative vitamin deficiency can occur when excess thyroid hormone is secreted, unless at the same time increased quantities of vitamins are available.

PHYSIOLOGIC EFFECTS OF THYROID HORMONE ON DIFFERENT BODILY MECHANISMS

Effect on Basal Metabolic Rate. Because thyroid hormone increases metabolism in most cells of the body (with the exception of the brain, retina, spleen, testes, and lungs), excessive quantities of the hormone can occasionally increase the basal metabolic rate to as much as 100 per cent above normal. However, in most patients with severe hyperthyroidism the basal metabolic rate ranges between 40 and 60 per cent above normal. On the other hand, when no thyroid hormone is produced, the basal metabolic rate falls almost to half normal; that is, the basal metabolic rate becomes −30 to −45, as discussed in Chapter 71. Figure 76–5 shows the approximate relationship between the daily supply of thyroid hormones and the basal metabolic rate. Extreme amounts of the hormones are required to cause very high basal metabolic rates.

Effect on Body Weight. Greatly increased thyroid hormone production almost always decreases the body weight, and greatly decreased production almost always increases the body weight; but these effects do not always occur, because thyroid hormone increases the appetite, and this may overbalance the change in the metabolic rate.

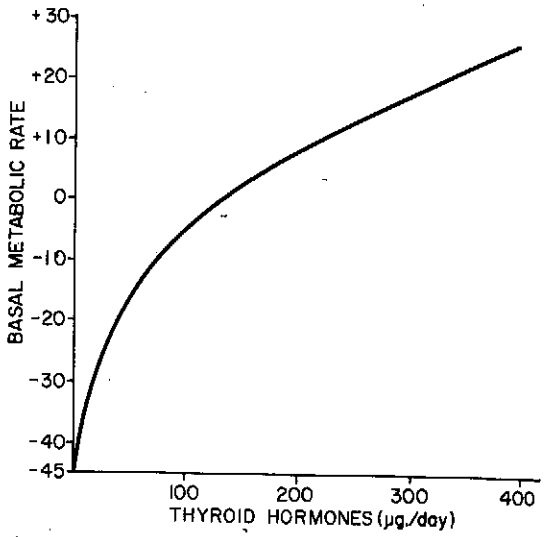

Figure 76–5. Relationship of thyroid hormone daily rate of secretion to the basal metabolic rate.

Effect on Growth. Because protein synthesis cannot occur normally in the absence of thyroid hormone, the growth effect of growth hormone from the pituitary gland is not significant without the concurrent presence of thyroid hormone in the body fluids. There are two conditions in which this effect on growth is especially evident: First, in growing children who are hypothyroid, the rate of growth is greatly retarded. Second, in growing children who are hyperthyroid, excessive skeletal growth often occurs, causing the child to become considerably taller than otherwise. However, the epiphyses close at an early age so that the eventual height of the adult may be shortened.

Effect on the Cardiovascular System. Because increased metabolism induced by thyroid hormone increases the demand of the tissues for nutrient substances, the following effects occur in the cardiovascular system in hyperthyroidism and the opposite effects occur in hypothyroidism:

Blood Flow and Cardiac Output. Increased metabolism in the tissues causes more rapid utilization of oxygen than normally and causes greater than normal quantities of metabolic end-products to be released from the tissues. These effects cause vasodilatation in most of the body tissues, thus increasing blood flow in almost all areas of the body. Especially does the rate of blood flow in the skin increase because of the increased necessity for heat elimination.

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