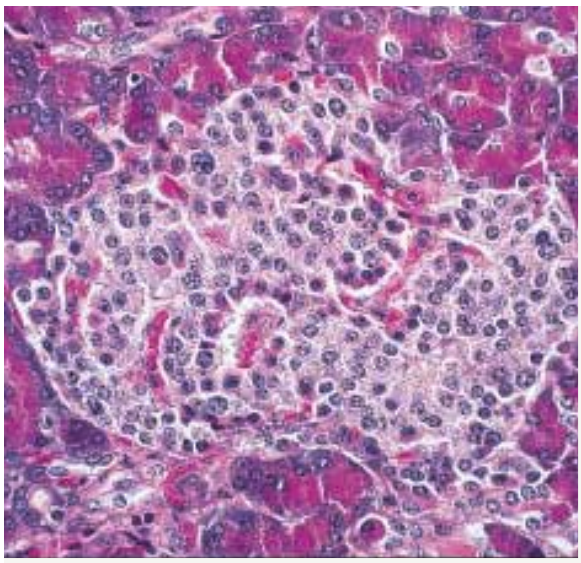

CHAPTER 18

Regulation of Organic Metabolism, Growth, and Energy Balance

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Chapter 4 introduced the concepts of energy and of organic metabolism at the level of the individual cell. This chapter deals with a variety of topics that are concerned in one way or another with those same concepts, but for the entire body. First we describe how the metabolic pathways for carbohydrate, fat, and protein are controlled so as to provide continuous sources of energy to the various tissues and organs at all times. The next topic is how the metabolic changes that underlie body growth occur and are controlled. Finally, we describe the determinants of total-body energy balance in terms of energy intake and output and how the regulation of body temperature is achieved.

SECTION A

CONTROL AND INTEGRATION OF CARBOHYDRATE, PROTEIN, AND FAT METABOLISM

Events of the Absorptive and Postabsorptive States

Mechanisms have evolved for survival during alternating periods of plenty and fasting. We speak of two functional states or periods: the **absorptive state,** during which ingested nutrients are entering the blood from the gastrointestinal tract, and the **postabsorptive state,** during which the gastrointestinal tract is empty of nutrients and energy must be supplied by the body's own stores. Since an average meal requires approximately 4 h for complete absorption, our usual three-meal-a-day pattern places us in the postabsorptive state during the late morning and afternoon and almost the entire night. We shall refer to going more than 24 h without eating as fasting.

During the absorptive period, some of the ingested nutrients supply the energy needs of the body, and the remainder are added to the body's energy stores, to be called upon during the next postabsorptive period. Total-body energy stores are adequate for the average person to easily withstand a fast of many weeks (provided that water is available).

Figures 18–1 and 18–2 summarize the major pathways to be described in this chapter. Although they may appear formidable at first glance, they should present little difficulty after we have described the component parts, and these figures should be referred to constantly during the following discussion.

Absorptive State

We shall assume, for this discussion, that an average meal contains all three of the major nutrients—carbohydrate, protein, and fat—with carbohydrate constituting most of the meal's energy content (calories). Recall from Chapter 17 that carbohydrate and protein are absorbed primarily as monosaccharides and amino acids, respectively, into the blood supplying the gastrointestinal tract. The blood leaves the gastrointestinal tract to go directly to the liver by way of the hepatic portal vein, allowing the liver to alter the nutrient composition of the blood before it returns to the heart to be pumped to the rest of the body. In contrast to carbohydrate and amino acids, fat is absorbed into the *lymph,* as triacylglycerols in chylomicrons; the lymph then drains into the systemic venous system. Thus, the liver does not get first crack at absorbed fat.

Absorbed Carbohydrate Some of the carbohydrate absorbed from the gastrointestinal tract is galactose and fructose, but since these sugars are either converted to glucose by the liver or enter essentially the same metabolic pathways as does glucose, we shall simply refer to absorbed carbohydrate as glucose.

Much of the absorbed glucose enters various body cells and is catabolized to carbon dioxide and water, providing the energy for ATP formation (Chapter 4). Indeed, and this is a key point, glucose is the body's major energy source during the absorptive state. In this regard, it should be recognized that skeletal muscle makes up the majority of body mass and is the major consumer of metabolic fuel, even at rest.

Skeletal muscle not only catabolizes glucose during the absorptive phase, but converts some of the glucose to the polysaccharide glycogen, which is then stored in the muscle.

Adipose-tissue cells (adipocytes) also catabolize glucose for energy, but the most important fate of glucose in adipocytes during the absorptive phase is its transformation to fat (triacylglycerols). Glucose is the precursor of both α-glycerol phosphate and fatty acids, and these molecules are then linked together to form triacylglycerols.

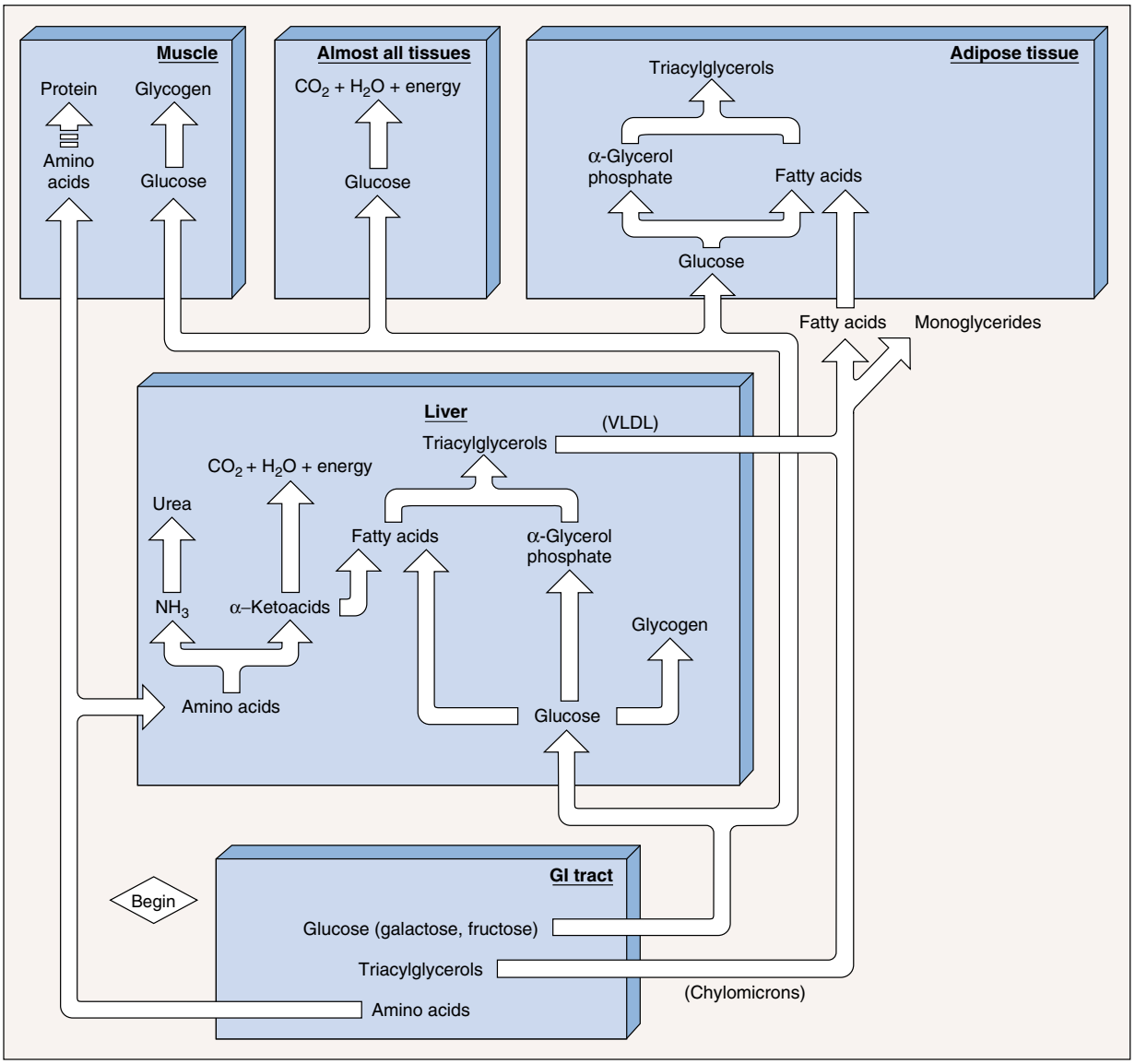

FIGURE 18–1

Major metabolic pathways of the absorptive state. The arrow from amino acids to protein in muscle is dashed to denote the fact that excess amino acids are not stored as protein (see text). All arrows between boxes denote transport of the substance via the blood. VLDL = very low density lipoproteins.

Another large fraction of the absorbed glucose enters the liver cells. This is a very important point: During the absorptive period, there is net *uptake* of glucose by the liver. It is either stored as glycogen, as in skeletal muscle, or transformed to α-glycerol phosphate and fatty acids, which are then used to synthesize triacylglycerols, as in adipose tissue. Some of the fat synthesized from glucose in the liver is stored there, but most is packaged, along with specific proteins, into molecular aggregates of lipids and proteins called lipoproteins. These aggregates are secreted by the liver cells and enter the blood. They are called **very low density lipoproteins (VLDL)** because they contain much more fat than protein, and fat is less dense than protein. The synthesis of VLDL by liver cells occurs by processes similar to those for synthesis of chylomicrons by intestinal mucosal cells, as described in Chapter 17.

Once in the bloodstream, VLDL complexes, being quite large, do not readily penetrate capillary walls. Instead, their triacylglycerols are hydrolyzed mainly to

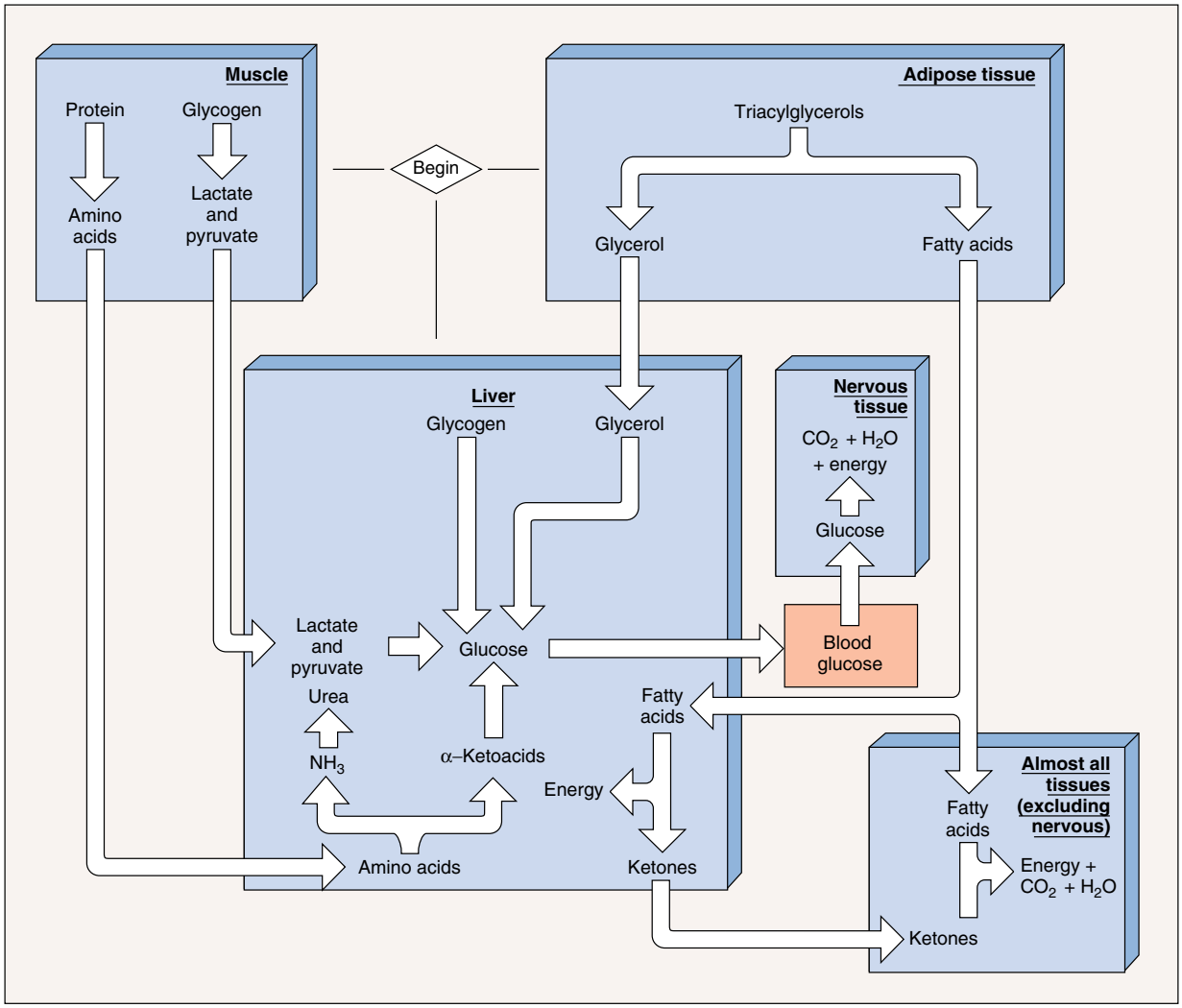

FIGURE 18–2
Major metabolic pathways of the postabsorptive state. The central focus is regulation of the blood glucose concentration. All arrows between boxes denote transport of the substance via the blood.

monoglycerides (glycerol linked to one fatty acid chain) and fatty acids by the enzyme **lipoprotein lipase,** which is located on the blood-facing surface of capillary endothelial cells, especially those in adipose tissue. In adipose-tissue capillaries, the fatty acids generated by this enzyme's action diffuse across the capillary wall and into the adipocytes. There they combine with α-glycerol phosphate, supplied by glucose metabolites, to form triacylglycerols once again. Thus, most of the fatty acids in the VLDL triacylglycerol originally synthesized from glucose by the *liver* end up being stored in triacylglycerol in *adipose tissue.* (The monoglycerides formed in the blood by the action of lipoprotein lipase in adipose-tissue capillaries circulate to the liver where they are metabolized.)

To summarize, the major fates of glucose during the absorptive phase are utilization for energy, storage as glycogen in liver and skeletal muscle, and storage as fat in adipose tissue.

Absorbed Triacylglycerols As described in Chapter 17, almost all absorbed chylomicrons enter the lymph, which flows into the systemic circulation. The biochemical processing of these chylomicron triacylglycerols in plasma is quite similar to that just described for VLDL produced by the liver. The fatty acids of plasma chylomicrons are released, mainly within adipose-tissue capillaries, by the action of endothelial lipoprotein lipase. The released fatty acids then enter adipocytes and combine with α-glycerol phosphate,

synthesized in the adipocytes from glucose metabolites, to form triacylglycerols.

The importance of glucose for triacylglycerol synthesis in adipocytes cannot be overemphasized. Adipocytes do not have the enzyme required for phosphorylation of glycerol, and so α-glycerol phosphate can be formed in these cells *only* from glucose metabolites and not from glycerol or any other fat metabolites.

In contrast to α-glycerol phosphate, there are three major sources of the fatty acids found in adipose-tissue triacylglycerol: (1) glucose that enters adipose tissue and is converted to fatty acids; (2) glucose that is converted in the liver to VLDL triacylglycerols, which are transported via the blood to the adipose tissue; and (3) ingested triacylglycerols transported to adipose tissue in chylomicrons. As we have seen, sources (2) and (3) require the action of lipoprotein lipase to release the fatty acids from the circulating triacylglycerols.

This description has emphasized the *storage* of ingested fat. For simplicity, we have not shown in Figure 18–1 that a fraction of the ingested fat is not stored but is oxidized during the absorptive state by various organs to provide energy. The relative amounts of carbohydrate and fat used for energy during the absorptive period depend largely on the content of the meal.

Absorbed Amino Acids A minority of the absorbed amino acids enter liver cells. They are used to synthesize a variety of proteins, including liver enzymes and plasma proteins, or they are converted to carbohydrate-like intermediates known as **α-ketoacids** by removal of the amino group (deamination, Chapter 4). The amino groups are used to synthesize urea, which enters the blood and is excreted by the kidneys. The α-ketoacids can enter the Krebs tricarboxylic acid cycle and be catabolized to provide energy for the liver cells, or they can be converted to fatty acids, thereby participating in fat synthesis by the liver.

Most ingested amino acids are not taken up by the liver cells, however, but enter other cells (Figure 18–1), where they may be used to synthesize proteins. We have simplified Figure 18–1 by showing "nonliver" amino acid uptake only by muscle, because muscle contains by far the largest amount of body protein. It should be emphasized, however, that all cells require a constant supply of amino acids for protein synthesis and participate in the dynamics of protein metabolism.

Protein synthesis is represented by a dashed arrow in the muscle box in Figure 18–1 to call attention to an important fact: There is a net synthesis of protein during the absorptive period, but this basically just replaces the proteins catabolized during the postabsorptive period. In other words, excess amino acids are not *stored* as protein in the sense that glucose is stored as glycogen or that both glucose and fat are stored as fat. Rather, ingested amino acids in excess of those needed to maintain a stable protein turnover are merely converted to carbohydrate or fat. Therefore, eating large amounts of protein does not in itself cause increases in body protein. This discussion does not apply to growing children, who manifest a continuous increase in body protein, or to adults who are actively building body mass as, for example, by weight lifting.

TABLE 18–1 Summary of Nutrient Metabolism during the Absorptive Period

1. Energy is provided primarily by absorbed carbohydrate.
2. There is net uptake of glucose by the liver.
3. Some carbohydrate is stored as glycogen in liver and muscle, but most carbohydrate and fat in excess of that utilized for energy are stored mainly as fat in adipose tissue.
4. There is some synthesis of body proteins, but many of the amino acids in dietary protein are utilized for energy or converted to fat.

Nutrient metabolism during the absorptive period is summarized in Table 18–1.

Postabsorptive State

As the absorptive period ends, net synthesis of glycogen, fat, and protein ceases, and net catabolism of all these substances begins to occur. The overall significance of these events can be understood in terms of the essential problem during the postabsorptive period: No glucose is being absorbed from the intestinal tract, yet the plasma glucose concentration must be maintained because the brain normally utilizes only glucose for energy. Too low a plasma glucose concentration can result in alterations of neural activity ranging from subtle impairment of mental function to coma and even death.

The events that maintain plasma glucose concentration fall into two categories: (1) reactions that provide sources of blood glucose, and (2) glucose sparing because of fat utilization.

Sources of Blood Glucose The sources of blood glucose during the postabsorptive period are as follows (Figure 18–2):

1. **Glycogenolysis,** the hydrolysis of glycogen stores, occurs in the liver and skeletal muscle. In the liver, glucose is formed by this process and enters the blood. Hepatic glycogenolysis, a rapidly occurring event, is the first line of defense in maintaining plasma glucose concentration. The amount of glucose available from this source, however, can supply the body's needs for only a few hours.

Glycogenolysis also occurs in skeletal muscle, which contains approximately the same amount of glycogen as the liver. However, muscle, unlike liver, lacks the enzyme necessary to form glucose from the glucose 6-phosphate formed during glycogenolysis (Chapter 4). Instead, the glucose 6-phosphate undergoes glycolysis within the muscle to yield pyruvate and lactate. These substances enter the blood, circulate to the liver, and are converted into glucose, which can then leave the liver cells to enter the blood. Thus, muscle glycogen contributes to the blood glucose indirectly via the liver.

2. The catabolism of triacylglycerols yields glycerol and fatty acids, a process termed **lipolysis.** The major site of lipolysis is adipose tissue, and the glycerol and fatty acids then enter the blood. The glycerol reaching the liver is converted to glucose. Thus, an important source of glucose during the postabsorptive period is the glycerol released when adipose-tissue triacylglycerol is broken down.
3. A few hours into the postabsorptive period, protein becomes the major source of blood glucose. Large quantities of protein in muscle and, to a lesser extent, other tissues can be catabolized without serious cellular malfunction. There are, of course, limits to this process, and continued protein loss during a prolonged fast ultimately means functional disintegration, sickness, and death. Before this point is reached, however, protein breakdown can supply large quantities of amino acids, particularly alanine, that enter the blood and are picked up by the liver, which converts them, via the α-ketoacid pathway, to glucose.

In items 1 through 3 above, we described the synthesis by the liver of glucose from pyruvate, lactate, glycerol, and amino acids. Synthesis from any of these precursors is known as **gluconeogenesis**—that is, "new formation of glucose." During a 24-h fast, gluconeogenesis provides approximately 180 g of glucose. (The liver is not the only organ capable of gluconeogenesis; the kidneys also perform gluconeogenesis, but mainly during a prolonged fast.)

Glucose Sparing (Fat Utilization) The 180 g of glucose per day produced by gluconeogenesis in the liver (and kidneys) during fasting supplies 720 kcal. As described later in this chapter, normal total energy expenditure for an average adult equals 1500 to 3000 kcal/day. Accordingly, gluconeogenesis cannot supply all the body's energy needs. The following essential adjustment must therefore take place during the transition from the absorptive to the postabsorptive state: Most organs and tissues markedly reduce their glucose catabolism and increase their fat utilization, the latter becoming the major energy source. This metabolic adjustment, termed **glucose sparing,** "spares" the glucose produced by the liver for use by the nervous system.

TABLE 18–2 Summary of Nutrient Metabolism during the Postabsorptive Period

1. Glycogen, fat, and protein syntheses are curtailed, and net breakdown occurs.
2. Glucose is formed in the liver both from the glycogen stored there and by gluconeogenesis from blood-borne lactate, pyruvate, glycerol, and amino acids. The kidneys also perform gluconeogenesis during a prolonged fast.
3. The glucose produced in the liver (and kidneys) is released into the blood, but its utilization for energy is greatly reduced in muscle and other nonneural tissues.
4. Lipolysis releases adipose-tissue fatty acids into the blood, and the oxidation of these fatty acids by most cells and of ketones produced from them by the liver provides most of the body's energy supply.
5. The brain continues to use glucose but also starts using ketones as they build up in the blood.

The essential step in this adjustment is lipolysis, the catabolism of adipose-tissue triacylglycerol, which liberates glycerol and fatty acids into the blood. We described lipolysis in the previous section in terms of its importance in providing *glycerol* to the liver for conversion to glucose. Now, we focus on the liberated *fatty acids,* which circulate bound to plasma albumin. [Despite this binding to protein, they are known as free fatty acids (FFA) in that they are "free" of glycerol.] The circulating fatty acids are picked up and metabolized by almost all tissues, *excluding the nervous system.* They provide energy in two ways (Chapter 4): (1) They first undergo beta-oxidation to yield hydrogen atoms (that go on to oxidative phosphorylation) and acetyl CoA; and (2) the acetyl CoA enters the Krebs cycle and is catabolized to carbon dioxide and water.

The liver is unique, however, in that most of the acetyl CoA it forms from fatty acids during the postabsorptive state does not enter the Krebs cycle but is processed into three compounds collectively called **ketones** (or ketone bodies). (Note that ketones are not the same as α-ketoacids, which, as we have seen, are metabolites of amino acids.) Ketones are released into the blood and provide an important energy source during prolonged fasting for the many tissues, *including the brain,* capable of oxidizing them via the Krebs cycle. One of the ketones is acetone, some of which is exhaled

and accounts for the distinctive breath odor of individuals undergoing prolonged fasting or, as we shall see, suffering from severe untreated diabetes mellitus.

The net result of fatty acid and ketone utilization during fasting is provision of energy for the body and sparing of glucose for the brain. Moreover, as just emphasized, the brain can use ketones for an energy source, and it does so increasingly as ketones build up in the blood during the first few days of a fast. The survival value of this phenomenon is very great: When the brain reduces its glucose requirement by utilizing ketones, much less protein breakdown is required to supply amino acids for gluconeogenesis. Accordingly, the protein stores will last longer, and the ability to withstand a long fast without serious tissue disruption is enhanced.

Table 18–2 summarizes the events of the postabsorptive period. The combined effects of glycogenolysis, gluconeogenesis, and the switch to fat utilization are so efficient that, after several days of complete fasting, the plasma glucose concentration is reduced by only a few percent. After 1 month, it is decreased only 25 percent.

Endocrine and Neural Control of the Absorptive and Postabsorptive States

We now turn to the endocrine and neural factors that control and integrate these metabolic pathways. We shall focus primarily on the following questions, summarized in Figure 18–3: (1) What controls net anabolism of protein, glycogen, and triacylglycerol in the absorptive phase, and net catabolism in the postabsorptive phase? (2) What induces primarily glucose utilization by cells for energy during the absorptive phase, but fat utilization during the postabsorptive phase? (3) What drives net glucose uptake by the liver during the absorptive phase, but gluconeogenesis and glucose release during the postabsorptive phase?

The most important controls of these transitions from feasting to fasting, and vice versa, are two pancreatic hormones—insulin and glucagon. Also playing a role are the hormone epinephrine, from the adrenal medulla, and the sympathetic nerves to liver and adipose tissue.

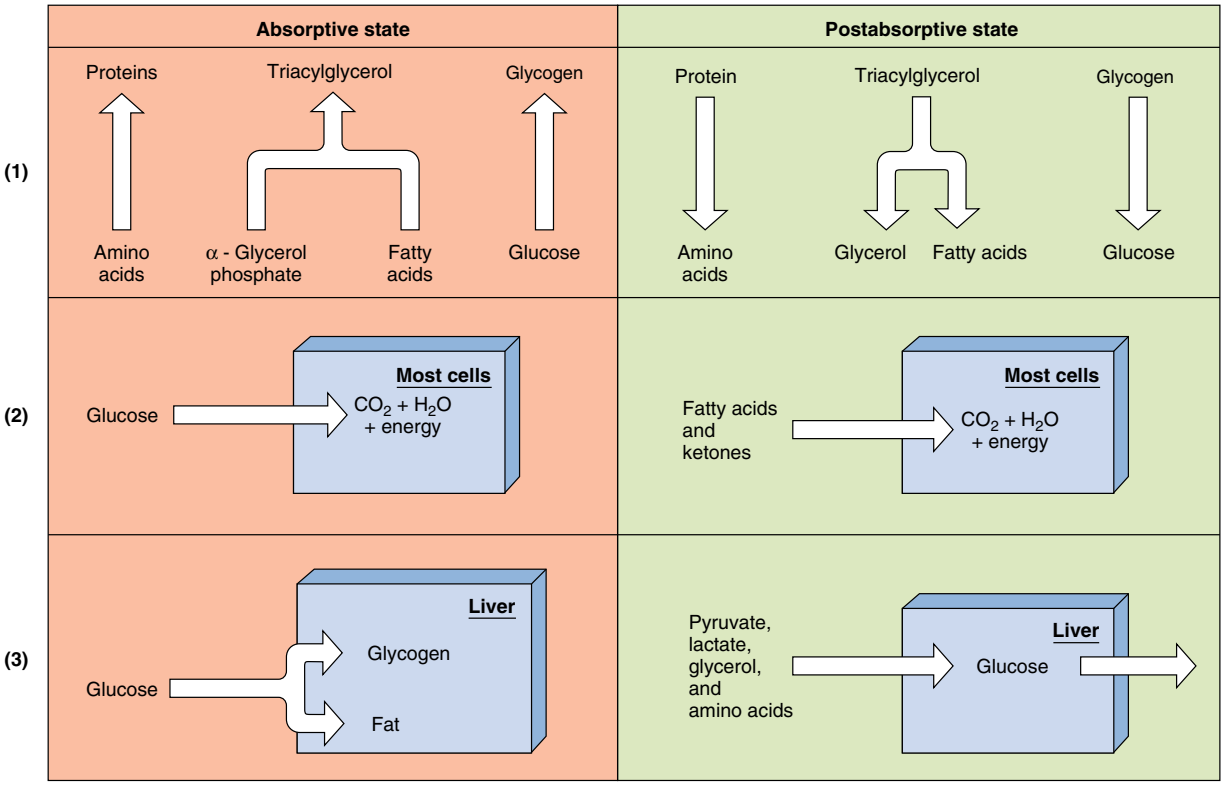

FIGURE 18–3

Summary of critical points in transition from the absorptive state to the postabsorptive state. The term "absorptive state" could be replaced with "actions of insulin," and the term "postabsorptive state" with "results of decreased insulin." The numbers at the left margin refer to discussion in the text.

Insulin and glucagon are peptides secreted by the **islets of Langerhans,** clusters of endocrine cells in the pancreas. Appropriate histological techniques reveal several distinct types of islet cells, each of which secretes a different hormone. The **beta cells** (or B cells) are the source of insulin, and the **alpha cells** (or A cells) of glucagon. (There is at least one other hormone—somatostatin—secreted by still other islet cells, but the function of this pancreatic hormone in human beings is not yet fully established.)

Insulin

Insulin is the most important controller of organic metabolism. Its secretion, and hence plasma concentration, are increased during the absorptive state and decreased during the postabsorptive state. For simplicity, insulin's many actions are often divided into two broad categories: (1) *metabolic effects* on carbohydrate, lipid, and protein synthesis, and (2) *growth-promoting effects* on DNA synthesis, cell division, and cell differentiation. This section deals only with the metabolic effects; the growth-promoting effects are described later in this chapter.

The metabolic effects of insulin are exerted mainly on muscle cells (both cardiac and skeletal), adipose-tissue cells, and liver cells. The most important responses of these target cells are summarized in Figure 18–4. Compare the top portion of this figure to Figure 18–1 and to the left panel of Figure 18–3 and you will see that these responses to an increase in insulin are the same as the events of the absorptive-state pattern. Conversely, the effects of a reduction in plasma insulin are the same as the events of the postabsorptive pattern in Figure 18–2 and the right panel of Figure 18–3. The reasons for these correspondences is that *an increased plasma concentration of insulin is the major cause*

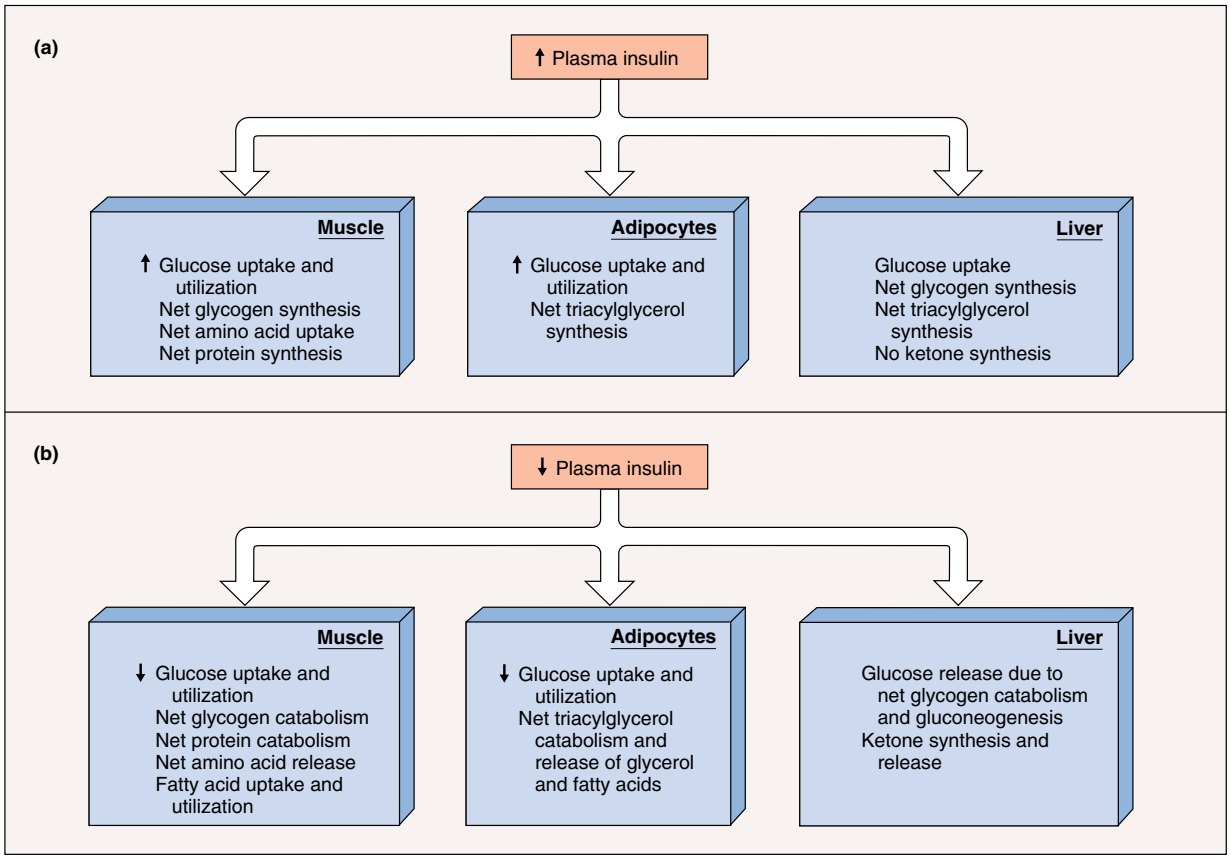

FIGURE 18–4

Summary of overall target-cell responses to (a) an increase or (b) a decrease in the plasma concentration of insulin. The responses in (a) are virtually identical to the absorptive state events of Figure 18–1 and the left panel of Figure 18–3; the responses in (b) are virtually identical to the postabsorptive state events of Figure 18–2 and the right panel of Figure 18–3. The biochemical events that underlie these responses to insulin are shown in Figure 18–6.

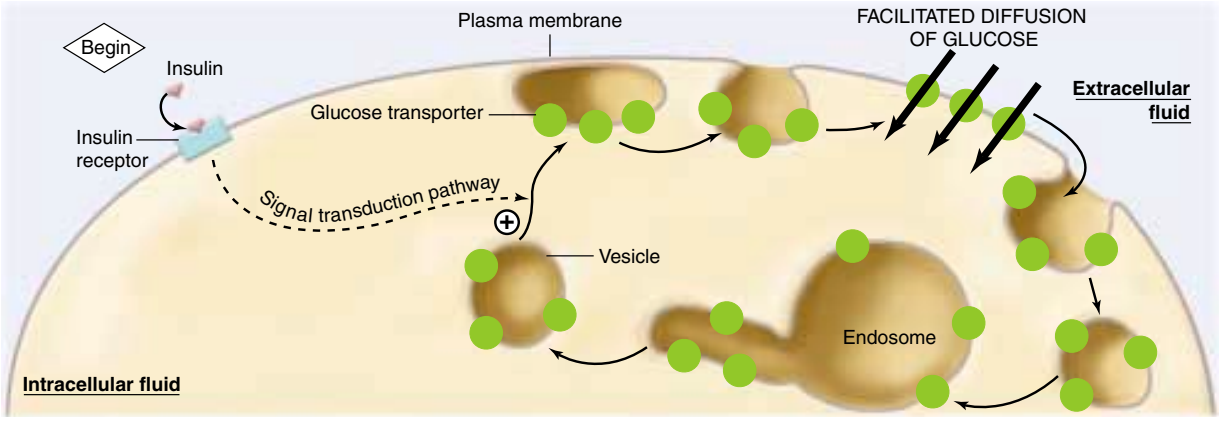

FIGURE 18–5
Stimulation by insulin of the translocation of glucose transporters from cytoplasmic vesicles to the plasma membrane in muscle cells and adipose-tissue cells. Note that these transporters are constantly recycled by endocytosis from the plasma membrane back through endosomes into vesicles. As long as insulin levels are elevated, the entire cycle continues and the number of transporters in the plasma membrane stays high. In contrast, when insulin levels decrease, the cycle is broken, the vesicles accumulate in the cytoplasm, and the number of transporters in the plasma membrane decreases.

of all the absorptive-state events, and a decreased plasma concentration of insulin is the major cause of all the postabsorptive events.

Like all peptide hormones, insulin induces its effects by binding to specific receptors in the plasma membrane of its target cells. This binding triggers a variety of signal transduction pathways that influence the target-cells' plasma-membrane transport proteins and intracellular enzymes. Thus, for example, in muscle cells and adipose-tissue cells an increased insulin concentration stimulates cytoplasmic vesicles that contain a particular type of glucose transporter (GLUT-4) in their membrane to fuse with the plasma membrane (Figure 18–5). The increased number of plasma-membrane glucose transporters resulting from this fusion then causes a greater rate of glucose movement from the extracellular fluid into the cells by facilitated diffusion. Recall from Chapter 6 that glucose enters virtually all cells of the body by facilitated diffusion; there are multiple subtypes of glucose transporters that mediate this process, however, and the subtype—GLUT-4—that is regulatable by insulin is found mainly in muscle and adipose-tissue cells.

A description of the many enzymes whose activities and/or concentrations are influenced by insulin is beyond the scope of this book, but the overall pattern is illustrated in Figure 18–6 for reference and to illustrate several principles. It is important here not to lose sight of the forest for the trees: The essential information (the "forest") to understand about insulin's actions is the target cells' ultimate responses—that is, the material summarized in Figure 18–4. Figure 18–6 merely shows some of the specific biochemical reactions (the "trees") that underlie these responses.

A major principle illustrated by Figure 18–6 is that, in *each* of its target cells, insulin brings about its ultimate responses by multiple actions. Let us take its effects on muscle cells as an example. In these cells, insulin favors glycogen formation and storage by (1) increasing glucose transport into the cell, (2) stimulating the key enzyme (glycogen synthase) that catalyzes the rate-limiting step in glycogen synthesis, and (3) inhibiting the key enzyme (glycogen phosphorylase) that catalyzes glycogen catabolism. Thus, insulin favors glucose transformation to and storage as glycogen in muscle through three pathways. Similarly, for protein synthesis in muscle cells, insulin (1) increases the number of active plasma-membrane transporters for amino acids, thereby increasing amino acid transportation to the cells, (2) stimulates the ribosomal enzymes that mediate the synthesis of protein from these amino acids, and (3) inhibits the enzymes that mediate protein catabolism.

Control of Insulin Secretion The major controlling factor for insulin secretion is the plasma glucose concentration. An increase in plasma glucose concentration, as occurs after a meal, acts on the pancreas to stimulate insulin secretion, whereas a decrease inhibits secretion. The feedback nature of this system is shown in Figure 18–7: Following a meal, the rise in plasma glucose concentration stimulates insulin secretion, and the insulin stimulates entry of glucose into muscle and adipose tissue, as well as net uptake, rather than net

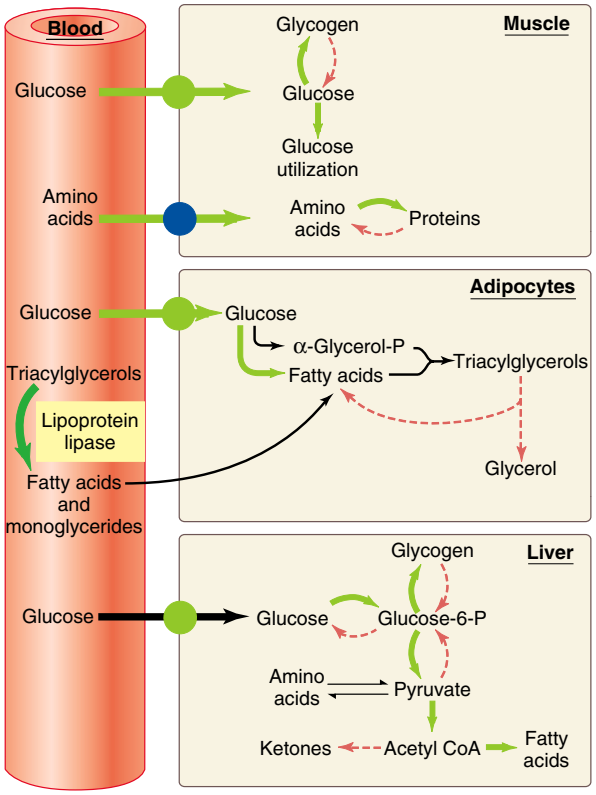

FIGURE 18–6

Reference illustration of the key biochemical events that underlie those responses of target cells to insulin summarized in Figure 18–4. Each green arrow denotes a process stimulated by insulin, whereas a dashed red arrow denotes inhibition by insulin. Except for the effects on the transport proteins for glucose and amino acids, all other effects are exerted on insulin-sensitive enzymes. The bowed arrows denote pathways whose reversibility is mediated by different enzymes (Chapter 4); such enzymes are commonly the ones influenced by insulin and other hormones. The black arrows are processes that are not *directly* affected by insulin but are enhanced in the presence of increased insulin as the result of mass-action.

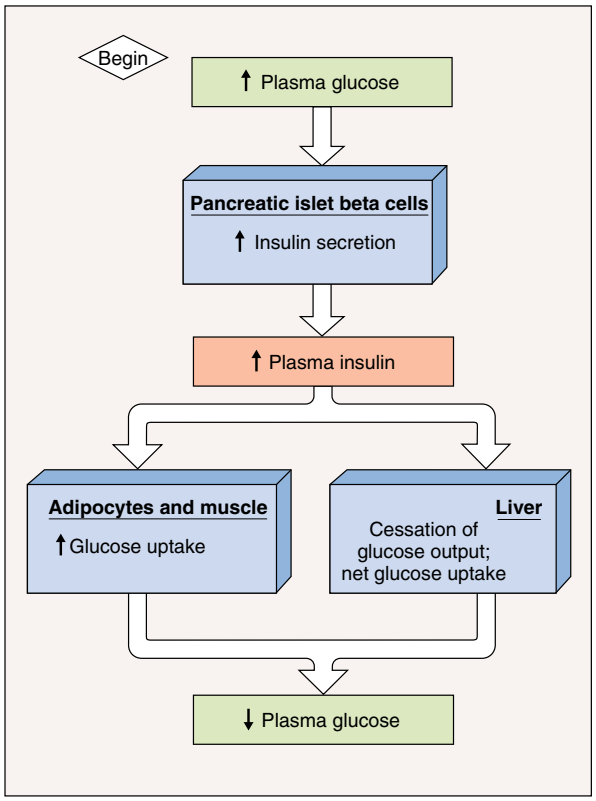

FIGURE 18–7

Nature of plasma glucose control over insulin secretion.

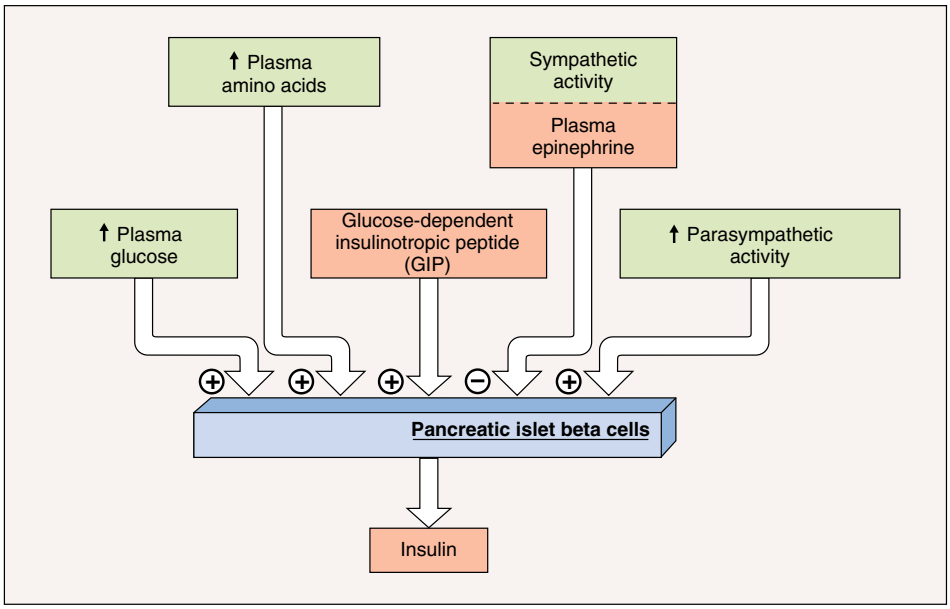

FIGURE 18–8
Major controls of insulin secretion. GIP is a gastrointestinal hormone.

output, of glucose by the liver. These effects eventually reduce the blood concentration of glucose to its premeal level, thereby removing the stimulus for insulin secretion, which returns to its previous level.

In addition to plasma glucose concentration, there are numerous other insulin-secretion controls (Figure 18–8). One is the plasma concentration of certain amino acids, an elevated amino acid concentration causing enhanced insulin secretion. This is another negative-feedback control: Amino acid concentrations increase after ingestion of a protein-containing meal, and the increased plasma insulin stimulates uptake of these amino acids by muscle (and other cells as well).

There are also important hormonal controls over insulin secretion. For example, a hormone—glucose-dependent insulinotropic peptide (GIP)—secreted by endocrine cells in the gastrointestinal tract in response to eating stimulates the release of insulin. This provides a feedforward component to glucose regulation during ingestion of a meal; thus insulin secretion rises earlier and to a greater extent than it would have if plasma glucose were the only controller.

Finally, the autonomic neurons to the islets of Langerhans also influence insulin secretion. Activation of the parasympathetic neurons, which occurs during ingestion of a meal, stimulates secretion of insulin and constitutes a second type of feedforward regulation. In contrast, activation of the sympathetic neurons to the islets or an increase in the plasma concentration of epinephrine (the hormone secreted by the adrenal medulla) inhibits insulin secretion. The significance of this relationship for the body's response to low plasma glucose **(hypoglycemia),** stress, and exercise—all situations in which sympathetic activity is increased—will be described later in this chapter.

To repeat, insulin plays the primary role in controlling the metabolic adjustments required for feasting or fasting. Other hormonal and neural factors, however, also play significant roles. They all oppose the action of insulin in one way or another and are known as **glucose-counterregulatory controls.** Of these, the most important is glucagon.

Glucagon

As noted earlier, **glucagon** is the peptide hormone produced by the alpha cells of the pancreatic islets. The major physiological effects of glucagon are all on the liver and are opposed to those of insulin (Figure 18–9): (1) increased glycogen breakdown, (2) increased gluconeogenesis, and (3) increased synthesis of ketones. Thus, the overall results of glucagon's effects are to increase the plasma concentrations of glucose and ketones, which are important for the postabsorptive period.

From a knowledge of these effects, one would logically suppose that glucagon secretion should increase during the postabsorptive period and prolonged fasting, and such is the case. The major stimulus for glucagon secretion at these times is hypoglycemia. The adaptive value of such a reflex is obvious: A decreasing

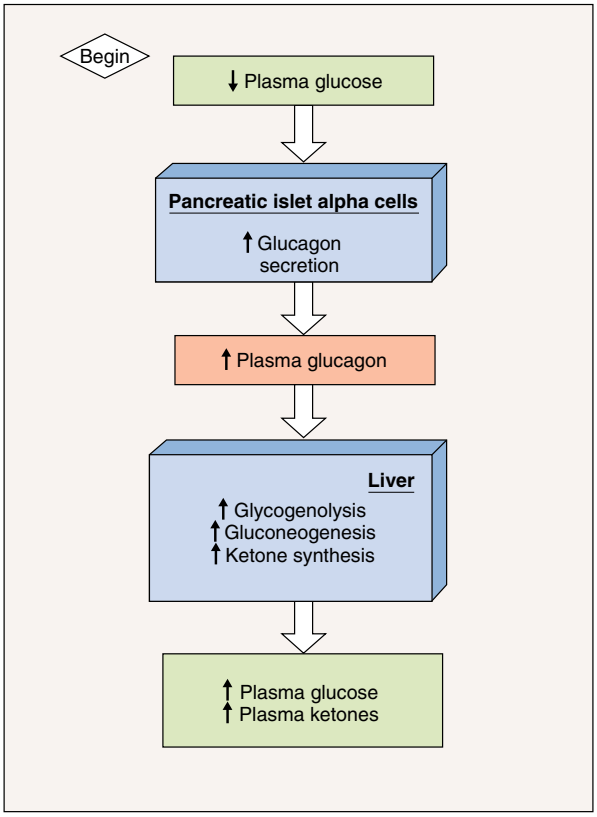

FIGURE 18–9
Nature of plasma glucose control over glucagon secretion.

plasma glucose concentration induces increased release of glucagon, which, by its effects on metabolism, serves to restore normal blood glucose concentration by glycogenolysis and gluconeogenesis while at the same time supplying (if the fast is prolonged) ketones for cell utilization. Conversely, an increased plasma glucose concentration inhibits glucagon's secretion, thereby helping to return the plasma glucose concentration toward normal. Thus, during the postabsorptive state plasma insulin concentration is low and plasma glucagon concentration is high, and this combined change accounts almost entirely for the transition from the absorptive to the postabsorptive state. Said in a different way, this shift is best explained by a rise in the glucagon: insulin ratio in the plasma.

The secretion of glucagon, like that of insulin, is controlled not only by the plasma concentration of glucose and other nutrients but also by neural and hormonal inputs to the islets. For example, the sympathetic nerves to the islets stimulate glucagon secretion—just the opposite of their effect on insulin secretion. The adaptive significance of this relationship for exercise and stress will be described subsequently.

Epinephrine and Sympathetic Nerves to Liver and Adipose Tissue

As noted earlier, epinephrine and the sympathetic nerves to the pancreatic islets inhibit insulin secretion and stimulate glucagon secretion. In addition, epinephrine also affects nutrient metabolism directly (Figure 18–10). Its major direct effects include stimulation of (1) glycogenolysis in both the liver and skeletal muscle, (2) gluconeogenesis in the liver, and (3) lipolysis in adipocytes. Activation of the sympathetic nerves to the liver and adipose tissue elicits essentially the same responses by these organs as does circulating epinephrine.

Thus, enhanced sympathetic nervous system activity exerts effects on organic metabolism—increased plasma concentrations of glucose, glycerol, and fatty acids—that are opposite those of insulin.

As might be predicted from these effects, hypoglycemia leads reflexly to increases in both epinephrine secretion and sympathetic-nerve activity to the liver and adipose tissue. This is the same stimulus that, as described above, leads to increased secretion of glucagon, although the receptors and pathways are totally different. When the plasma glucose concentration decreases, glucose receptors in the central nervous system (and, possibly, the liver) initiate the reflexes that lead to increased activity in the sympathetic pathways to the adrenal medulla, liver, and adipose tissue. The adaptive value of the response is the same as that for the glucagon response to hypoglycemia: Blood glucose returns toward normal, and fatty acids are supplied for cell utilization.

In the compensatory response to *acute* hypoglycemia, the increased activity of the sympathetic nervous system is less important than a reduced insulin concentration and an increased glucagon concentration, but nevertheless contributes. In contrast, sympathetic nervous system activity *decreases* during *prolonged* fasting or ingestion of low-calorie diets; the adaptive significance of this change—reduction of the body's rate of energy utilization—is discussed later in this chapter.

Other Hormones

In addition to the three hormones already described in this section, there are many others that have various effects on organic metabolism. The secretion of all these other hormones, however, is not primarily keyed to the transitions between the absorptive and postabsorptive states. Instead, their secretion is controlled by other factors, and these hormones are for the most part involved in homeostatic processes described elsewhere in this book. Nonetheless, the effects of two of them—cortisol and growth hormone—on nutrient metabolism are important enough to warrant description here.

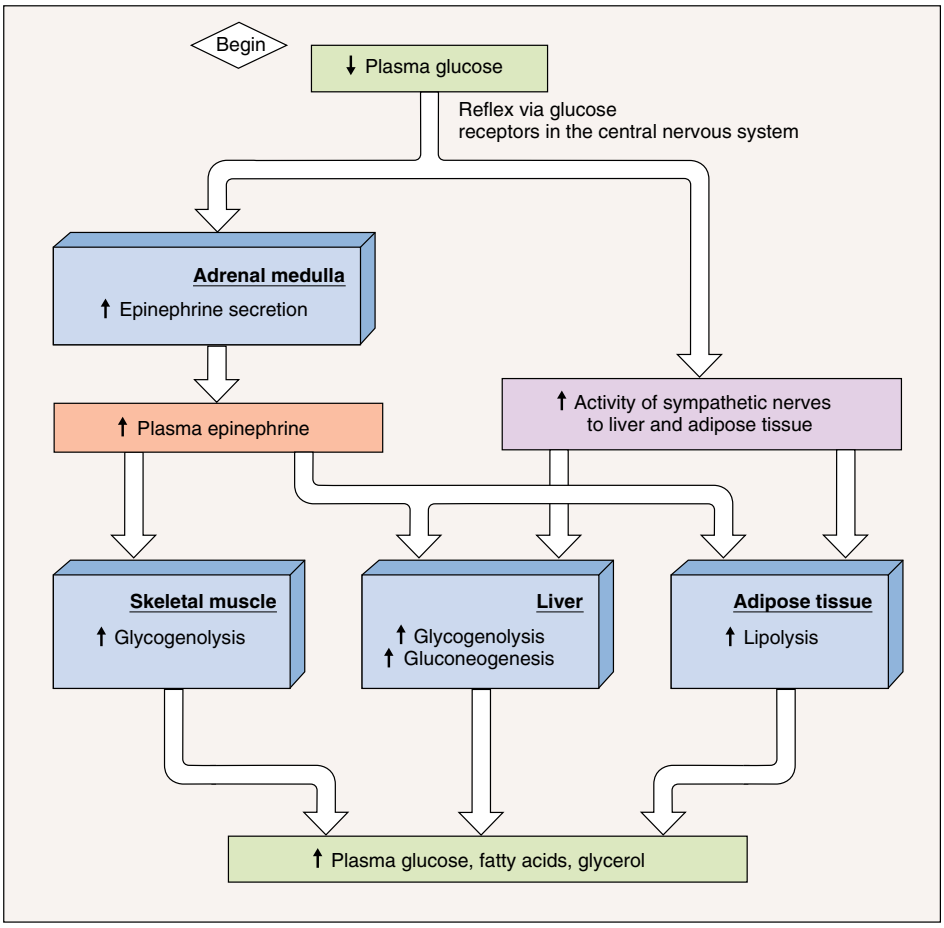

FIGURE 18–10
Participation of the sympathetic nervous system in the response to a low plasma glucose concentration (hypoglycemia). Glycogenolysis in skeletal muscle contributes to increased plasma glucose by releasing lactate and pyruvate, which are converted to glucose in the liver.

Cortisol Cortisol, the major glucocorticoid produced by the adrenal cortex, plays an essential "permissive" role in the adjustments to fasting. We have described how fasting is associated with stimulation of both gluconeogenesis and lipolysis; however, neither of these critical metabolic transformations occurs to the usual degree in a person deficient in cortisol. In other words, the plasma cortisol level need not *rise* during fasting and usually does not, but the presence of even small amounts of cortisol in the blood somehow maintains the concentrations of the key liver and adipose-tissue enzymes required for gluconeogenesis and lipolysis. Therefore, in response to fasting, people with a cortisol deficiency develop hypoglycemia serious enough to interfere with brain function.

Moreover, cortisol can play more than a permissive role when its plasma concentration does increase, as occurs during stress (Chapter 20). In high concentration, cortisol elicits many metabolic events ordinarily associated with fasting (Table 18–3). Clearly, here is another hormone, in addition to glucagon and epinephrine, that can exert actions opposite those of insulin. Indeed, persons with very

TABLE 18–3 Effects of Cortisol on Organic Metabolism

1. Basal concentrations are permissive for stimulation of gluconeogenesis and lipolysis in the postabsorptive state
2. Increased plasma concentrations cause:
   a. Increased protein catabolism
   b. Increased gluconeogenesis
   c. Decreased glucose uptake by muscle cells and adipose-tissue cells
   d. Increased triacylglycerol breakdown

Net result: Increased plasma concentrations of amino acids, glucose, and free fatty acids

TABLE 18-4 Summary of Glucose-Counterregulatory Controls*

	Glucagon	Epinephrine	Cortisol	Growth Hormone
Glycogenolysis	√	√		
Gluconeogenesis	√	√	√	√
Lipolysis		√	√	√
Inhibition of: glucose uptake by muscle cells and adipose-tissue cells			√	√

*A √ indicates that the hormone stimulates the process; no √ indicates that the hormone has no major physiological effect on the process. Epinephrine stimulates glycogenolysis in both liver and skeletal muscle, whereas glucagon does so only in liver.

high plasma levels of cortisol, due either to abnormally high secretion or to cortisol administration for medical reasons (Chapter 20), can develop symptoms similar to those seen in individuals with insulin deficiency.

Growth Hormone The primary physiological effects of growth hormone are to stimulate both growth and protein anabolism, as described later in this chapter. Compared to these effects, those it exerts on carbohydrate and lipid metabolism are minor. Nonetheless, as is true for cortisol, either severe deficiency or marked excess of growth hormone does produce significant abnormalities in lipid and carbohydrate metabolism. Growth hormone's effects on these nutrients, in contrast to those on protein metabolism, are similar to those of cortisol and opposite those of insulin. Growth hormone (1) renders adipocytes more responsive to lipolytic stimuli, (2) increases gluconeogenesis by the liver, and (3) reduces the ability of insulin to cause glucose uptake by muscle and adipose tissue. These three effects are often termed growth hormone's "anti-insulin effects."

Summary of Hormonal Controls

To a great extent, insulin may be viewed as the "hormone of plenty." Its secretion and plasma concentration are increased during the absorptive period and decreased during postabsorption, and these changes are adequate to cause most of the metabolic changes associated with these periods. In addition, opposed in various ways to insulin's effects are the actions of four major glucose-counterregulatory controls—glucagon, epinephrine and the sympathetic nerves to the liver and adipose tissue, cortisol, and growth hormone (Table 18–4). Glucagon and the sympathetic nervous system are activated during the postabsorptive period (or in any other situation with hypoglycemia) and definitely play roles in preventing hypoglycemia, glucagon being the more important. The rates of secretion of cortisol and growth hormone are not usually coupled to the absorptive-postabsorptive pattern; nevertheless, their presence in the blood at basal concentrations is necessary for normal adjustment of lipid and carbohydrate metabolism to the postabsorptive period, and excessive amounts of either hormone cause abnormally elevated plasma glucose concentrations.

Fuel Homeostasis in Exercise and Stress

During exercise large quantities of fuels must be mobilized to provide the energy required for muscle contraction. As described in Chapter 11, these fuels include plasma glucose and fatty acids as well as the muscle's own glycogen.

The plasma glucose used during exercise is supplied by the liver, both by breakdown of its glycogen stores and by gluconeogenesis—conversion of pyruvate, lactate, glycerol, and amino acids to glucose. The glycerol is made available to the liver by a marked increase in adipose-tissue lipolysis, with a resultant release of glycerol and fatty acids into the blood, the fatty acids serving, along with glucose, as a fuel source for the exercising muscle.

What happens to plasma glucose concentration during exercise? It changes very little in short-term, mild to moderate exercise and may even increase slightly with strenuous short-term activity. However, during prolonged exercise (Figure 18–11), more than 90 min, plasma glucose concentration does decrease, but usually by less than 25 percent. Clearly, glucose output by the liver increases approximately in proportion to increased glucose utilization during exercise, at least until the later stages of prolonged exercise when it begins to lag somewhat.

The metabolic profile seen in an exercising individual—increases in hepatic glucose production, triacylglycerol breakdown, and fatty acid utilization—is similar to that seen in a fasting person, and the neuroendocrine controls are also the same. Exercise is characterized by a fall in insulin secretion and a rise in glucagon secretion (Figure 18–11), and the changes in the plasma concentrations of these two hormones are the major controls during exercise. In addition there is increased activity of the sympathetic nervous system (including increased secretion of epinephrine) and increased secretion of cortisol and growth hormone.

What triggers increased glucagon secretion and decreased insulin secretion during exercise? One signal, at least during *prolonged* exercise, is the modest decrease in plasma glucose that occurs (Figure 18–11); this is the same signal that controls the secretion of these hormones in fasting. Other inputs at all intensities of exercise are increased circulating epinephrine and enhanced activity of the sympathetic neurons supplying the pancreatic islets. Thus, the increased sympathetic nervous system activity characteristic of exercise not only contributes directly to fuel mobilization by acting on the liver and adipose tissue, but contributes indirectly by inhibiting the secretion of insulin and stimulating that of glucagon. This sympathetic output is not triggered by changes in plasma glucose concentration but is mediated by the central nervous system as part of the "programmed" neural response to exercise.

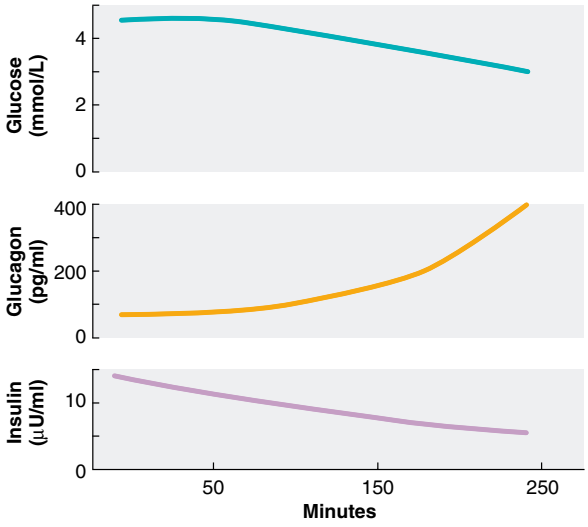

FIGURE 18–11

Plasma concentrations of glucose, glucagon, and insulin during prolonged (250 min) moderate exercise at a fixed intensity.

Adapted from Felig and Wahren.

One component of the response to exercise is quite different from the response to fasting: In exercise, glucose uptake and utilization by the muscles are increased, whereas in fasting they are markedly reduced. How is it that, during exercise, the movement, via facilitated diffusion, of glucose into muscle can remain high in the presence of reduced plasma insulin and increased plasma concentrations of cortisol and growth hormone, all of which decrease glucose uptake by skeletal muscle? By an as-yet-unidentified mechanism, muscle contraction causes migration of an intracellular store of glucose transporters to the plasma membrane.

Exercise and the postabsorptive state are not the only situations characterized by the neuroendocrine profile of decreased insulin and increased glucagon, sympathetic activity, cortisol, and growth hormone. This profile also occurs in response to a variety of nonspecific stresses, both physical and emotional. The adaptive value of these neuroendocrine responses to stress is that the resulting metabolic shifts prepare the body for exercise ("fight or flight") in the face of real or threatened injury. In addition, the amino acids liberated by catabolism of body protein stores because of decreased insulin and increased cortisol not only provide energy via gluconeogenesis but also constitute a potential source of amino acids for tissue repair should injury occur. The subject of stress and the body's responses to it are further described in Chapter 20.

Diabetes Mellitus

The name "diabetes," meaning "syphon" or "running through," denotes the increased urinary volume excreted by people suffering from this disease. "Mellitus," meaning "sweet," distinguishes this urine from the large quantities of nonsweet ("insipid") urine produced by persons suffering from vasopressin deficiency. As described in Chapter 16, the latter disorder is known as diabetes insipidus, and the unmodified word "diabetes" is often used as a synonym for ***diabetes mellitus,*** a disease that affects nearly 15 million people in the United States.

Diabetes can be due to a deficiency of insulin or to a hyporesponsiveness to insulin, for it is not one but several diseases with different causes. Classification of these diseases rests on how much insulin the person is secreting and whether therapy requires the administration of insulin. In ***insulin-dependent diabetes mellitus (IDDM),*** or type 1 diabetes, the hormone is completely or almost completely absent from the islets of Langerhans and the plasma, and therapy with insulin is essential (this protein hormone cannot be given orally but must be injected because gastrointestinal enzymes would digest it). In ***noninsulin-dependent diabetes mellitus (NIDDM),*** or type 2 diabetes, the hormone is

often present in plasma at near-normal or even above-normal levels, and therapy does not require administration of insulin (although such administration may be beneficial).

IDDM is less common, affecting 15 percent of diabetic patients. It is due to the total or near-total destruction of the pancreatic beta cells by the body's own white blood cells (autoimmune disease, Chapter 20). The triggering events for this autoimmune response are not yet fully established. As noted above, treatment of IDDM always involves the administration of insulin. It is likely that in the not-too-distant future, transplantation of islet cells into the individual with IDDM will be possible.

Because of their insulin deficiency, untreated patients with IDDM always have elevated plasma glucose concentrations. This occurs both because glucose fails to enter insulin's target cells normally and because the liver continuously makes glucose—via glycogenolysis and gluconeogenesis—and releases it into the blood. Another result of the insulin deficiency is marked lipolysis with resultant elevation of plasma glycerol and fatty acids. Marked ketone formation by the liver is also present.

If extreme, these metabolic changes culminate in the acute life-threatening emergency called ***diabetic ketoacidosis*** (Figure 18–12). Some of the problems are due to the effects that a markedly elevated plasma glucose concentration produces on renal function. In Chapter 16, we pointed out that a normal person does not excrete glucose because all glucose filtered at the renal corpuscle is reabsorbed by the tubules. However, the elevated plasma glucose of diabetes may so increase the filtered load of glucose that the maximum tubular reabsorptive capacity is exceeded and large amounts of glucose are excreted. For the same reasons, large amounts of ketones may also appear in the urine. These urinary losses deplete the body of nutrients and lead to weight loss. Far worse, however, is the fact that these unreabsorbed solutes cause an osmotic diuresis (Chapter 16)—marked urinary excretion of sodium and water, which can lead, by the sequence of events shown in Figure 18–12, to hypotension, brain damage, and death.

The other serious abnormality in diabetic ketoacidosis is the increased plasma hydrogen-ion concentration caused by the accumulation of ketones, two of which are acids. This increased hydrogen-ion concentration causes brain dysfunction that can contribute to the development of coma and death.

Diabetic ketoacidosis is seen only in patients with untreated IDDM—that is, those with almost total inability to secrete insulin. However, 85 percent of diabetics are in the NIDDM category and never develop metabolic derangements severe enough to go into diabetic ketoacidosis. NIDDM is a disease mainly of overweight adults, typically starting in middle life. Given the earlier mention of progressive weight loss in IDDM as a symptom of diabetes, it may seem contradictory that most people with NIDDM are overweight. The paradox is resolved when one realizes that people with NIDDM, in contrast to those with IDDM, do not excrete enough glucose in the urine to cause weight loss.

There are several factors that combine to cause NIDDM. One major problem is target-cell hyporesponsiveness to insulin, termed ***insulin resistance.*** Obesity accounts for much of the insulin resistance in NIDDM, for obesity in any person—diabetic or not—induces some degree of insulin resistance, particularly in adipose-tissue cells. (One theory is that the excess adipose tissue overproduces a messenger that causes downregulation of insulin-responsive glucose transporters.) However, additional components of insulin resistance, not related to obesity and not yet understood, also usually occur with NIDDM.

Most people with NIDDM not only have insulin resistance but also have a defect in the ability of their beta cells to secrete insulin in response to a rise in plasma glucose concentration. In other words, although insulin resistance is the primary factor inducing hyperglycemia in NIDDM, an as-yet-unidentified defect in beta-cell function prevents these cells from responding to the hyperglycemia in normal fashion.

The major therapy for obese persons with NIDDM is weight reduction, since obesity is a major cause of insulin resistance. An exercise program is also very important, because insulin responsiveness is increased by frequent endurance-type exercise, independent of changes in body weight. This occurs, at least in part, because training causes a substantial increase in the total number of plasma-membrane glucose transporters in both skeletal muscles and adipocytes.

If plasma glucose concentration is not adequately controlled by a program of weight reduction, exercise, and dietary modification (specifically low-fat diets), then the person may be given orally active drugs that lower plasma glucose concentration by a variety of mechanisms. For example, the ***sulfonylureas*** lower plasma glucose by acting on the beta cells to stimulate insulin secretion. Finally, in some cases the use of insulin itself is warranted.

Unfortunately, people with either IDDM or NIDDM tend to develop a variety of chronic abnormalities, including atherosclerosis, kidney failure, small-vessel and nerve disease, susceptibility to infection, and blindness. Elevated plasma glucose contributes to most of these abnormalities either by causing the intracellular accumulation of certain glucose metabolites that exert harmful effects on cells when present in high concentrations, or by linking glucose to proteins, thereby affecting their function.

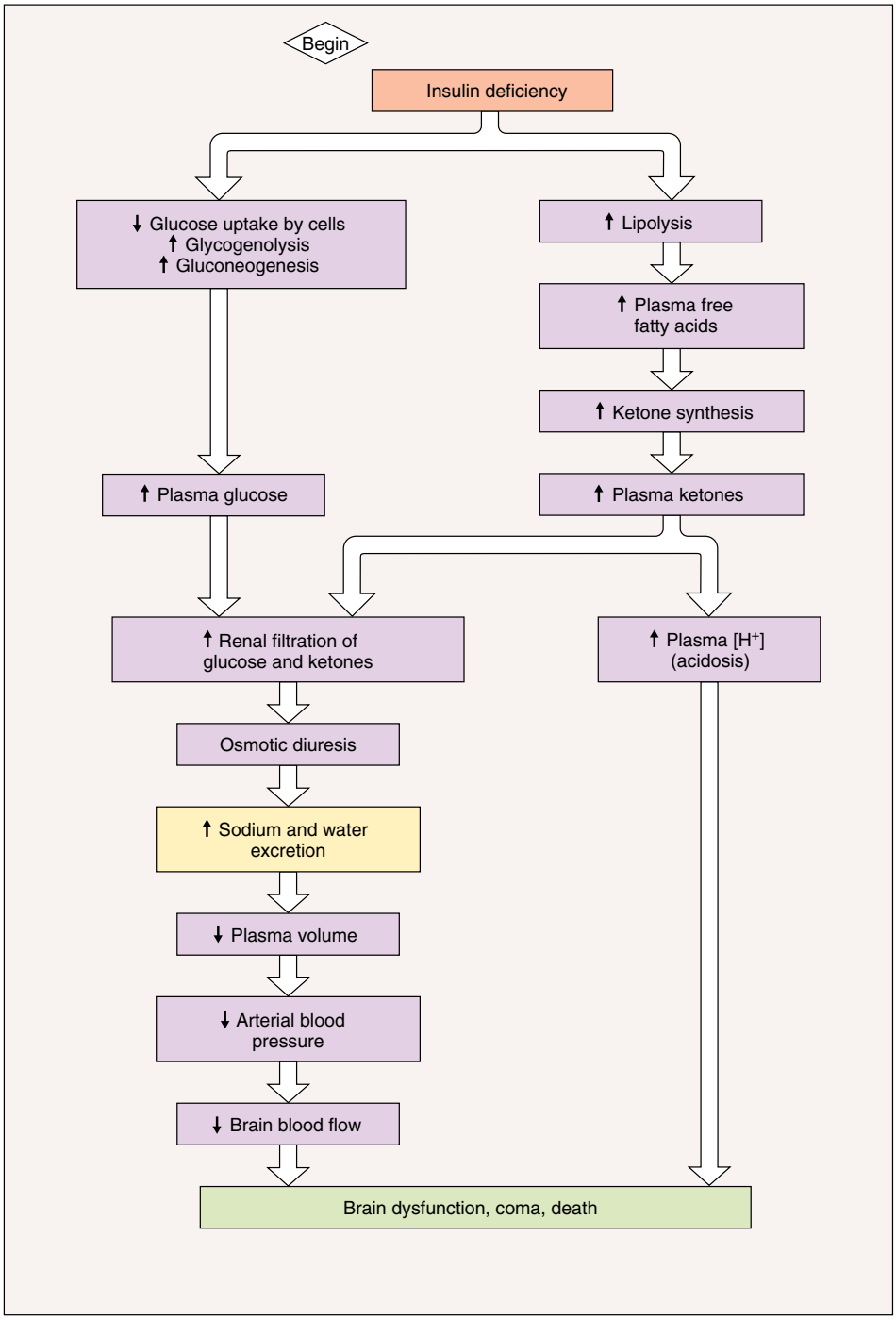

FIGURE 18–12
Diabetic ketoacidosis: Events caused by severe untreated insulin deficiency in insulin-dependent diabetes mellitus.

This discussion of diabetes has focused on insulin, but it is now clear that the hormones that elevate plasma glucose concentration may contribute to the severity of the disease. Glucagon is quite important in this regard. Most diabetics, particularly those with IDDM, have inappropriately high plasma glucagon concentrations, which contribute to the metabolic dysfunction typical of diabetes. The reason for this is that insulin normally inhibits glucagon secretion, and the low insulin of IDDM releases glucagon secretion from this inhibition.

Finally, as we have seen, all the systems that raise plasma glucose concentration are activated during stress, which explains why stress exacerbates the symptoms of diabetes. Since diabetic ketoacidosis itself constitutes a severe stress, a positive-feedback cycle is triggered in which a marked lack of insulin induces ketoacidosis, which elicits activation of the glucose-counterregulatory systems, which worsens the ketoacidosis.

Hypoglycemia as a Cause of Symptoms

As we have seen, "hypoglycemia" means a low plasma glucose concentration. Plasma glucose concentration can drop to very low values, usually during the postabsorptive state, in persons with several types of organic disorders. This is termed ***fasting hypoglycemia,*** and the relatively uncommon disorders responsible for it can be understood in terms of the regulation of blood glucose concentration. They include (1) an excess of insulin due to an insulin-producing tumor, a drug that stimulates insulin secretion, or the taking of too much insulin by a diabetic; and (2) a defect in one or more of the glucose-counterregulatory controls, for example, inadequate glycogenolysis and/or gluconeogenesis due to liver disease, glucagon deficiency, or cortisol deficiency.

Fasting hypoglycemia causes many symptoms. Some—increased heart rate, trembling, nervousness, sweating, and anxiety—are accounted for by activation of the sympathetic nervous system caused reflexly by the hypoglycemia. Other symptoms, such as headache, confusion, dizziness, uncoordination, and slurred speech, are direct consequences of too little glucose reaching the brain. More serious brain effects, including convulsions and coma, can occur if the plasma glucose concentration becomes low enough.

In contrast, low plasma glucose concentration has *not* been shown routinely to produce either acute or chronic symptoms of fatigue, lethargy, loss of libido, depression, or many other symptoms for which popular opinion frequently holds it responsible. Most experts believe that most of the symptoms popularly ascribed to hypoglycemia have other causes.

Regulation of Plasma Cholesterol

In the previous section, we described the flow of lipids to and from adipose tissue in the form of fatty acids and triacylglycerols complexed with proteins. One very important lipid—**cholesterol**—was not mentioned earlier because it, unlike the fatty acids and triacylglycerols, serves not as a metabolic fuel but rather as a precursor for plasma membranes, bile salts, steroid hormones, and other specialized molecules. Thus, cholesterol has many important functions in the body. Unfortunately, it can also cause problems. Specifically, high plasma concentrations of cholesterol enhance the development of ***atherosclerosis,*** the arterial thickening that leads to heart attacks, strokes, and other forms of cardiovascular damage (Chapter 14).

A schema for cholesterol balance is illustrated in Figure 18–13. The two sources of cholesterol are dietary

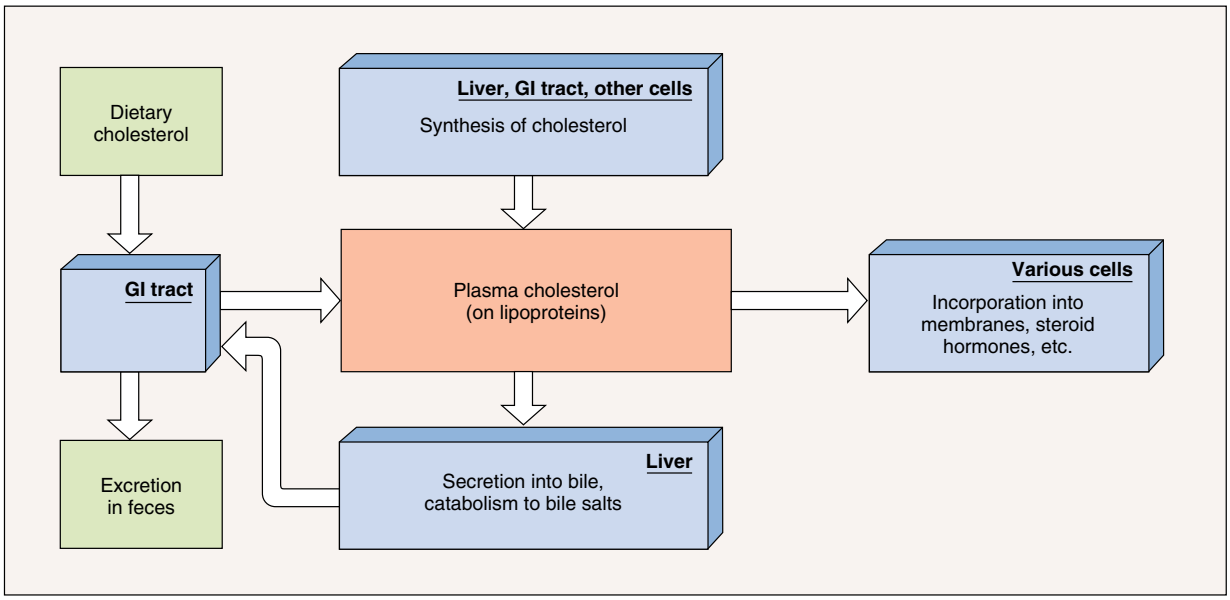

FIGURE 18–13
Cholesterol balance.

cholesterol and cholesterol synthesized within the body. Dietary cholesterol comes from animal sources, egg yolk being by far the richest in this lipid (a single egg contains about 250 mg of cholesterol). Not all ingested cholesterol is absorbed into the blood, however—much of it simply passes through the length of the gastrointestinal tract and is excreted in the feces.

What about cholesterol synthesis within the body? Almost all cells can synthesize some of the cholesterol required for their own plasma membranes, but most cannot do so in adequate amounts and depend upon receiving cholesterol from the blood. This is also true of the endocrine cells that produce steroid hormones from cholesterol. Thus, most cells *remove* cholesterol from the blood. In contrast, the liver and cells lining the gastrointestinal tract can produce large amounts of cholesterol, most of which *enters* the blood.

Now for the other side of cholesterol balance—the pathways, all involving the liver, for net cholesterol loss from the body. First of all, some plasma cholesterol is picked up by liver cells and secreted into the bile, which carries it to the intestinal tract. Here it is treated much like ingested cholesterol, some being absorbed back into the blood and the remainder being excreted in the feces. Second, much of the cholesterol picked up by the liver cells is metabolized into bile salts (Chapter 17). After their production by the liver, these bile salts, like secreted cholesterol, flow through the bile duct into the small intestine. (As described in Chapter 17, many of these bile salts are then reclaimed by absorption back into the blood across the wall of the lower small intestine.)

The liver is clearly the center of the cholesterol universe, for it can add newly synthesized cholesterol to the blood or it can remove cholesterol from the blood, secreting it into the bile or metabolizing it to bile salts. The homeostatic control mechanisms that keep plasma cholesterol relatively constant operate on all of these hepatic processes, but the single most important response involves cholesterol production. The synthesis of cholesterol by the liver is inhibited whenever dietary—and therefore plasma—cholesterol is increased. This is because cholesterol inhibits the enzyme critical for cholesterol synthesis by the liver.

Thus, as soon as the plasma cholesterol level starts rising because of increased cholesterol ingestion, hepatic synthesis is inhibited, and plasma concentration remains close to its original value. Conversely, when dietary cholesterol is reduced and plasma cholesterol begins to fall, hepatic synthesis is stimulated (released from inhibition), and this increased production opposes any further fall. The sensitivity of this negative-feedback control of cholesterol synthesis differs greatly from person to person, but it is the major reason why, for most people, it is difficult to change plasma cholesterol very much in either direction by altering only dietary cholesterol.

Thus far, the relative constancy of plasma cholesterol has been emphasized. There are, however, environmental and physiological factors that can significantly alter plasma cholesterol concentrations. Perhaps the most important of these factors are the quantity and type of dietary fatty acids. Ingesting saturated fatty acids, the dominant fatty acids of animal fat (particularly high in red meats, most cheeses, and whole milk), raises plasma cholesterol. In contrast, eating either polyunsaturated fatty acids (the dominant plant fatty acids) or monounsaturated fatty acids such as those in olive or peanut oil, lowers plasma cholesterol. The various fatty acids exert their effects on plasma cholesterol by altering cholesterol synthesis, excretion, and metabolism to bile salts.

A variety of drugs now in common use are also capable of lowering plasma cholesterol by influencing one or more of the metabolic pathways for cholesterol—for example, inhibiting the critical enzyme for hepatic cholesterol synthesis—or by interfering with intestinal absorption of bile salts.

Based on studies of the relationship between plasma cholesterol levels and cardiovascular diseases, recommendations from the National Institutes of Health call a total plasma cholesterol below 200 mg/deciliter [a deciliter (dl) is 100 ml] "desirable," 200–239 mg/dl "borderline high," and 240 mg/dl or greater "high."

The story is more complicated than this, however, since not all plasma cholesterol has the same function or significance for disease. Like most other lipids, cholesterol circulates in the plasma as part of various lipoprotein complexes. These include chylomicrons (Chapter 17), VLDL (this chapter), **low-density lipoproteins (LDL),** and **high-density lipoproteins (HDL).** LDL are the main cholesterol carriers, and they *deliver* cholesterol to cells throughout the body. LDL bind to plasma-membrane receptors specific for a protein component of the LDL, and the LDL are taken up by the cell by absorptive endocytosis. In contrast to LDL, HDL *remove* excess cholesterol from blood and tissue, including the cholesterol-loaded cells of atherosclerotic plaques (Chapter 14). They then deliver this cholesterol to the liver, which secretes it into the bile or converts it to bile salts. HDL also delivers cholesterol to steroid-producing endocrine cells. Uptake of the HDL by the liver and these endocrine cells is facilitated by the presence in their plasma membranes of large numbers of receptors specific for HDL, which bind to the receptors and then are taken into the cells.

LDL cholesterol is often designated "bad" cholesterol since high levels of it in the plasma are associated with increased deposition of cholesterol in arterial walls and higher incidences of heart attacks. (The designation "bad" should not obscure the fact that LDL are essential for supplying cells with the cholesterol they require to synthesize cell membranes and, in the case of the gonads and adrenal glands, steroid hormones.) Using the same criteria, HDL cholesterol has been designated "good" cholesterol.

The best single indicator of the likelihood of developing atherosclerotic heart disease is, therefore, not *total* plasma cholesterol but rather the *ratio* of plasma LDL-cholesterol to plasma HDL-cholesterol—the lower the ratio, the lower the risk. Cigarette smoking, a known risk factor for heart attacks, lowers plasma HDL, whereas weight reduction (in overweight persons) and regular exercise increase it. Estrogen not only lowers LDL but raises HDL, which explains, in part, why premenopausal women have so much less coronary artery disease than men. After menopause, the cholesterol values and coronary artery disease rates in women not on hormone-replacement therapy (Chapter 19) become similar to those in men.

SECTION A SUMMARY

Events of the Absorptive and Postabsorptive States

I. During absorption, energy is provided primarily by absorbed carbohydrate, and net synthesis of glycogen, triacylglycerol, and protein occurs.
   a. Some absorbed carbohydrate not used for energy is converted to glycogen, mainly in the liver and skeletal muscle, but most is converted, in liver and adipocytes, to α-glycerol phosphate and fatty acids, which then combine to form triacylglycerol. The liver releases its triacylglycerols in very low density lipoproteins, the fatty acids of which are picked up by adipocytes.
   b. The fatty acids of some absorbed triacylglycerol are used for energy, but most are rebuilt into fat in adipose tissue.
   c. Some absorbed amino acids are converted to proteins, but excess amino acids are converted to carbohydrate and fat.
   d. There is a net upake of glucose by the liver.

II. In the postabsorptive state, blood glucose level is maintained by a combination of glucose production by the liver and a switch from glucose utilization to fatty acid and ketone utilization by most tissues.
   a. Synthesis of glycogen, fat, and protein is curtailed, and net breakdown of these molecules occurs.
   b. The liver forms glucose by glycogenolysis of its own glycogen and by gluconeogenesis from lactate and pyruvate (from breakdown of muscle glycogen), glycerol (from adipose-tissue lipolysis), and amino acids (from protein catabolism).
   c. Glycolysis is decreased, and most of the body's energy supply comes from the oxidation of fatty acids released by adipose-tissue lipolysis and of ketones produced from fatty acids by the liver.
   d. The brain continues to use glucose but also starts using ketones as they build up in the blood.

Endocrine and Neural Control of the Absorptive and Postabsorptive States

I. The major hormones secreted by the pancreatic islets of Langerhans are insulin by the beta cells and glucagon by the alpha cells.

II. Insulin is the most important hormone controlling metabolism.
   a. In muscle, it stimulates glucose uptake, glycolysis, and net synthesis of glycogen and protein; in adipose tissue, it stimulates glucose uptake and net synthesis of triacylglycerol; in liver, it inhibits gluconeogenesis and glucose release and stimulates the net synthesis of glycogen and triacylglycerols.
   b. The major stimulus for insulin secretion is an increased plasma glucose concentration, but secretion is also influenced by many other factors, which are summarized in Figure 18–8.

III. Glucagon, epinephrine, cortisol, and growth hormone all exert effects on carbohydrate and lipid metabolism that are opposite, in one way or another, to those of insulin. They raise plasma concentrations of glucose, glycerol, and fatty acids.
   a. Glucagon's physiological actions are all on the liver, where it stimulates glycogenolysis, gluconeogenesis, and ketone synthesis.
   b. The major stimulus for glucagon secretion is hypoglycemia, but secretion is also stimulated by other inputs, including the sympathetic nerves to the islets.
   c. Epinephrine released from the adrenal medulla in response to hypoglycemia stimulates glycogenolysis in the liver and muscle, gluconeogenesis in liver, and lipolysis in adipocytes. The sympathetic nerves to liver and adipose tissue exert effects similar to those of epinephrine.
   d. Cortisol is permissive for gluconeogenesis and lipolysis; in higher concentrations, it stimulates gluconeogenesis and blocks glucose uptake. These last two effects are also exerted by growth hormone.

Fuel Homeostasis in Exercise and Stress

I. During exercise, the muscles use as their energy sources plasma glucose, plasma fatty acids, and their own glycogen.
   a. Glucose is provided by the liver, and fatty acids are provided by adipose-tissue lipolysis.
   b. The changes in plasma insulin, glucagon, and epinephrine are similar to those that occur during the postabsorptive period and are mediated mainly by the sympathetic nervous system.

II. Stress causes hormonal changes similar to those caused by exercise.

Diabetes Mellitus

I. Insulin-dependent diabetes is due to absolute insulin deficiency and can lead to diabetic ketoacidosis.

II. Noninsulin-dependent diabetes is usually associated with obesity and is caused by a combination of insulin resistance and a defect in beta-cell responsiveness to elevated plasma glucose concentration. Plasma insulin concentration is usually normal or elevated.

Regulation of Plasma Cholesterol

I. Plasma cholesterol is a precursor for the synthesis of plasma membranes, bile salts, and steroid hormones.

II. Cholesterol synthesis by the liver is controlled so as to homeostatically regulate plasma cholesterol concentration; it varies inversely with ingested cholesterol.
III. The liver also secretes cholesterol into the bile and converts it to bile salts.
IV. Plasma cholesterol is carried mainly by low-density lipoproteins, which deliver it to cells; high-density lipoproteins carry cholesterol from cells to the liver and steroid-producing cells. The LDL/HDL ratio correlates with the incidence of coronary heart disease.

SECTION A KEY TERMS

absorptive state
postabsorptive state
very low density lipoproteins (VLDL)
lipoprotein lipase
α-ketoacids
glycogenolysis
lipolysis
gluconeogenesis
glucose sparing
ketones
islets of Langerhans
beta cells
alpha cells
insulin
hypoglycemia
glucose-counterregulatory controls
glucagon
cholesterol
low-density lipoproteins (LDL)
high-density lipoproteins (HDL)

SECTION A REVIEW QUESTIONS

1. Using a diagram, summarize the events of the absorptive period.
2. In what two organs does major glycogen storage occur?
3. How do the liver and adipose tissue metabolize glucose during the absorptive period?
4. How does adipose tissue metabolize absorbed triacylglycerol, and what are the three major sources of the fatty acids in adipose tissue triacylglycerol?
5. What happens to most of the absorbed amino acids when a high-protein meal is ingested?
6. Using a diagram, summarize the events of the postabsorptive period; include the four sources of blood glucose and the pathways leading to ketone formation.
7. Distinguish between the roles of glycerol and free fatty acids during fasting.
8. List the overall responses of muscle, adipose tissue, and liver to insulin. What effects occur when plasma insulin concentration decreases?
9. List five inputs controlling insulin secretion, and state the physiological significance of each.
10. List the effects of glucagon on the liver and their consequences.
11. List two inputs controlling glucagon secretion, and state the physiological significance of each.
12. List four metabolic effects of epinephrine and the sympathetic nerves to the liver and adipose tissue, and state the net results of each.
13. List the permissive effects of cortisol and the effects that occur when plasma cortisol concentration increases.
14. List three effects of growth hormone on carbohydrate and lipid metabolism.
15. Which hormones stimulate gluconeogenesis? Glycogenolysis in liver? Glycogenolysis in skeletal muscle? Lipolysis? Blockade of glucose uptake?
16. Describe how plasma glucose, insulin, glucagon, and epinephrine levels change during exercise and stress. What causes the changes in the concentrations of the hormones?
17. Describe the metabolic disorders of severe insulin-dependent diabetes.
18. How does obesity contribute to noninsulin-dependent diabetes?
19. Hypersecretion of which hormones can induce a diabetic state?
20. Using a diagram, describe the sources of cholesterol gain and loss. Include three roles of the liver in cholesterol metabolism, and state the controls over these processes.
21. What are the effects of saturated and unsaturated fatty acids on plasma cholesterol?
22. What is the significance of the ratio of LDL cholesterol to HDL cholesterol?

SECTION B

CONTROL OF GROWTH

Growth is a complex process influenced by genetics, endocrine function, and a variety of environmental factors, including nutrition and the presence of infection. The process involves cell division and net protein synthesis throughout the body, but a person's height is determined specifically by bone growth, particularly of the vertebral column and legs.

Bone Growth

As described in Chapter 16, bone is a living tissue consisting of a protein (collagen) matrix upon which calcium salts, particularly calcium phosphates, are deposited. A growing long bone is divided, for descriptive purposes, into the ends, or **epiphyses,** and

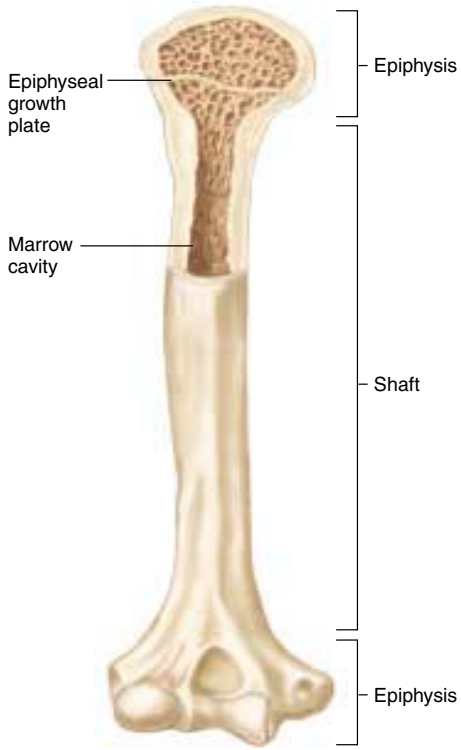

FIGURE 18–14
Anatomy of a long bone during growth.

the remainder, the **shaft.** The portion of each epiphysis that is in contact with the shaft is a plate of actively proliferating cartilage, the **epiphyseal growth plate** (Figure 18–14). **Osteoblasts,** the bone-forming cells (Chapter 16), at the shaft edge of the epiphyseal growth plate convert the cartilaginous tissue at this edge to bone while new cartilage is simultaneously being laid down in the interior of the plate by cells called **chondrocytes.** In this manner, the epiphyseal growth plate remains intact (indeed, actually widens) and is gradually pushed away from the center of the bony shaft as the latter lengthens.

Linear growth of the shaft can continue as long as the epiphyseal growth plates exist, but ceases when the plates are themselves ultimately converted to bone as a result of hormonal influences at puberty. This is known as **epiphyseal closure** and occurs at different times in different bones. Accordingly, a person's **bone age** can be determined by x-raying the bones and determining which ones have undergone epiphyseal closure.

As shown in Figure 18–15, children manifest two periods of rapid increase in height, one during the first two years of life and the second during puberty. Note that increase in height is not necessarily correlated with the rates of growth of specific organs.

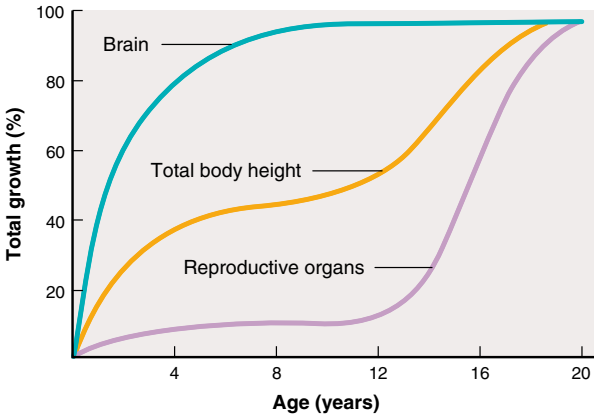

FIGURE 18–15
Relative growth in brain, total body height (a measure of long-bone and vertebral growth), and reproductive organs. Note that brain growth is nearly complete by the age 5, whereas maximal height (maximal bone lengthening) and reproductive-organ size are not reached until the late teens.

The pubertal growth spurt lasts several years in both sexes, but growth during this period is greater in boys. This, plus the fact that boys grow more before puberty because they begin puberty approximately two years later than girls, accounts for the differences in average height between men and women.

Environmental Factors Influencing Growth

Adequacy of nutrient supply and freedom from disease are the primary environmental factors influencing growth. Lack of sufficient amounts of any of the essential amino acids, essential fatty acids, vitamins, or minerals interferes with growth. Total protein and sufficient nutrients to provide energy must also be adequate.

The growth-inhibiting effects of malnutrition can be seen at any time of development but are most profound when they occur very early in life. Thus, maternal malnutrition may cause growth retardation in the fetus. Since low birth weight is strongly associated with increased infant mortality, prenatal malnutrition causes increased numbers of prenatal and early postnatal deaths. Moreover, irreversible stunting of brain development may be caused by prenatal malnutrition. During infancy and childhood, too, malnutrition can interfere with both intellectual development and total-body growth.

Following a temporary period of stunted growth due to malnutrition or illness, and given proper nutrition and recovery from illness, a child manifests a remarkable growth spurt **(catch-up growth)** that brings

the child up to the normal height expected for his or her age. The mechanism that accounts for this accelerated growth is unknown.

Hormonal Influences on Growth

The hormones most important to human growth are growth hormone, insulin-like growth factors I and II, thyroid hormones, insulin, testosterone, and estrogens, all of which exert widespread effects. In addition to all these hormones, there is a huge group of peptide **growth factors,** including the insulin-like growth factors, most of which act as paracrine and autocrine agents to stimulate differentiation and/or cell division of certain cell types.

The general term for a chemical that stimulates cell division is a **mitogen.** There are also peptide **growth-inhibiting factors** that modulate growth by inhibiting cell division in specific tissues. Numbering more than 60 at present, the growth factors and growth-inhibiting factors are usually produced by multiple cell types rather than by discrete endocrine glands.

The physiology of growth factors and growth-inhibiting factors is important not just for understanding control of normal growth, but also because these factors may be involved in the development of ***cancer.*** Thus, some ***oncogenes*** (genes that are involved in causing cancer, Chapter 5) code for proteins that are identical to or very similar to growth factors, growth-factor receptors, or postreceptor components of growth-factor signal transduction pathways. The problem is that these proteins have lost important regulatory constraints on their activity. For example, one oncogene codes for a version of the receptor for epidermal growth factor that is always in the activated state even in the absence of the growth factor. This activated receptor imparts a continuous growth signal to the cells containing it.

The various hormones and growth factors do not all stimulate growth at the same periods of life. For example, fetal growth is largely independent of growth hormone, the thyroid hormones, and the sex steroids, all of which importantly stimulate growth during childhood and adolescense.

Growth Hormone and Insulin-Like Growth Factors

Growth hormone, secreted by the anterior pituitary, has little or no effect on fetal growth as we have just mentioned, but is the single most important hormone for postnatal growth. Its major growth-promoting effect is stimulation (indirect, as we shall see) of cell division in its many target tissues. Thus, growth hormone promotes bone lengthening by stimulating maturation and cell division of the chondrocytes in the epiphyseal plates, thereby continuously widening the plates and providing more cartilaginous material for bone formation.

An excess of growth hormone during childhood produces ***giantism,*** whereas deficiency produces ***dwarfism.*** When excess growth hormone is secreted in adults after epiphyseal closure, it cannot lengthen the bones further, but it does produce the disfiguring bone thickening and overgrowth of other organs known as ***acromegaly.***

Importantly, growth hormone exerts its cell division-stimulating (mitogenic) effect not *directly* on cells but rather *indirectly* through the mediation of a mitogen whose synthesis and release are induced by growth hormone. This mitogen is called **insulin-like growth factor I (IGF-I)** (also known as somatomedin C). Despite its name, this messenger has its own unique effects. Under the influence of growth hormone, IGF-I is secreted by the liver, enters the blood and functions as a hormone. In addition, growth hormone stimulates the secretion of IGF-I by many other types of cells, including bone, and at these sites IGF-I functions as an autocrine or paracrine agent. The relative importance of IGF-I as a hormone versus autocrine/paracrine agent in any given organ or tissue remains controversial.

Current concepts of how growth hormone and IGF-I interact on the epiphyseal plates of bone are as follows: (1) Growth hormone stimulates the chondrocyte precursor cells (prechondrocytes) and/or young differentiating chondrocytes in the epiphyseal plates to differentiate into chondrocytes; (2) during this differentiation, the cells begin both to secrete IGF-I and to become responsive to IGF-I; (3) the IGF-I then acts as an autocrine or paracrine agent (probably along with blood-borne IGF-I) to stimulate the differentiating chondrocytes to undergo cell division.

The importance of IGF-I in mediating the major growth-promoting effect of growth hormone is illustrated by the fact that dwarfism can be due not only to decreased secretion of growth hormone but also to decreased production of IGF-I or failure of the tissues to respond to IGF-I. For example, one uncommon form of short stature (termed ***growth hormone insensitivity syndrome***), is due to a genetic mutation that causes the growth hormone receptor to fail to respond to growth hormone; the result is failure to produce IGF-I in response to growth hormone.

The secretion and activity of IGF-I can be influenced by the nutritional status of the individual and by many hormones other than growth hormone. For example, malnutrition during childhood inhibits the production of IGF-I even through plasma growth hormone concentration is elevated and should be stimulating IGF-I secretion. To take another example, estrogen stimulates the secretion of IGF-I by cells of the uterus and ovaries.

TABLE 18–5 Major Effects of Growth Hormone

1. Promotes growth: Induces precursor cells in bone and other tissues to differentiate and secrete insulin-like growth factor I (IGF-I), which stimulates cell division. Also stimulates secretion of IGF-I by liver.
2. Stimulates protein synthesis, predominantly in muscle.
3. Anti-insulin effects:
   a. Renders adipocytes more responsive to lipolytic stimuli
   b. Stimulates gluconeogenesis
   c. Reduces the ability of insulin to stimulate glucose uptake

In addition to its specific growth-promoting effect on cell division via IGF-I, growth hormone directly stimulates protein synthesis in various tissues and organs, particularly muscle. It does this by increasing amino acid uptake by cells and both the synthesis and activity of ribosomes. All these events are essential for protein synthesis. This anabolic effect on protein metabolism facilitates the ability of tissues and organs to enlarge. Table 18–5 summarizes the multiple effects of growth hormone, all of which have been described in this chapter.

The control of growth hormone secretion was described in Chapter 10 (Figure 10–21). Briefly, the control system begins with two of the hypophysiotropic hormones secreted by the hypothalamus. Growth hormone secretion is stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin. As a result of changes in these two signals, which are virtually 180 degrees out of phase with each other (that is, one is high when the other is low), growth hormone secretion occurs in episodic bursts and manifests a striking diurnal rhythm. During most of the day, there is little or no growth hormone secreted, although bursts may be elicited by certain stimuli, including stress, hypoglycemia, and exercise. In contrast, 1 to 2 h after a person falls asleep, one or more larger, prolonged bursts of secretion may occur. (The negative-feedback controls that growth hormone and IGF-I exert on the hypothalamus and anterior pituitary are summarized in Figure 10–21.)

In addition to the hypothalamic controls, a variety of hormones—notably the sex hormones, insulin, and the thyroid hormones, as described below—influence the secretion of growth hormone. The net result of all these inputs is that the total 24-h secretion rate of growth hormone is highest during adolescence (the period of most rapid growth), next highest in children, and lowest in adults. The decreased growth hormone secretion associated with aging is responsible, in part, for the decrease in lean-body and bone mass, the expansion of adipose tissue, and the thinning of the skin that occur at that time.

The availability of large quantities of human growth hormone produced by recombinant-DNA technology has greatly facilitated the treatment of children with short stature due to deficiency of growth hormone. Controversial at present is the administration of growth hormone to short children who do not have growth hormone deficiency, to athletes in an attempt to increase muscle mass, and to normal elderly persons to reverse the growth hormone–related aging changes described in the previous paragraph.

As noted above, growth hormone plays little if any role in prenatal growth (that is, growth of the embryo and fetus). One would suppose, therefore, that this would also be true for IGF-I, but such is not the case: IGF-I is required for normal fetal total-body growth and, specifically, for normal maturation of the fetal nervous system. The stimulus for IGF-I secretion during prenatal life is unknown.

Finally, it should be noted that there is another messenger—**insulin-like growth factor II (IGF-II)**—that is closely related to IGF-I. IGF-II, the secretion of which is *independent* of growth hormone, is also a crucial mitogen during the prenatal period. It continues to be secreted throughout life, but its postnatal function is not known.

Thyroid Hormones

The thyroid hormones (TH)—thyroxine (T_4) and triiodothyronine (T_3)—are essential for normal growth because they are required for both the synthesis of growth hormone and the growth-promoting effects of that hormone. Accordingly, infants and children with ***hypothyroidism*** (deficient thyroid function) manifest retarded growth due to slowed bone growth.

Quite distinct from its growth-promoting effect, TH is permissive for normal development of the central nervous system during fetal life. Inadequate production of maternal and fetal TH due to severe iodine deficiency during pregnancy is one of the world's most common preventable causes of mental retardation, termed ***endemic cretinism.***

This effect on brain development must be distinguished from other stimulatory effects TH exerts on the nervous system throughout life, not just during infancy. A hypothyroid person exhibits sluggishness and poor mental function, and these effects are completely reversible at any time with administration of TH. Conversely, a person with ***hyperthyroidism*** (excessive secretion of TH) is jittery and hyperactive.

Insulin

It should not be surprising that adequate amounts of insulin are necessary for normal growth since insulin is, in all respects, an anabolic hormone. Its inhibitory effect on protein degradation is particularly important with regard to growth.

In addition to this general anabolic effect, however, insulin exerts direct, specific growth-promoting effects on cell differentiation and cell division during fetal life (and possibly during childhood). Moreover, insulin is required for normal production of IGF-I.

Sex Hormones

As will be described in Chapter 19, sex hormone secretion (testosterone in the male and estrogen in the female) begins in earnest between the ages of 8 and 10 and progressively increases to reach a plateau over the next 5 to 10 years. A normal pubertal growth spurt, which reflects growth of the long bones and vertebrae, requires this increased production of the sex hormones. The major growth-promoting effect of the sex hormones is to stimulate the secretion of growth hormone and IGF-I.

Unlike growth hormone, however, the sex hormones not only stimulate bone growth, but ultimately *stop* it by inducing epiphyseal closure. The dual effects of the sex hormones explain the pattern seen in adolescence—rapid lengthening of the bones culminating in complete cessation of growth for life.

In addition to these dual effects on bone, testosterone, but not estrogen, exerts a direct anabolic effect on protein synthesis in many nonreproductive organs and tissues of the body. This accounts, at least in part, for the increased muscle mass of men, compared with women.

This is also why synthetic testosterone-like agents termed ***anabolic steroids*** [or a hormone—dehydroepiandrosterone (DHEA)—that is converted in the body to testosterone] are sometimes used by athletes—both male and female—in an attempt to increase their muscle mass and strength. However, these steroids have multiple potential toxic side effects (for example, liver damage, increased risk of prostate cancer, and infertility). Moreover, in females they can produce masculinization.

Cortisol

Cortisol, the major hormone secreted by the adrenal cortex in response to stress, can have potent *antigrowth* effects under certain conditions. When present in high concentration, it inhibits DNA synthesis and stimulates protein catabolism in many organs, and it inhibits bone growth. Moreover, it causes bone breakdown by inhibiting osteoblasts and stimulating osteoclasts (Chapter 16). It also inhibits the secretion of growth hormone. For all these reasons, in children, the elevation in plasma cortisol that accompanies infections and other stresses is, at least in part, responsible for the retarded growth that occurs with illness.

As we shall see in Chapter 20, cortisol and very similar steroids are commonly used medically in persons with arthritis or other inflammatory disorders. A side effect of such treatment is increased protein catabolism and bone breakdown. One must carefully distinguish cortisol-type steroids (glucocorticoids) from testosterone-type steroids (anabolic steroids).

This completes our survey of the major hormones that affect growth. Their actions are summarized in Table 18–6.

TABLE 18–6 Major Hormones Influencing Growth

Hormone	Principal Actions
Growth hormone	Major stimulus of postnatal growth: Induces precursor cells to differentiate and secrete insulin-like growth factor I (IGF-I), which stimulates cell division Stimulates secretion of IGF-I by liver Stimulates protein synthesis
Insulin	Stimulates fetal growth Stimulates postnatal growth by stimulating secretion of IGF-I Stimulates protein synthesis
Thyroid hormones	Permissive for growth hormone's secretion and actions Permissive for development of the central nervous system
Testosterone	Stimulates growth at puberty, in large part by stimulating the secretion of growth hormone Causes eventual epiphyseal closure Stimulates protein synthesis in male
Estrogen	Stimulates the secretion of growth hormone at puberty Causes eventual epiphyseal closure
Cortisol	Inhibits growth Stimulates protein catabolism

Compensatory Growth

We have dealt thus far only with growth during *childhood*. During adult life, a specific type of regenerative growth known as **compensatory growth,** can occur in many human organs. For example, after the surgical removal of one kidney, the cells of the other kidney begin to manifest increased cell division, and the kidney ultimately grows until its total mass approaches the initial mass of the two kidneys combined. Many growth factors and hormones participate in compensatory growth, but the precise signals that trigger the process are not known. Moreover, these signals very likely differ from organ to organ. Of particular importance is the release of angiogenic factors (Chapter 14) since availability of blood flow is a major determinant of how large an organ can become.

SECTION B SUMMARY

Bone Growth

I. A bone lengthens as osteoblasts at the shaft edge of the epiphyseal growth plates convert cartilage to bone while new cartilage is being laid down in the plates.
II. Growth ceases when the plates are completely converted to bone.

Environmental Factors Influencing Growth

I. The major environmental factors influencing growth are nutrition and disease.
II. Malnutrition during in utero life may produce irreversible stunting and mental deficiency.

Hormonal Influences on Growth

I. Growth hormone is the major stimulus of postnatal growth.
   a. It stimulates the release of IGF-I from the liver and many other cells, and IGF-I then acts locally (and perhaps also as a hormone) to stimulate cell division.
   b. Growth hormone also acts directly on cells to stimulate protein synthesis.
   c. Growth hormone secretion is highest during adolescence.
II. Because thyroid hormones are required for growth hormone synthesis and the growth-promoting effects of this hormone, they are essential for normal growth during childhood and adolescence. They are also permissive for brain development during infancy.
III. Insulin stimulates growth mainly during in utero life.
IV. Mainly by stimulating growth hormone secretion, testosterone and estrogen promote bone growth during adolescence, but these hormones also cause epiphyseal closure. Testosterone also stimulates protein synthesis.
V. Cortisol in a high concentration inhibits growth and stimulates protein catabolism.

SECTION B KEY TERMS

epiphysis
shaft
epiphyseal growth plate
osteoblast
chondrocyte
epiphyseal closure
bone age
catch-up growth
growth factor
mitogen
growth-inhibiting factor
insulin-like growth factor I (IGF-I)
insulin-like growth factor II (IGF-II)
compensatory growth

SECTION B REVIEW QUESTIONS

1. Describe the process by which bone is lengthened.
2. What are the effects of malnutrition on growth?
3. List the major hormones that control growth.
4. Describe the relationship between growth hormone and IGF-I and the roles of each in growth.
5. What are the effects of growth hormone on protein synthesis?
6. What is the status of growth hormone secretion at different stages of life?
7. State the effects of the thyroid hormones on growth and development.
8. Describe the effects of testosterone on growth, cessation of growth, and protein synthesis. Which of these effects are shared by estrogen?
9. What is the effect of cortisol on growth?

SECTION C

REGULATION OF TOTAL-BODY ENERGY BALANCE AND TEMPERATURE

Basic Concepts of Energy Expenditure

The breakdown of organic molecules liberates the energy locked in their molecular bonds. This is the energy cells use to perform the various forms of biological work—muscle contraction, active transport, and molecular synthesis. The first law of thermodynamics states that energy can be neither created nor destroyed, but can be converted from one form to another. Thus, internal energy liberated (ΔE) during breakdown of an organic molecule can either appear as heat (H) or be used to perform work (W).

$$\Delta E = H + W$$

During metabolism, about 60 percent of the energy released from organic molecules appears immediately as heat, and the rest is used for work. The energy used for work must first be incorporated into molecules of ATP, the subsequent breakdown of which serves as the immediate energy source for the work. It is essential to realize that the body is not a heat engine since it is totally incapable of converting heat to work, but the heat released in its chemical reactions is valuable for maintaining body temperature.

Biological work can be divided into two general categories: (1) **external work**—movement of external objects by contracting skeletal muscles; and (2) **internal work**—all other forms of work, including skeletal-muscle activity not used in moving external objects. As just stated, much of the energy liberated from nutrient catabolism appears immediately as heat. What may not be obvious is that all internal work, too, is ultimately transformed to heat except during periods of growth. For example, internal work is performed during cardiac contraction, but this energy appears ultimately as heat generated by the friction of blood flow through the blood vessels.

Thus, the total energy liberated when organic nutrients are catabolized by cells may be transformed into body heat, appear as external work, or be stored in the body in the form of organic molecules. The **total energy expenditure** of the body is therefore given by the equation

Total energy expenditure =
Internal heat produced + External work + Energy stored

Metabolic Rate

The unit for energy in metabolism is the **kilocalorie (kcal),** which is the amount of heat required to raise the temperature of one liter of water one degree celsius. (In the field of nutrition, the three terms "Calorie" with a capital C, "large calorie," and "kilocalorie" are synonyms; they are all 1000 "calories," with a small c.) Total energy expenditure per unit time is called the **metabolic rate.**

Since many factors cause the metabolic rate to vary (Table 18–7), the most common method for evaluating it specifies certain standardized conditions,

TABLE 18–7 Some Factors Affecting the Metabolic Rate

Age (↓ with ↑ age) Sex (women less than men at any given size) Height, weight, and body surface area Growth Pregnancy, menstruation, lactation Infection or other disease Body temperature Recent ingestion of food Prolonged alteration in amount of food intake Muscular activity Emotional stress Environmental temperature Circulating levels of various hormones, especially epinephrine and thyroid hormone Sleep (↓ during sleep)	(An increase in any of these factors causes an increase in metabolic rate.)

TABLE 18–8 Major Functions of the Thyroid Hormones (TH)

1. Required for normal maturation of the nervous system in the fetus and infant
Deficiency: Mental retardation (cretinism)
2. Required for normal bodily growth because they facilitate the secretion of and response to growth hormone
Deficiency: Deficient growth in children
3. Required for normal alertness and reflexes at all ages
Deficiency: Mentally and physically slow and lethargic
Excess: Restless, irritable, anxious, wakeful
4. Major determinant of the rate at which the body produces heat during the basal metabolic state
Deficiency: Low BMR, sensitivity to cold, decreased food appetite
Excess: High BMR, sensitivity to heat, increased food appetite, increased catabolism of nutrients
5. Facilitates the activity of the sympathetic nervous system by stimulating the synthesis of one class of receptors (beta receptors) for epinephrine and norepinephrine
Excess: Symptoms similar to those observed with activation of the sympathetic nervous system (for example, increased heart rate)

and measures what is known as the **basal metabolic rate (BMR).** In the basal condition, the subject is at mental and physical rest in a room at a comfortable temperature and has not eaten for at least 12 h. These conditions are arbitrarily designated "basal," even though the metabolic rate during sleep may be less than the BMR. The BMR is often termed the "metabolic cost of living," and most of it is expended by the heart, liver, kidneys, and brain. For the following discussion, it must be emphasized that the term "BMR" can be applied to a person's metabolic rate only when the specified conditions are met; thus, a person who has recently eaten or is exercising has a metabolic rate but not a *basal* metabolic rate. The next sections describe several of the important determinants of BMR and metabolic rate.

Thyroid Hormones The thyroid hormones are the single most important determinant of BMR regardless of size, age, or sex. TH increases the oxygen consumption and heat production of most body tissues, a notable exception being the brain. This ability to increase BMR is termed a **calorigenic effect.** One mechanism of this effect is that TH increases synthesis of uncoupling proteins found in the inner mitochondrial membrane of most human cells; these proteins reduce the amount of ATP produced and increase the amount of heat generated when fuels are oxidized.

Long-term excessive TH, as in persons with hyperthyroidism, induces a host of effects secondary to the calorigenic effect. For example, the increased metabolic demands markedly increase hunger and food intake; the greater intake frequently remains inadequate to meet the metabolic needs, and net catabolism of protein and fat stores leads to loss of body weight. Also, the greater heat production activates heat-dissipating mechanisms (skin vasodilation and sweating), and the person suffers from marked intolerance to warm environments. In contrast, the hypothyroid individual complains of cold intolerance.

The calorigenic effect of TH is only one of a bewildering variety of effects exerted by these hormones. With one exception—facilitation of the activity of the sympathetic nervous system (described in Chapter 10), the major functions of the thyroid hormones have all been described in this chapter and are listed for reference in Table 18–8.

As described in Chapter 10, secretion of the thyroid hormones is stimulated by the anterior pituitary hormone, thyroid stimulating hormone (TSH), itself stimulated by the hypophysiotropic hormone, thyrotropin releasing hormone (TRH). The thyroid hormones, in turn, exert an inhibitory effect on the hypothalamo-pituitary system. What is unusual about this entire hormonal system is that there is no known stimulus that activates this system in a way that leads to the negative-feedback elimination of the stimulus (as, for example, the way changes in plasma glucose influence insulin secretion). It is as though the thyroid hormones simply set a background tone for the various parameters, like BMR, that they influence.

Epinephrine Epinephrine is another hormone that exerts a calorigenic effect. (This effect may be related to the hormone's stimulation of glycogen and triacylglycerol catabolism, since ATP splitting and energy

TABLE 18–9 Energy Expenditure during Different Types of Activity for a 70-kg (154-lb) Person

Form of Activity	Energy kcal/h
Lying still, awake	77
Sitting at rest	100
Typewriting rapidly	140
Dressing or undressing	150
Walking on level, 4.3 km/h (2.6 mi/h)	200
Bicycling on level, 9 km/h (5.5 mi/h)	304
Walking on 3 percent grade, 4.3 km/h (2.6 mi/h)	357
Sawing wood or shoveling snow	480
Jogging, 9 km/h (5.3 mi/h)	570
Rowing, 20 strokes/min	828

liberation occur in both the breakdown and subsequent resynthesis of these molecules.) Thus, when epinephrine secretion by the adrenal medulla is stimulated, the metabolic rate rises. This accounts for part of the greater heat production associated with emotional stress, although increased muscle tone also contributes.

Food-Induced Thermogenesis The ingestion of food rapidly increases the metabolic rate by 10 to 20 percent for a few hours after eating. This effect is known as **food-induced thermogenesis.** Ingested protein produces the greatest effect, carbohydrate and fat, less. Most of the increased heat production is secondary to processing of the absorbed nutrients by the liver, not to the energy expended by the gastrointestinal tract in digestion and absorption. It is to avoid the contribution of food-induced thermogenesis that BMR tests must be performed in the postabsorptive state.

To reiterate, food-induced thermogenesis is the *rapid* increase in energy expenditure in response to ingestion of a meal. As we shall see, *prolonged* alterations in food intake (either increased or decreased total calories) also have significant effects on metabolic rate but are not termed food-induced thermogenesis.

Muscle Activity The factor that can most increase metabolic rate is altered skeletal-muscle activity. Even minimal increases in muscle contraction significantly increase metabolic rate, and strenuous exercise may raise energy expenditure more than fifteenfold (Table 18–9). Thus, depending on the degree of physical activity, total energy expenditure may vary for a normal young adult from a value of approximately 1500 kcal/24 h to more than 7000 kcal/24 h (for a lumberjack). Changes in muscle activity also account in part for the changes in metabolic rate that occur during sleep (decreased muscle contraction), during exposure to a low environmental temperature (increased muscle contraction and shivering), and with strong emotions.

Regulation of Total-Body Energy Stores

The laws of thermodynamics dictate that the total energy expenditure (metabolic rate) of the body must equal the total energy intake. We have already identified the ultimate forms of energy expenditure: internal heat production, external work, and net molecular synthesis (energy storage). The source of input is the energy contained in ingested food. Therefore:

Energy from food intake =
Internal heat produced + External work + Energy stored

Our equation includes no term for loss of fuel from the body via excretion of nutrients because, in normal persons, only negligible losses occur via the urine, feces, and as sloughed hair and skin. In certain diseases, however, the most important being diabetes, urinary losses of organic molecules may be quite large and would have to be included in the equation.

Let us now rearrange the equation to focus on energy storage:

Energy stored =
Energy from food intake − (Internal heat produced + External work)

Thus, whenever energy intake differs from the sum of internal heat produced and external work, changes in energy storage occur; that is, the total-body energy content increases or decreases. Normally, as we have seen, energy storage, except in growing children, is mainly in the form of fat in adipose tissue.

It is worth emphasizing at this point that "body weight" and "total-body energy content" are not synonymous terms, although there is a popular tendency to equate the two. Body weight is determined not only by the amount of fat, carbohydrate, and protein in the body, but also by the amounts of water, bone, and other minerals. For example, an individual can lose body weight quickly as the result of sweating or an unusual increase in urinary output, or can gain large amounts of weight as a result of water retention, as occurs, for example, during heart failure (Chapter 14). Moreover, even focusing only on the nutrients, a constant body weight does not mean that total-body energy content is constant. The reason is that 1 g of fat contains 9 kcal, whereas 1 g of either carbohydrate or protein contains 4 kcal. Thus, for example, aging is usually associated with a gain of fat and a loss of protein; the result is that even though the person's body weight may stay

constant, the total-body energy content has increased. Despite these qualifications, however, in the remainder of this chapter changes in body weight are equated with changes in total-body energy content and, more specifically, changes in body fat stores.

Body weight in adults is usually regulated around a relatively constant set point. Theoretically this constancy can be achieved by reflexly adjusting caloric intake and/or energy expenditure in response to changes in body weight. It has long been assumed that regulation of caloric intake is the only important adjustment, and this process will be described in the next section. However, there is growing evidence that energy expenditure can also be reflexly adjusted in response to changes in body weight, and we describe it first.

A typical demonstration of this process in human beings is as follows: Total daily energy expenditure was measured in nonobese subjects at their usual body weight and again after they were caused either to lose 10 percent of their body weight by underfeeding or to gain 10 percent by overfeeding. At their new body weight, the overfed subjects manifested a large (15 percent) increase in both resting and nonresting energy expenditure, and the underfed subjects a similar decrease. These changes in energy expenditure were much greater than could be accounted for simply by the altered metabolic mass of the body or having to move a larger or smaller body.

The generalization that emerges from this and other similar studies is that a dietary-induced change in total-body energy stores triggers, in negative-feedback fashion, an alteration in energy expenditure that opposes the gain or loss of energy stores. This phenomenon helps explain why some dieters lose about 5 to 10 lbs of fat fairly easily and then become stuck at a plateau. It also helps explain why some very thin people have difficulty trying to gain much weight. Another unsettled question is whether such "metabolic resistance" to changes in body weight persists indefinitely or is only a transient response to rapid changes in body weight.

Control of Food Intake

The control of food intake can be analyzed in the same way as any other biological control system. As the previous section emphasized, the variable being maintained relatively constant in this system is total-body energy content, more specifically, total fat stores. Accordingly, an essential component of such a control system is a hormone—**leptin**—synthesized by adipose-tissue cells themselves, and released from the cells in proportion to the amount of fat in the adipose tissue. This hormone acts on the hypothalamus to cause a reduction in food intake (by inhibiting the release of neuropeptide Y, a hypothalamic neurotransmitter that stimulates eating). Leptin also stimulates the metabolic rate and, therefore, probably plays an important role in the changes in energy expenditure that occur in response to overfeeding or underfeeding, as described in the previous section. Thus, as illustrated in Figure 18–16, leptin functions in a negative-feedback system to maintain total-body energy content constant by "telling" the brain how much fat is being stored.

Leptin may turn out to exert many other effects on the hypothalamus and anterior pituitary. For example, during long-term fasting, there is a marked decrease in the secretion of the sex steroids and thyroid hormones, and an increase in the secretion of adrenal glucocorticoids. In experimental animals, these effects were almost completely eliminated by administering leptin. This suggests that leptin normally exerts a stimulatory effect on the pathways that control the secretion of these hormones (the possible role of leptin in puberty is described in Chapter 19).

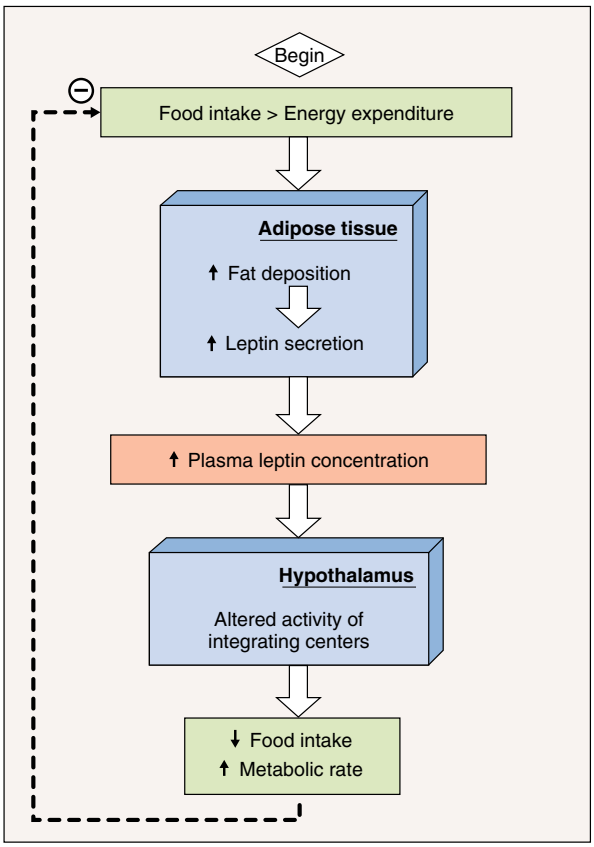

FIGURE 18–16
Role of leptin in the control of total-body energy stores.

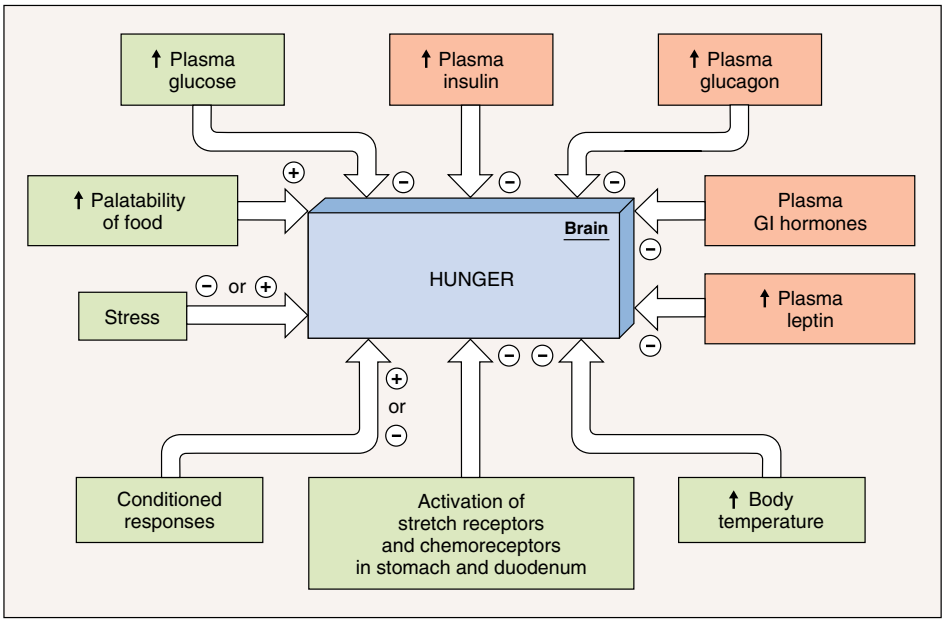

FIGURE 18–17
Short-term inputs controlling food intake. The minus signs denote hunger suppression, and the plus signs denote hunger stimulation.

It should be emphasized that leptin is crucial for *long-term* matching of caloric intake to energy expenditure. In addition, it is thought that various other signals act on the hypothalamus (and other brain areas) over short periods of time to regulate individual meal length and frequency (Figure 18–17). These **satiety signals** cause the person to cease feeling hungry and set the time period before hunger returns once again. For example, the rate of insulin-dependent glucose utilization by certain areas of the hypothalamus rises during eating, and this probably constitutes a satiety signal. Insulin, which increases during food absorption, also acts directly as a satiety signal. The increase in metabolic rate induced by eating tends to raise body temperature slightly, which acts as yet another satiety signal. Finally, there are satiety signals initiated by the presence of food within the gastrointestinal tract: These include neural signals triggered by stimulation of both stretch receptors and chemoreceptors in the stomach and duodenum, as well as by several of the hormones (cholecystokinin, for example) released from the stomach and duodenum during eating.

Food intake is also strongly influenced by the reinforcement, both positive and negative, of such things as smell, taste, and texture. In addition, the behavioral concepts of reinforcement, drive, and motivation, described in Chapter 13, must be incorporated into any comprehensive theory of food-intake control.

Another significant factor that can increase food intake is stress, as demonstrated by controlled experiments in animals.

Overweight and Obesity

The definition of ***overweight*** is a functional one, a state in which an increased amount of fat in the body results in a significant impairment of health from a variety of diseases, notably hypertension, atherosclerosis, heart disease, and diabetes. ***Obesity*** denotes a particularly large accumulation of fat—that is, being extremely overweight. The difficulty for scientists has been in establishing just how much fat constitutes "overweight"—that is, in determining at what point fat accumulation begins to constitute a health risk. This is evaluated by epidemiological studies that correlate disease rates with some measure of the amount of fat in the body. Presently, the preferred simple method for assessing the latter is not the body weight but the **body mass index (BMI),** which is calculated by dividing the weight (in kilograms) by the square of the height (in meters). For example, a 70-kg person with a height of 180 cm would have a BMI of 21.6 ($70/1.8^2$).

In 1998, the National Institutes of Health issued guidelines that categorize people with BMIs of greater than 25 as overweight (that is, as having some increased health risk because of excess fat) and those with greater than 30 as obese, with a markedly

increased health risk. According to these criteria, more than half of U.S. women and men age 20 and older are now considered overweight, and nearly one-quarter are clinically obese! These guidelines, however, are quite controversial. First, the large number of epidemiological studies that have been performed do not always agree as to where along the continuum of BMIs between 25 and 30 health risks begin to occur. Second, even granting increased risk above a BMI of 25, many experts believe that the studies do not always account for confounding factors associated with being overweight or even obese, particularly a sedentary lifestyle; they believe that the increased health risk may actually be due to lack of physical activity, not body fat per se. (This question is particularly interesting and subject to study now that there are quite a few people who are overweight or even obese but are physically fit due to exercise programs.) Third, these experts feel that even if being overweight is risky, there is inadequate long-term evidence that weight loss leads to a longer life in otherwise healthy persons categorized as overweight.

To add to the complexity, there is growing evidence that not just total fat but where the fat is located has important consequences. Specifically, people with mostly abdominal fat ("apples") are at greater risk for developing serious conditions such as diabetes and cardiovascular diseases than people whose fat is mainly in the lower body ("pears")—on the buttocks and thighs. There is presently no agreement as to the explanation of this phenomenon, but it is known that there are important differences in the physiology of adipose-tissue cells in these regions. For example, adipose-tissue cells in the abdomen are much more adept at breaking down fat stores and releasing the products into the blood. Moreover, these cells are also more responsive to the hormone cortisol, which may partially explain why chronic stress seems to be associated with greater amounts of abdominal fat (stress is discussed in Chapter 20).

What is known about the underlying causes of obesity? Identical twins who have been separated soon after birth and raised in different households manifest strikingly similar body weights and incidences of obesity as adults; such studies have indicated that genetic factors play an important role in obesity. It has been postulated that natural selection favored the evolution in our ancestors of "thrifty genes," which boosted the ability to store fat from each feast in order to sustain people through the next fast. Given today's relative surfeit in many countries of the world, such an adaptation would now be a liability.

Despite the importance of genetic factors, psychological, cultural, and social factors can also be important; for example, the increasing incidence of obesity in the United States and other industrialized nations during the past few generations cannot be explained by changes in our genes.

Much recent research has focused on possible abnormalities in the leptin system as a cause of obesity. In mice that have severe hereditary obesity, the gene—*ob*—that codes for leptin is mutated so that adipose-tissue cells produce either an abnormal, inactive leptin or no leptin at all. The same is not true, however, for the vast majority of obese people: The leptin secreted by these people is normally active, and leptin concentrations in the blood are elevated, not reduced. This indicates that leptin secretion is not at fault in these people. This is not really surprising since most obesity researchers believe that there must be multiple genes that interact with one another and with environmental factors to influence a person's susceptibility to gain weight.

The methods and goals of treating obesity are presently undergoing extensive rethinking. An increase in body fat must be due to an excess of food intake over the metabolic rate, and low-calorie diets have long been the mainstay of therapy. However, it is now clear that such diets *alone* have limited effectiveness in obese people; over 90 percent regain all or most of the lost weight within 5 years. Another important reason for the ineffectiveness of such diets is that, as described earlier, the person's metabolic rate drops, sometimes falling low enough to prevent further weight loss on as little as 1000 calories a day. Related to this, many obese people continue to gain weight or remain in stable energy balance on a caloric intake equal to or less than the amount consumed by people of normal weight. These persons must either have less physical activity than normal or have lower basal metabolic rates. Finally, at least half of obese people—those who are more than 20 percent overweight—who try to diet down to desirable weights suffer medically, physically, and psychologically. This is what would be expected if the body were "trying" to maintain body weight (more specifically fat stores) at the higher set point.

Such studies, taken together, indicate that crash diets are not an effective long-term method for controlling weight. Instead one should set caloric intake at a level that can be maintained for the rest of one's life; such an intake in an overweight individual should lead to a slow steady weight loss of no more than 1 lb per week until the body weight stabilizes at a new, lower level. Most important, any program of weight loss should include increased physical activity of the endurance type. The exercise itself utilizes calories (though depressingly few), but more importantly exercise partially offsets the tendency, described earlier, for the metabolic rate to decrease during long-term caloric restriction and weight loss. Also, the combination of exercise and caloric restriction causes the person to lose more fat and less protein than with caloric

TABLE 18–10 Summary of National Research Council Dietary Recommendations

1. Reduce total fat intake to 30 percent or less of calories. Reduce saturated fatty acid intake to less than 10 percent of calories and the intake of cholesterol to less than 300 mg daily.
2. Every day eat five or more servings of a combination of vegetables and fruits, especially green and yellow vegetables and citrus fruits. Also, increase starches and other complex carbohydrates by eating six or more daily servings of a combination of breads, cereals, and legumes.
3. Maintain protein intake at moderate levels.
4. Balance food intake and physical activity to maintain appropriate body weight.
5. Alcohol consumption is not recommended. For those who drink alcoholic beverages, limit consumption to the equivalent of 1 ounce of pure alcohol in a single day.
6. Limit total daily intake of salt to 6 g or less.
7. Maintain adequate calcium intake.
8. Avoid taking dietary supplements in excess of the RDA (Recommended Dietary Allowance) in any one day.
9. Maintain an optimal intake of fluoride, particularly during the years of primary and secondary tooth formation and growth.

restriction alone. To restate the information of the previous two sentences in terms of control systems, exercise seems to lower the set point around which the body regulates total-body fat stores.

As an exercise in energy balance, let us calculate how rapidly a person can expect to lose weight on a reducing diet (assuming, for simplicity, no change in energy expenditure). Suppose an individual whose steady-state metabolic rate per 24 h is 2000 kcal goes on a 1000 kcal/day diet. How much of the person's own body fat will be required to supply this additional 1000 kcal/day? Since fat contains 9 kcal/g:

$$\frac{1000 \text{ kcal/day}}{9 \text{ kcal/g}} = 111 \text{ g/day, or } 777 \text{ g/week}$$

Approximately another 77 g of water is lost from the adipose tissue along with this fat (adipose tissue is 10 percent water), so that the grand total for 1 week's loss equals 854 g, or 1.8 lb. Thus, even on this rather severe diet, the person can reasonably expect to lose approximately this amount of weight per week, assuming no decrease in metabolic rate occurs. Actually, the amount of weight lost during the first week will probably be considerably greater since a large amount of *water* may be lost early in the diet, particularly when the diet contains little carbohydrate. This early loss is not really elimination of excess fat but often underlies the extravagant claims made for fad diets.

Eating Disorders: Anorexia Nervosa and Bulimia

The two major eating disorders are found almost exclusively in adolescent girls and young women. The typical person with ***anorexia nervosa*** becomes pathologically afraid of gaining weight and reduces her food intake so severely that she may die of starvation. It is not known whether the cause of anorexia nervosa is primarily psychological or biological. There are many other abnormalities associated with it—loss of menstrual periods, low blood pressure, low body temperature, altered secretion of many hormones. It is likely that these are simply the result of starvation, although it is possible that some represent signs, along with the eating disturbances, of primary hypothalamic malfunction.

Bulimia is recurrent episodes of binge eating. It is usually associated with regular employment of self-induced vomiting, laxatives, or diuretics, as well as strict dieting, fasting, or vigorous exercise to prevent weight gain. Like individuals with anorexia nervosa, those with bulimia manifest a persistent overconcern with body weight, although they are generally within 10 percent of their ideal weight. It, too, is accompanied by a variety of physiological abnormalities, but it is unknown whether they are causal or secondary.

What Should We Eat?

In the last few years, more and more dietary factors have been associated with the cause or prevention of many diseases, including not only coronary heart disease but hypertension, cancer, birth defects, osteoporosis, and a variety of other chronic diseases. These associations come mainly from animal studies, epidemiologic studies on people, and basic research concerning potential mechanisms. The problem is that the findings are often difficult to interpret and may be conflicting. To synthesize all this material in the form of simple clear recommendations to the general public is a monumental task, and all such attempts have been subjected to intense criticism. We present, in Table 18–10, one of the most commonly used sets, that issued by the National Research Council.

Regulation of Body Temperature

Animals, including people, capable of maintaining their body temperatures within very narrow limits are termed **homeothermic.** The relatively constant and high body temperature frees biochemical reactions from fluctuating with the external temperature. However, the maintenance of a relatively high body temperature (approximately 37°C, in normal persons) imposes a requirement for precise regulatory mechanisms, since further large elevations of temperature cause nerve malfunction and protein denaturation. Some people suffer convulsions at a body temperature of 41°C (106°F), and 43°C is considered to be the absolute limit for survival.

Several important generalizations about normal human body temperature should be stressed at the outset: (1) Oral temperature averages about 0.5°C less than rectal, which is generally used as an estimate of internal temperature (also known as core body temperature); thus, not all parts of the body have the same temperature. (2) Internal temperature varies several degrees in response to activity pattern and changes in external temperature. (3) There is a characteristic circadian fluctuation of about 1°C (Figure 18–18), temperature being lowest during the night and highest during the day. (4) An added variation in women is a higher temperature during the second half of the menstrual cycle.

If temperature is viewed as a measure of heat "concentration," temperature regulation can be studied by our usual balance methods. The total heat content gained or lost by the body is determined by the *net difference* between heat produced and heat loss. Maintaining a constant body temperature means that, in the steady state, heat production must equal heat loss. The basic principles of heat production were described earlier in this chapter in the section on metabolic rate, and those of heat loss are described next. Then we will present the reflexes that play upon these processes specifically to regulate body temperature.

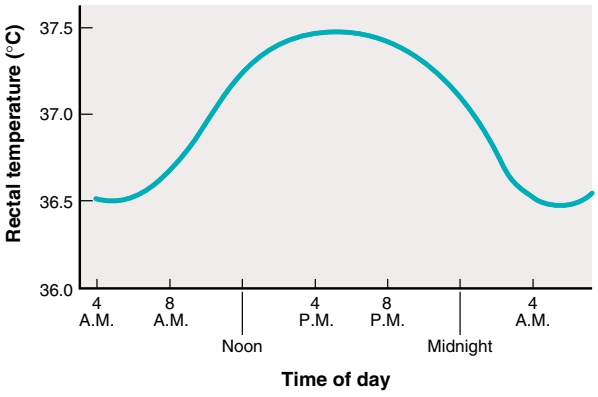

FIGURE 18–18
Circadian changes in core (measured as rectal) body temperature in normal males and in normal females in the first half of the menstrual cycle.
Adapted from Scales et al.

Mechanisms of Heat Loss or Gain

The surface of the body can lose heat to the external environment by radiation, conduction, and convection (Figure 18–19) and by the evaporation of water. Before defining each of these processes, however, it must be emphasized that radiation, conduction, and convection can under certain circumstances lead to heat *gain*, instead of heat loss.

Radiation is the process by which the surfaces of all objects constantly emit heat in the form of electromagnetic waves. The rate of emission is determined by the temperature of the radiating surface. Thus, if the body surface is warmer than the various surfaces in the environment, net heat is lost from the body, the rate being directly dependent upon the temperature difference between the surfaces.

Conduction is the loss or gain of heat by transfer of thermal energy during collisions between adjacent molecules. In essence, heat is "conducted" from molecule to molecule. The body surface loses or gains heat by conduction through direct contact with cooler or warmer substances, including the air or water.

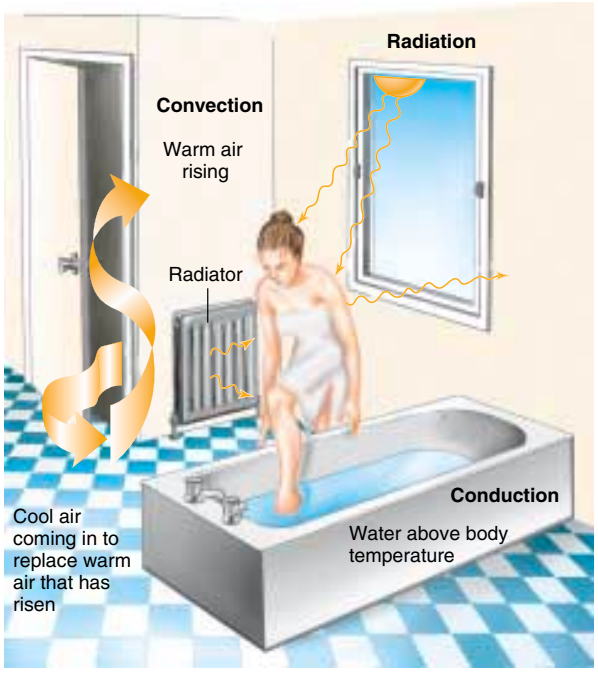

FIGURE 18–19
Mechanisms of heat transfer.

Convection is the process whereby conductive heat loss or gain is aided by movement of the air or water next to the body. For example, air next to the body is heated by conduction, moves away, and carries off the heat just taken from the body. The air that moved away is replaced by cooler air, which in turn follows the same pattern. Convection is always occurring because warm air is less dense and therefore rises, but it can be greatly facilitated by external forces such as wind or fans. Thus, convection aids conductive heat exchange by continuously maintaining a supply of cool air. Henceforth we shall also imply convection when we use the term "conduction."

Because of the great importance of air movement in aiding heat loss, attempts have been made to quantify the cooling effect of combinations of air speed and temperature. The most useful tool is the **wind-chill index,** which states the hypothetical temperature with *no* wind that would provide the same cooling effect as the actual temperature and wind velocity. For example, the wind-chill index would be −10°C if an object in a 5°C windy environment cooled as fast as it would if the temperature were actually −10°C and there was no wind at all.

Evaporation of water from the skin and membranes lining the respiratory tract is the other major process for loss of body heat. A very large amount of energy—600 kcal/L—is required to transform water from the liquid to the gaseous state. Thus, whenever water vaporizes from the body's surface, the heat required to drive the process is conducted from the surface, thereby cooling it.

Temperature-Regulating Reflexes

Temperature regulation offers a classic example of a biological control system (we used it as our example of such systems in Figure 7–1). The balance between heat production and heat loss is continuously being disturbed, either by changes in metabolic rate (exercise being the most powerful influence) or by changes in the external environment that alter heat loss or gain. The resulting changes in body temperature are detected by thermoreceptors, which initiate reflexes that change the output of various effectors so that heat production and/or loss are changed and body temperature is restored toward normal.

Figure 18–20 summarizes the specific components of these reflexes. There are two categories of thermoreceptors, one in the skin (**peripheral thermoreceptors,** described in Chapter 9) and the other **(central thermoreceptors)** in deep body structures, including the hypothalamus, spinal cord, and abdominal organs. Since it is the core body temperature, not the skin temperature, that is being maintained relatively constant, the central thermoreceptors provide the essential negative-feedback component of the reflexes. The peripheral thermoreceptors provide feedforward information, as described in Chapter 7, and also account for one's ability to identify a hot or cold area of the skin.

An area of the hypothalamus serves as the primary overall integrator of the reflexes, but other brain centers also exert some control over specific components of the reflexes.

Output from the hypothalamus and the other brain areas to the effectors is via: (1) sympathetic nerves to the sweat glands, skin arterioles, and the adrenal medulla; and (2) motor neurons to the skeletal muscles.

Control of Heat Production Changes in muscle activity constitute the major control of heat production for temperature regulation. The first muscle changes in response to a decrease in core body temperature are a gradual and general increase in skeletal-muscle contraction. This may lead to shivering, which consists of oscillating rhythmical muscle contractions and relaxations occurring at a rapid rate. During shivering, the efferent motor nerves to the skeletal muscles are influenced by descending pathways under the primary control of the hypothalamus. Because almost no external work is performed by shivering, virtually all the energy liberated by the metabolic machinery appears as internal heat and is known as **shivering thermogenesis.** People also use their muscles for voluntary heat-producing activities such as foot stamping and hand clapping.

Thus far, our discussion has focused primarily on the muscle response to *cold;* the opposite muscle reactions occur in response to heat. Basal muscle contraction is reflexly decreased, and voluntary movement is also diminished. These attempts to reduce heat production are relatively limited, however, both because basal muscle contraction is quite low to start with and because any increased core temperature produced by the heat acts *directly* on cells to increase metabolic rate.

Muscle contraction is not the only process controlled in temperature-regulating reflexes. In most experimental animals, chronic cold exposure induces an increase in metabolic rate (heat production) that is not due to increased muscle activity and is termed **nonshivering thermogenesis.** Its causes are an increased adrenal secretion of epinephrine and increased sympathetic activity to adipose tissue, with some contribution by thyroid hormone as well. However, nonshivering thermogenesis is quite minimal, if present at all, in adult human beings, and there is no increased secretion of thyroid hormone in response to cold. Nonshivering thermogenesis does occur in infants.

Control of Heat Loss by Radiation and Conduction For purposes of temperature control, it is convenient to view the body as a central core surrounded by a shell consisting of skin and subcutaneous tissue; we shall refer to this complex outer shell simply as skin.

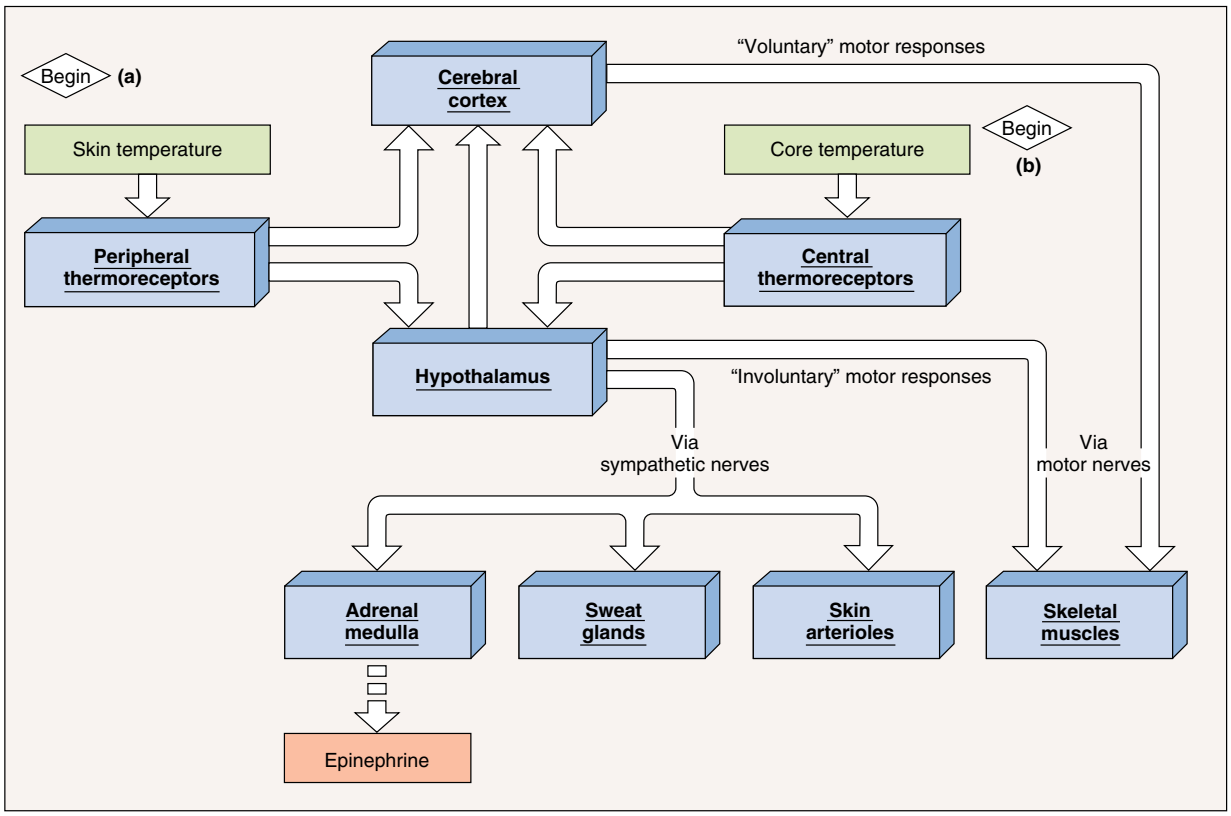

FIGURE 18–20

Summary of temperature-regulating mechanisms beginning with (a) peripheral thermoreceptors and (b) central thermoreceptors. The dashed arrow from the adrenal medulla indicates that this hormonal pathway is of minor importance in adult human beings. The solid arrows denote neural pathways. The hypothalamus influences sympathetic nerves via descending pathways.

It is the temperature of the central core that is being regulated at approximately 37°C. As we shall see, the temperature of the outer surface of the skin changes markedly.

If the skin were a perfect insulator, no heat would ever be lost from the core. The temperature of the outer skin surface would equal the environmental temperature, and net conduction would be zero. The skin is not a perfect insulator, however, and so the temperature of its outer surface generally is somewhere between that of the external environment and that of the core.

The skin's effectiveness as an insulator is subject to physiological control by a change in the blood flow to it. The more blood reaching the skin from the core, the more closely the skin's temperature approaches that of the core. In effect, the blood vessels diminish the insulating capacity of the skin by carrying heat to the surface to be lost to the external environment. These vessels are controlled largely by vasoconstrictor sympathetic nerves, the firing rate of which is reflexly increased in response to cold and decreased in response to heat. There is also a population of sympathetic neurons to the skin whose neurotransmitters (as yet unidentified) cause active *vasodilation*. Certain areas of skin participate much more than others in all these vasomotor responses, and so skin temperatures vary with location.

Finally, there are three *behavioral* mechanisms for altering heat loss by radiation and conduction: changes in surface area, changes in clothing, and choice of surroundings. Curling up into a ball, hunching the shoulders, and similar maneuvers in response to cold reduce the surface area exposed to the environment, thereby decreasing heat loss by radiation and conduction. In human beings, clothing is also an important component of temperature regulation, substituting for the insulating effects of feathers in birds and fur in other mammals. The outer surface of the clothes forms the true "exterior" of the body surface. The skin loses heat directly to the air space trapped by the clothes, which in turn pick up heat from the inner air layer and

TABLE 18–11 Summary of Effector Mechanisms in Temperature Regulation

Desired Effect	Mechanism
	STIMULATED BY COLD (SEE ALSO FIGURE 7–2)
Decrease heat loss	1. Vasoconstriction of skin vessels
	2. Reduction of surface area (curling up, etc.)
	3. Behavioral response (put on warmer clothes, raise thermostat setting, etc.)
Increase heat production	1. Increased muscle tone
	2. Shivering and increased voluntary activity
	3. Increased secretion of epinephrine (minimal in adults)
	4. Increased food appetite
	STIMULATED BY HEAT
Increase heat loss	1. Vasodilation of skin vessels
	2. Sweating
	3. Behavioral response (put on cooler clothes, turn on fan, etc.)
Decrease heat production	1. Decreased muscle tone and voluntary activity
	2. Decreased secretion of epinephrine (minimal in adults)
	3. Decreased food appetite

transfer it to the external environment. The insulating ability of clothing is determined primarily by the thickness of the trapped air layer.

Clothing is important not only at low temperatures but also at very high temperatures. When the environmental temperature is greater than body temperature, conduction favors heat *gain* rather than heat loss. Heat gain also occurs by radiation during exposure to the sun. People therefore insulate themselves in such situations by wearing clothes. The clothing, however, must be loose so as to allow adequate movement of air to permit evaporation (see below). White clothing is cooler since it reflects more radiant energy, which dark colors absorb. Loose-fitting, light-colored clothes are far more cooling than going nude in a hot environment and during direct exposure to the sun.

The third behavioral mechanism for altering heat loss is to seek out warmer or colder surroundings, as for example by moving from a shady spot into the sunlight. Raising or lowering the thermostat of a house or turning on an air conditioner also fits this category.

Control of Heat Loss by Evaporation Even in the absence of sweating, there is loss of water by diffusion through the skin, which is not waterproof. A similar amount is lost from the respiratory lining during expiration. These two losses are known as **insensible water loss** and amount to approximately 600 ml/day in human beings. Evaporation of this water accounts for a significant fraction of total heat loss. In contrast to this passive water loss, sweating requires the active secretion of fluid by **sweat glands** and its extrusion into ducts that carry it to the skin surface.

Production of sweat is stimulated by sympathetic nerves to the glands. (These nerves release acetylcholine rather than the usual sympathetic neurotransmitter norepinephrine.) Sweat is a dilute solution containing sodium chloride as its major solute. Sweating rates of over 4 L/h have been reported; the evaporation of 4 L of water would eliminate almost 2400 kcal from the body!

It is essential to recognize that sweat must evaporate in order to exert its cooling effect. The most important factor determining evaporation rate is the water-vapor concentration of the air—that is, the *relative humidity*. The discomfort suffered on humid days is due to the failure of evaporation; the sweat glands continue to secrete, but the sweat simply remains on the skin or drips off.

Integration of Effector Mechanisms Table 18–11 summarizes the effector mechanisms regulating temperature, none of which is an all-or-none response but a graded, progressive increase or decrease in activity. By altering heat loss, changes in skin blood flow alone can regulate body temperature over a range of environmental temperatures (approximately 25 to 30°C or 75 to 86°F for a nude individual) known as the **thermoneutral zone.** At temperatures lower than this, even maximal vasoconstriction cannot prevent heat loss from exceeding heat production, and the body must increase its heat production to maintain temperature. At environmental temperatures above the thermoneutral zone, even maximal vasodilation cannot eliminate heat as fast as it is produced, and another heat-loss mechanism—sweating—is therefore brought strongly

into play. Since at environmental temperatures above that of the body, heat is actually added to the body by radiation and conduction, evaporation is the sole mechanism for heat loss. A person's ability to tolerate such temperatures is determined by the humidity and by his/her maximal sweating rate. For example, when the air is completely dry, an individual can tolerate a temperature of 130°C (225°F) for 20 min or longer, whereas very moist air at 46°C (115°F) is bearable for only a few minutes.

Temperature Acclimatization

Changes in sweating onset, volume, and composition determine people's chronic adaptation to high temperatures. A person newly arrived in a hot environment has poor ability to do work; body temperature rises and severe weakness may occur. After several days, there is a great improvement in work tolerance, with much less increase in body temperature, and the person is said to have acclimatized to the heat (see Chapter 7 for a discussion of the concept of acclimatization). Body temperature does not rise as much because sweating begins sooner and the volume of sweat produced is greater.

There is also an important change in the composition of the sweat, namely, a marked reduction in its sodium concentration. This adaptation, which minimizes the loss of sodium from the body via sweat, is due to increased secretion of the adrenal mineralocorticoid hormone aldosterone. The sweat-gland secretory cells produce a solution with a sodium concentration similar to that of plasma, but some of the sodium is absorbed back into the blood as the secretion flows along the sweat-gland ducts toward the skin surface. Aldosterone stimulates this absorption in a manner identical to its stimulation of sodium reabsorption in the renal tubules.

Cold acclimatization has been much less studied than heat acclimatization because of the difficulty of subjecting individuals to total-body cold stress over long periods sufficient to produce acclimatization. Moreover, groups such as Eskimos that live in cold climates generally dress very warmly and so would not develop acclimatization to the cold.

Fever and Hyperthermia

Fever is an elevation of body temperature due to a "resetting of the thermostat" in the hypothalamus. A person with a fever still regulates body temperature in response to heat or cold but at a higher set point. The most common cause of fever is infection, but physical trauma and stress can also induce fever.

The onset of fever during infection is frequently gradual, but it is most striking when it occurs rapidly in the form of a chill. The brain thermostat is suddenly raised, the person feels cold, and marked vasoconstriction and shivering occur. The person also curls up and puts on more blankets. This combination of decreased heat loss and increased heat production serves to drive body temperature up to the new set point, where it stabilizes. It will continue to be regulated at this new value until the thermostat is reset to normal and the fever "breaks." The person then feels hot, throws off the covers, and manifests profound vasodilation and sweating.

What is the basis for the thermostat resetting? Chemical messengers collectively termed **endogenous pyrogen (EP)** are released from macrophages (as well as other cell types) in the presence of infection or other fever-producing stimulus. The next steps vary depending on the precise stimulus for the release of EP. As illustrated in Figure 18–21, in some cases EP probably circulates in the blood to act upon the thermoreceptors in the hypothalamus (and perhaps other brain areas), altering the rate of firing and their input to the integrating centers. In other cases, EP may be produced by macrophage-like cells in the liver and stimulate neural receptors there that give rise to afferent neural input to the hypothalamic thermoreceptors. In both cases, the immediate cause of the resetting is a local synthesis and release of prostaglandins within the hypothalamus. ***Aspirin*** reduces fever by inhibiting this prostaglandin synthesis (Chapter 7).

The term "EP" was coined at a time when the identity of the chemical messenger(s) was not known. At least one peptide, **interleukin 1 (IL-1),** is now known to function as an EP, but other peptides—for example, **interleukin 6 (IL-6)**—play a role too. In addition to their effects on temperature, IL-1 and the other peptides have many other effects (described in Chapter 20) that have the common denominator of enhancing resistance to infection and promoting the healing of damaged tissue. Also as described in Chapter 20, all these peptides belong to the large family of chemical messengers called cytokines.

The story is even more complicated, however, because in response to a rising temperature the hypothalamus and other tissues release messengers that prevent excessive fever or contribute to the resetting of body temperature when the fever-causing stimulus is eliminated. Such messengers are termed **endogenous cryogens.** One known endogenous cryogen is vasopressin, functioning in this regard as a neurotransmitter.

One would expect fever, which is such a consistent concomitant of infection, to play some important protective role, and most evidence suggests that such is the case. For example, increased body temperature stimulates a large number of the body's defensive responses to infection. The likelihood that fever is a

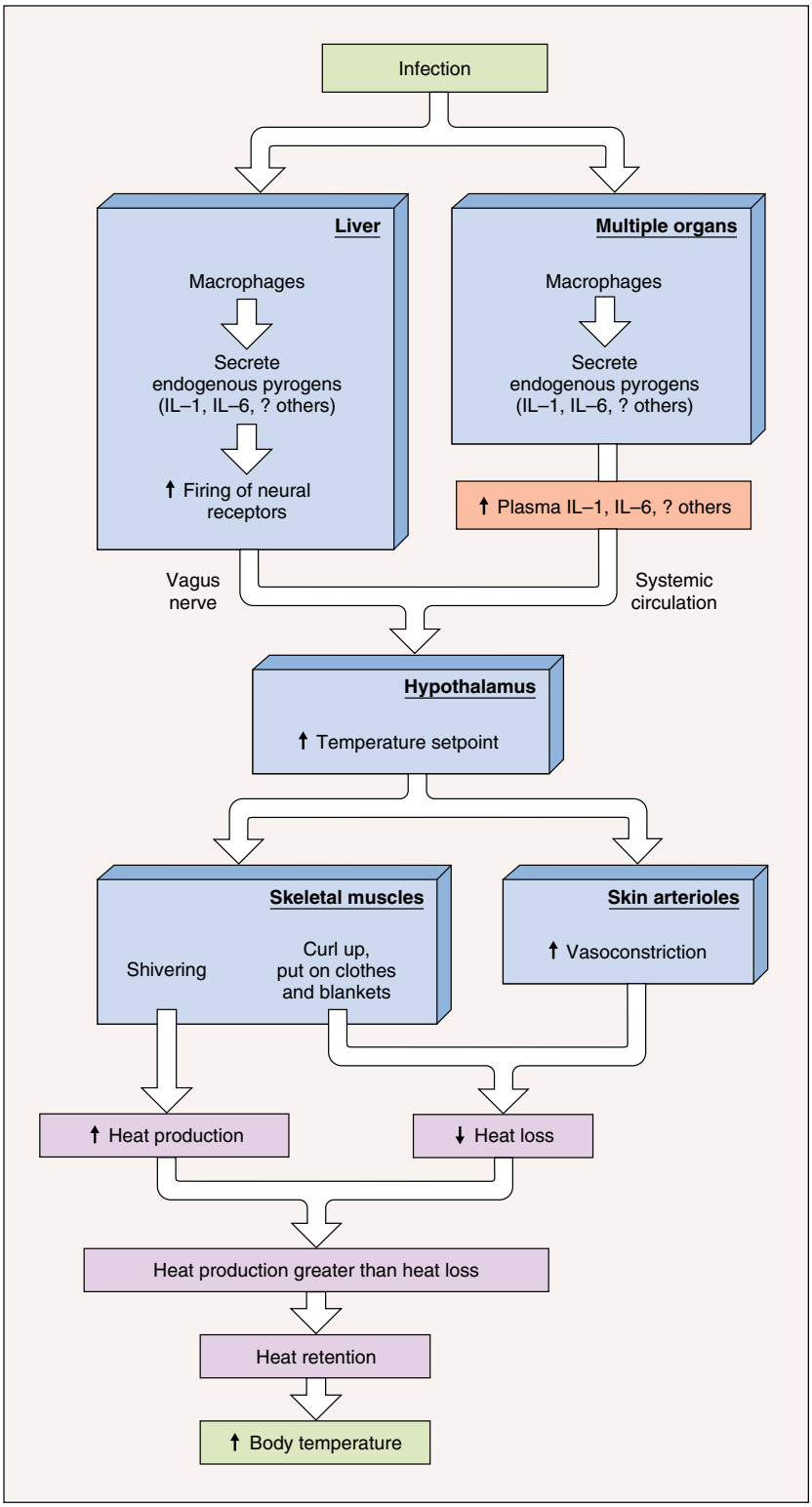

FIGURE 18–21
Pathway by which infection causes fever (IL-1 = interleukin 1, IL-6 = interleukin 6). Compare this figure to Figure 7–1: The effector responses are identical but they serve to keep body temperature *relatively constant* during exposure to cold (Figure 7–1) and *raise* body temperature during an infection (this figure).

beneficial response raises important questions concerning the use of aspirin and other drugs to suppress fever during infection. It must be emphasized that these questions apply to the usual modest fevers. There is no question that an extremely high fever can be harmful, particularly in its effects on the central nervous system, and must be vigorously opposed with drugs and other forms of therapy.

To reiterate, fever is an increased body temperature caused by an elevation of the thermal set point. When body temperature is elevated for any other reason—that is, when body temperature is above the set point—it is termed **hyperthermia.** The most common cause of hyperthermia in normal people is exercise; the rise in body temperature above set point is due to retention of some of the internal heat generated by the exercising muscles.

As shown in Figure 18–22, heat production rises immediately during the initial stage of exercise and exceeds heat loss, causing heat storage in the body and a rise in the core temperature. This rise in core temperature triggers reflexes, via the central thermoreceptors, for increased heat loss; with increased skin blood flow and sweating, the discrepancy between heat production and heat loss starts to diminish but does not disappear. Therefore core temperature continues to rise. Ultimately, core temperature will be high enough to drive, via the central thermoreceptors, the heat-loss reflexes at a rate such that heat loss once again equals heat production. At this point, core temperature stabilizes at this elevated value despite continued exercise.

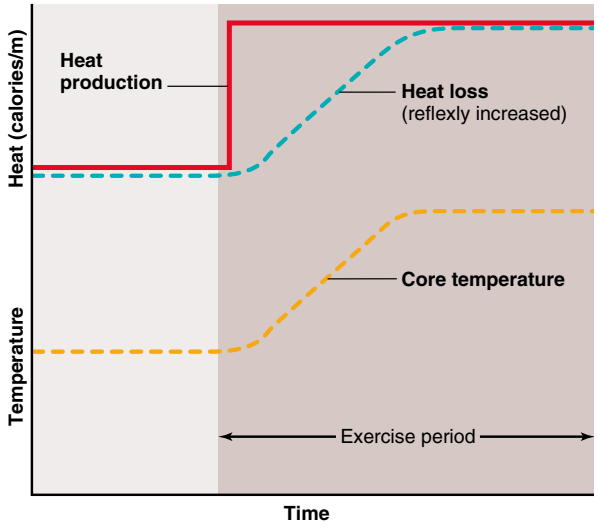

FIGURE 18–22
Thermal changes during exercise. Heat loss is reflexly increased, and when it once again equals heat production, core temperature stabilizes.

Heat Exhaustion and Heat Stroke *Heat exhaustion* is a state of collapse, often taking the form of fainting, due to hypotension brought on by (1) depletion of plasma volume secondary to sweating, and (2) extreme dilation of skin blood vessels. Thus, decreases in both cardiac output (due to the decreased plasma volume) and peripheral resistance (due to the vasodilation) contribute to the hypotension. Heat exhaustion occurs as a direct consequence of the activity of heat-loss mechanisms, and because these mechanisms have been so active, the body temperature is only modestly elevated. In a sense, heat exhaustion is a safety valve that, by forcing cessation of work in a hot environment when heat-loss mechanisms are overtaxed, prevents the larger rise in body temperature that would precipitate the far more serious condition of heat stroke.

In contrast to heat exhaustion, ***heat stroke*** represents a complete breakdown in heat-regulating systems so that body temperature keeps going up and up. It is an extremely dangerous situation characterized by collapse, delirium, seizures, or prolonged unconsciousness—all due to marked elevation of body temperature. It almost always occurs in association with exposure to or overexertion in hot and humid environments. In some individuals, particularly the elderly, heat stroke may appear with no apparent prior period of severe sweating, but in most cases, it comes on as the end stage of prolonged untreated heat exhaustion. Exactly what triggers the transition to heat stroke is not clear—impaired circulation to the brain due to dehydration is one factor—but the striking finding is that even in the face of a rapidly rising body temperature, the person fails to sweat. Heat stroke is a positive-feedback situation in which the rising body temperature directly stimulates metabolism—that is, heat production—which further raises body temperature.

SECTION C SUMMARY

Basic Concepts of Energy Expenditure

I. The energy liberated during a chemical reaction appears either as heat or work.
II. Total energy expenditure = heat produced + external work done + energy stored.
III. Metabolic rate is influenced by the many factors summarized in Table 18–7.
IV. Metabolic rate is increased by the thyroid hormones and epinephrine. The other functions of the thyroid hormones are summarized in Table 18–8.

Regulation of Total-Body Energy Stores

I. Energy storage as fat can be positive or negative when the metabolic rate is less than or greater than, respectively, the energy content of ingested food.
   a. Energy storage is regulated mainly by reflex adjustment of food intake.
   b. In addition, the metabolic rate increases or decreases to some extent when food intake is chronically increased or decreased, respectively.

II. Food intake is controlled by leptin, secreted by adipose-tissue cells, and a variety of satiety factors, as summarized in Figure 18–17.

III. Being overweight or obese, the result of an imbalance between food intake and metabolic rate, increases the risk of many diseases.

Regulation of Body Temperature

I. Core body temperature shows a circadian rhythm, being highest during the day and lowest at night.

II. The body exchanges heat with the external environment by radiation, conduction, convection, and evaporation of water from the body surface.

III. The hypothalamus and other brain areas contain the integrating centers for temperature-regulating reflexes, and both peripheral and central thermoreceptors participate in these reflexes.

IV. Body temperature is regulated by altering heat production and/or heat loss so as to change total body heat content.
   a. Heat production is altered by increasing muscle tone, shivering, and voluntary activity.
   b. Heat loss by radiation, conduction, and convection depends on the difference between the skin surface and the environment.
   c. In response to cold, skin temperature is decreased by decreasing skin blood flow through reflex stimulation of the sympathetic nerves to the skin. In response to heat, skin temperature is increased by inhibiting these nerves.
   d. Behavioral responses such as putting on more clothes also influence heat loss.
   e. Evaporation of water occurs all the time as insensible loss from the skin and respiratory lining. Additional water for evaporation is supplied by sweat, stimulated by the sympathetic nerves to the sweat glands.
   f. Increased heat production is essential for temperature regulation at environmental temperatures below the thermoneutral zone, and sweating is essential at temperatures above this zone.

V. Temperature acclimatization to heat is achieved by an earlier onset of sweating, an increased volume of sweat, and a decreased sodium concentration of the sweat.

VI. Fever is due to a resetting of the temperature set point so that heat production is increased and heat loss is decreased in order to raise body temperature to the new set point and keep it there. The stimulus is endogenous pyrogen, which is interleukin 1 and other peptides as well.

VII. The hyperthermia of exercise is due to the increased heat produced by the muscles.

SECTION C KEY TERMS

external work
internal work
total energy expenditure
kilocalorie (kcal)
metabolic rate
basal metabolic rate (BMR)
calorigenic effect
food-induced thermogenesis
leptin
satiety signal
body mass index (BMI)
homeothermic
radiation
conduction
convection
wind-chill index
evaporation
peripheral thermoreceptor
central thermoreceptor
shivering thermogenesis
nonshivering thermogenesis
insensible water loss
sweat gland
thermoneutral zone
fever
endogenous pyrogen (EP)
interleukin 1 (IL-1)
interleukin 6 (IL-6)
endogenous cryogens
hyperthermia

SECTION C REVIEW QUESTIONS

1. State the formula relating total energy expenditure, heat produced, external work, and energy storage.
2. What two hormones alter the basal metabolic rate?
3. State the equation for total-body energy balance. Describe the three possible states of balance with regard to energy storage.
4. What happens to the basal metabolic rate after a person has either lost or gained weight?
5. List five satiety signals.
6. List three beneficial effects of exercise in a weight-loss program.
7. Compare and contrast the four mechanisms for heat loss.
8. Describe the control of skin blood vessels during exposure to cold or heat.
9. With a diagram, summarize the reflex responses to heat or cold. What are the dominant mechanisms for temperature regulation in the thermoneutral zone and in temperatures below and above this range?
10. What changes are exhibited by a heat-acclimatized person?
11. Summarize the sequence of events leading to a fever and contrast this to the sequence leading to hyperthermia during exercise.

CHAPTER 18 CLINICAL TERMS

diabetes mellitus
insulin-dependent diabetes mellitus (IDDM)
noninsulin-dependent diabetes mellitus (NIDDM)
diabetic ketoacidosis
insulin resistance
sulfonylureas
fasting hypoglycemia
atherosclerosis
cancer
oncogene
giantism
dwarfism
acromegaly

growth hormone insensitivity syndrome
hypothyroidism
endemic cretinism
hyperthyroidism
anabolic steroids
overweight
obesity
anorexia nervosa
bulimia
heat exhaustion
heat stroke
aspirin

CHAPTER 18 THOUGHT QUESTIONS

(*Answers are given in Appendix A.*)

1. What happens to the triacylglycerol concentrations in the plasma and in adipose tissue after administration of a drug that blocks the action of lipoprotein lipase?
2. A resting, unstressed person has increased plasma concentrations of free fatty acids, glycerol, amino acids, and ketones. What situations might be responsible and what additional plasma measurement would distinguish among them?
3. A normal volunteer is given an injection of insulin. The plasma concentrations of which hormones increase?
4. If the sympathetic preganglionic fibers to the adrenal medulla were cut in an animal, would this eliminate the sympathetically mediated component of increased gluconeogenesis and lipolysis during exercise? Explain.
5. A patient with insulin-dependent diabetes suffers a broken leg. Would you advise this person to increase or decrease his dosage of insulin?
6. A person has a defect in the ability of her small intestine to absorb bile salts. What effect will this have on her plasma cholesterol concentration?
7. A well-trained athlete is found to have a moderately elevated plasma cholesterol concentration. What additional measurements would you advise this person to have done?
8. A full-term newborn infant is abnormally small. Is this most likely due to deficient growth hormone, deficient thyroid hormones, or deficient in utero nutrition?
9. Why might the administration of androgens to stimulate growth in a small 12-year-old male turn out to be counterproductive?
10. What are the sources of heat loss for a person immersed up to the neck in a 40°C bath?
11. Lizards can regulate their body temperatures only through behavioral means. Can you predict what they do when they are infected with bacteria?