CHAPTER 35

The Endocrine Pancreas

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CHAPTER OUTLINE

KEY CONCEPTS

1. The relative distribution of alpha, beta, and delta cells within each islet of Langerhans shows a distinctive pattern and suggests that there may be some paracrine regulation of secretion.
2. Plasma glucose is the primary physiological regulator of insulin and glucagon secretion, but amino acids, fatty acids, and some GI hormones also play a role.
3. Insulin has anabolic effects on carbohydrate, lipid, and protein metabolism in its target tissues, where it promotes the storage of nutrients.
4. Effects of glucagon on carbohydrate, lipid, and protein metabolism occur primarily in the liver and are catabolic in nature.
5. Type 1 diabetes mellitus results from the destruction of beta cells, whereas type 2 diabetes often results from a lack of responsiveness to circulating insulin.
6. Diabetes mellitus may produce both acute complications, such as ketoacidosis, and chronic secondary complications, such as peripheral vascular disease, neuropathy, and nephropathy.

The development of mechanisms for the storage of large amounts of metabolic fuel was an important adaptation in the evolution of complex organisms. The processes involved in the digestion, storage, and use of fuels require a high degree of regulation and coordination. The pancreas, which plays a vital role in these processes, consists of two functionally different groups of cells.

Cells of the **exocrine pancreas** produce and secrete digestive enzymes and fluids into the upper part of the small intestine. The **endocrine pancreas**, an anatomically small portion of the pancreas (1 to 2% of the total mass), produces hormones involved in regulating fuel storage and use.

For convenience, functions of the exocrine and endocrine portions of the pancreas are usually discussed separately. While this chapter focuses primarily on hormones of the endocrine pancreas, the overall function of the pancreas is to coordinate and direct a wide variety of processes related to the digestion, uptake, and use of metabolic fuels.

SYNTHESIS AND SECRETION OF THE ISLET HORMONES

The endocrine pancreas consists of numerous discrete clusters of cells, known as the islets of Langerhans, which are located throughout the pancreatic mass. The islets contain specific types of cells responsible for the secretion of the hormones insulin, glucagon, and somatostatin. Secretion of these hormones is regulated by a variety of circulating nutrients.

The Islets of Langerhans Are the Functional Units of the Endocrine Pancreas

The **islets of Langerhans** contain from a few hundred to several thousand hormone-secreting endocrine cells. The islets are found throughout the pancreas but are most abundant in the tail region of the gland. The human pancreas contains, on average, about 1 million islets, which vary in size from 50 to 300 μm in diameter. Each islet is separated from the surrounding acinar tissue by a connective tissue sheath.

Islets are composed of four hormone-producing cell types: insulin-secreting beta cells, glucagon-secreting alpha cells, somatostatin-secreting delta cells, and pancreatic polypeptide-secreting F cells. Immunofluorescent staining techniques have shown that the four cell types are arranged in each islet in a pattern suggesting a highly organized cellular community, in which paracrine influences may play an important role in determining hormone secretion rates (Fig. 35.1). Further evidence that cell-to-cell communica-

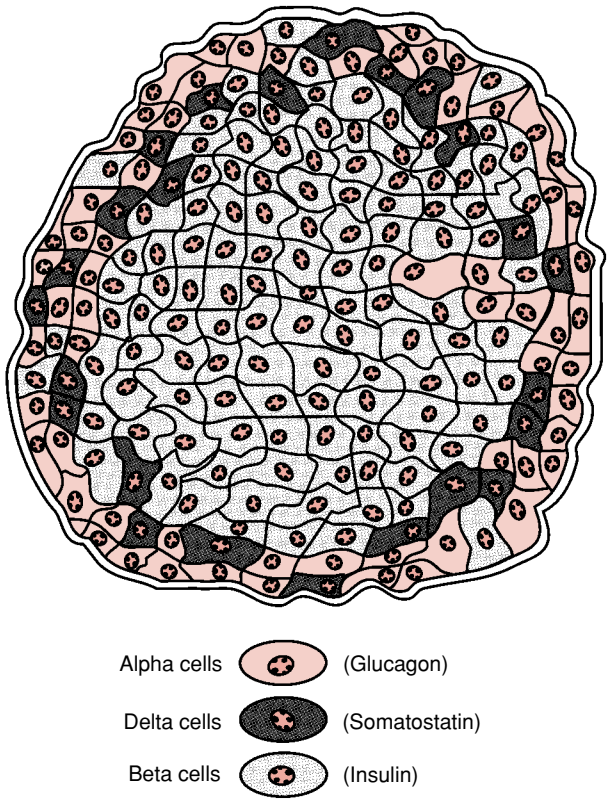

FIGURE 35.1 Major cell types in a typical islet of Langerhans. Note the distinct anatomical arrangement of the various cell types. (Modified from Orci L, Unger RH. Functional subdivision of islets of Langerhans and possible role of D cells. Lancet 1975;2:1243–1244.)

tion within the islet may play a role in regulating hormone secretion comes from the finding that islet cells have both gap junctions and tight junctions. Gap junctions link different cell types in the islets cells and potentially provide a means for the transfer of ions, nucleotides, or electrical current between cells. The presence of tight junctions between outer membrane leaflets of contiguous cells could result in the formation of microdomains in the interstitial space, which may also be important for paracrine communication. Although the existence of gap junctions and tight junctions in pancreatic islets is well documented, their exact function has not been fully defined.

The arrangement of the vascular supply to islets is also consistent with paracrine involvement in regulating islet secretion. Afferent blood vessels penetrate nearly to the center of the islet before branching out and returning to the surface of the islet. The innermost cells of the islet, therefore, receive arterial blood, while those cells nearer the surface receive blood-containing secretions from inner cells. Since there is a definite anatomical arrangement of cells in the islet (see Fig. 35.1), one cell type could affect the secretion of others. In general, the effluent from smaller islets passes through neighboring pancreatic acinar tissue before entering into the hepatic portal venous system. By contrast, the effluent from larger islets passes directly into the venous system without first perfusing adjacent acinar tissue. Therefore, islet hormones arrive in high concentrations in some areas of the exocrine pancreas before reaching peripheral tissues. However, the exact physiological significance of these arrangements is unknown.

Neural inputs also influence islet cell hormone secretion. Islet cells receive sympathetic and parasympathetic innervation. Responses to neural input occur as a result of activation of various adrenergic and cholinergic receptors (described below). Neuropeptides released together with the neurotransmitters may also be involved in regulating hormone secretion.

Beta Cells. In the early 1900s, M. A. Lane established a histochemical method by which two kinds of islet cells could be distinguished. He found that alcohol-based fixatives dissolved the secretory granules in most of the islet cells but preserved them in a small minority of cells. Water-based fixatives had the opposite effect.He named cells containing alcohol-insoluble granules A cells or alpha cells and those containing alcohol-soluble granules B cells or beta cells. Many years later, other investigators used immunofluorescence techniques to demonstrate that beta cells produce insulin and alpha cells produce glucagon.

Insulin-secreting **beta cells** are the most numerous cell type of the islet, comprising 70 to 90% of the endocrine cells. Beta cells typically occupy the most central space of the islets (see Fig. 35.1). They are generally 10 to 15 μm in diameter and contain secretory granules that measure 0.25 μm.

Alpha Cells. **Alpha cells** comprise most of the remaining cells of the islets. They are generally located near the periphery, where they form a cortex of cells surrounding the more centrally located beta cells. Blood vessels pass through the outer zone of the islet before extensive branching occurs. Inward extensions of the cortex may be present along the axes of blood vessels toward the center of the islet, giving the appearance that the islet is subdivided into small lobules.

Delta Cells. **Delta cells** are the sites of production of somatostatin in the pancreas. These cells are typically located in the periphery of the islet, often between beta cells and the surrounding mantle of alpha cells. Somatostatin produced by pancreatic delta cells is identical to that previously described in a neurotransmitter role (see Chapter 3) and as a hypothalamic hormone that inhibits growth hormone secretion by the anterior pituitary (see Chapter 32).

F Cells. **F cells** are the least abundant of the hormone-secreting cells of islets, representing only about 1% of the total cell population. The distribution of F cells is generally similar to that of delta cells. F cells secrete **pancreatic polypeptide**.

Increased Blood Glucose Stimulates the Secretion of Insulin

A variety of factors, including other pancreatic hormones, are known to influence insulin secretion. The primary physiological regulator of insulin secretion, however, is the blood glucose concentration.

Proinsulin Synthesis. The gene for insulin is located on the short arm of chromosome 11 in humans. Like other hormones and secretory proteins, insulin is first synthesized by ribosomes of the rough ER as a larger precursor peptide that is then converted to the mature hormone prior to secretion (see Chapter 31).

The insulin gene product is a 110-amino acid peptide, preproinsulin. Proinsulin consists of 86 amino acids (Fig. 35.2); residues 1 to 30 constitute what will form the B chain of insulin, residues 31 to 65 form the connecting peptide, and residues 66 to 86 constitute the A chain. (Note that "connecting peptide" should not be confused with "C-peptide.") In the process of converting proinsulin to insulin, two pairs of basic amino acid residues are clipped out of the proinsulin molecule, resulting in the formation of insulin and **C-peptide**, which are ultimately secreted from the beta cell in equimolar amounts.

It is of clinical significance that insulin and C-peptide are co-secreted in equal amounts. Measurements of circulating C-peptide levels may sometimes provide important information regarding beta cell secretory capacity that could not be obtained by measuring circulating insulin levels alone.

Insulin Secretion. Table 35.1 lists the physiologically relevant regulators of insulin secretion. As indicated previously, an elevated blood glucose level is the most important regulator of insulin secretion. In humans, the threshold value for glucose-stimulated insulin secretion is a plasma glucose concentration of approximately 100 mg/dL (5.6 mmol/L).

Based on studies using isolated animal pancreas preparations maintained *in vitro*, it has been determined that insulin is secreted in a biphasic manner in response to a marked increase in blood glucose. An initial burst of insulin secretion may last 5 to 15 minutes, resulting from the secretion of preformed insulin secretory granules. This response is followed by more gradual and sustained insulin secretion that results largely from the synthesis of new insulin molecules.

In addition to glucose, several other factors serve as important regulators of insulin secretion (see Table 35.1). These include dietary constituents, such as amino acids and fatty acids, as well as hormones and drugs. Among the amino acids, arginine is the most potent secretagogue for insulin. Among the fatty acids, long-chain fatty acids (16 to 18 carbons) generally are considered the most potent stimulators of insulin secretion. Several hormones secreted by the gastrointestinal tract, including gastric inhibitory peptide (GIP), gastrin, and secretin, promote insulin secretion. An oral dose of glucose produces a greater increment in insulin secretion than an equivalent intravenous dose because oral glucose promotes the secretion of GI hormones that

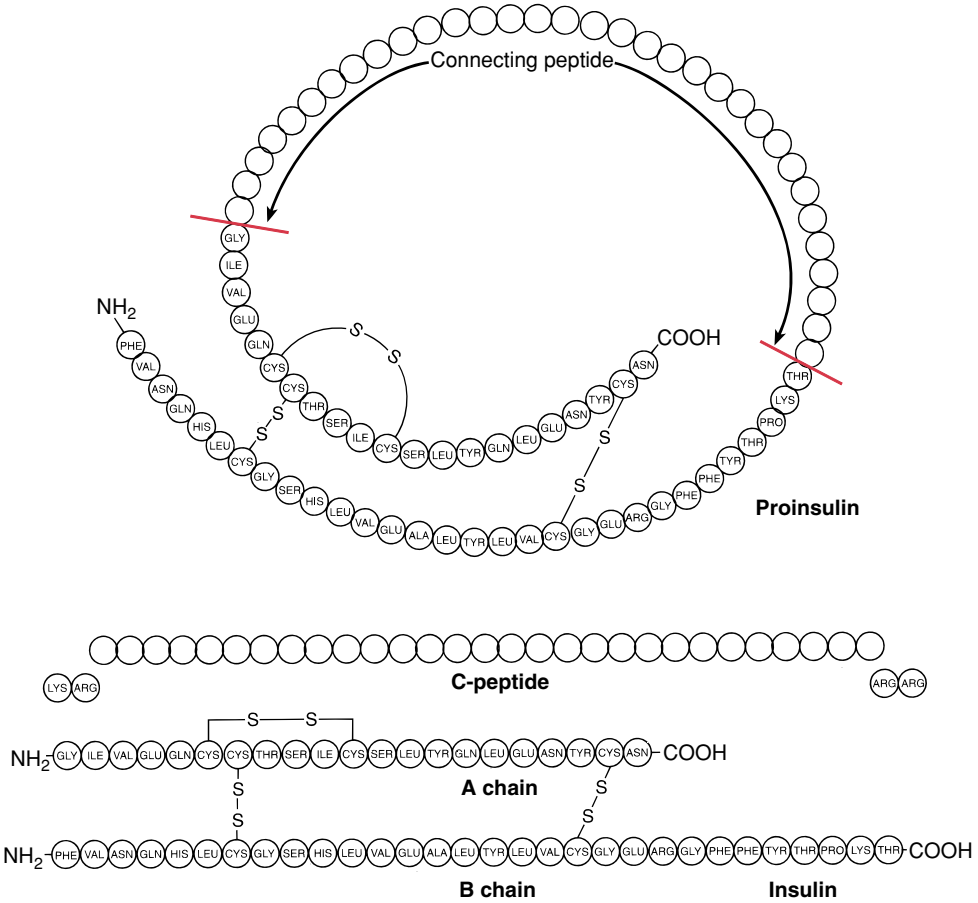

FIGURE 35.2 **The structure of proinsulin, C-peptide, and insulin.** Note that with the removal of two pairs of basic amino acids, proinsulin is converted into insulin and C-peptide.

TABLE 35.1 Factors Regulating Insulin Secretion from the Pancreas

Stimulatory agents or conditions	Hyperglycemia
	Amino acids
	Fatty acids, especially long-chain
	Gastrointestinal hormones, especially gastric inhibitory peptide (GIP), gastrin, and secretin
	Acetylcholine
	Sulfonylureas
Inhibitory agents or conditions	Somatostatin
	Norepinephrine
	Epinephrine

TABLE 35.2 Factors Regulating Glucagon Secretion From the Pancreas

Stimulatory agents or conditions	Hypoglycemia
	Amino acids
	Acetylcholine
	Norepinephrine
	Epinephrine
Inhibitory agents or conditions	Fatty acids
	Somatostatin
	Insulin

augment insulin secretion by the pancreas. Direct infusion of acetylcholine into the pancreatic circulation stimulates insulin secretion, reflecting the role of parasympathetic innervation in regulating insulin secretion. Sulfonylureas, a class of drugs used orally in the treatment of type 2 diabetes, promote insulin's action in peripheral tissues but also directly stimulate insulin secretion.

In addition to factors that stimulate insulin secretion, there are several potent inhibitors. Exogenously administered somatostatin is a strong inhibitor. It is presumed that pancreatic somatostatin plays a role in regulating insulin secretion, but the importance of this effect has not been fully established. Epinephrine and norepinephrine, the primary catecholamines, are also potent inhibitors of insulin secretion. This response would appear appropriate because during periods of stress and high catecholamine secretion, the desired response is mobilization of glucose and other nutrient stores. Insulin generally promotes the opposite response, and by inhibiting insulin secretion, the catecholamines produce their full effect without the opposing actions of insulin.

Decreased Blood Glucose Stimulates the Secretion of Glucagon

Similar to insulin, glucagon is first synthesized as part of a larger precursor protein. Glucagon secretion is regulated by many of the factors that also regulate insulin secretion. In most cases, however, these factors have the opposite effect on glucagon secretion.

Synthesis of Proglucagon. Glucagon is a simple 29-amino acid peptide. The initial gene product for glucagon, preproglucagon, is a much larger peptide. Like other peptide hormones, the "pre" piece is removed in the ER, and the prohormone is converted into a mature hormone as it is packaged and processed in secretory granules (see Chapter 31).

Secretion of Glucagon. The principal factors that influence glucagon secretion are listed in Table 35.2. With a few exceptions, this table is nearly a mirror image of Table 35.1, the factors that regulate insulin secretion. The primary regulator of glucagon secretion is blood glucose; specifically, a decrease in blood glucose below about 100 mg/dL promotes glucagon secretion. As with insulin, amino acids, especially arginine, are potent stimulators of glucagon secretion. Somatostatin inhibits glucagon secretion, as it does insulin secretion.

Increased Blood Glucose and Glucagon Stimulate the Secretion of Somatostatin

Somatostatin is first synthesized as a larger peptide precursor, preprosomatostatin. The hypothalamus also produces this protein, but the regulation of somatostatin secretion from the hypothalamus is independent of that from the pancreatic delta cells. Upon insertion of preprosomatostatin into the rough ER, it is initially cleaved and converted to prosomatostatin. The prohormone is converted into active hormone during packaging and processing in the Golgi apparatus.

Factors that stimulate pancreatic somatostatin secretion include hyperglycemia, glucagon, and amino acids. Glucose and glucagon are generally considered the most important regulators of somatostatin secretion.

The exact role of somatostatin in regulating islet hormone secretion has not been fully established. Somatostatin clearly inhibits both glucagon and insulin secretion from the alpha and beta cells of the pancreas, respectively, when it is given exogenously. The anatomic and vascular relationships of delta cells to alpha and beta cells further suggest that somatostatin may play a role in regulating both glucagon and insulin secretion. Although many of the data are circumstantial, it is generally accepted that somatostatin plays a paracrine role in regulating insulin and glucagon secretion from the pancreas.

METABOLIC EFFECTS OF INSULIN AND GLUCAGON

The endocrine pancreas secretes hormones that direct the storage and use of fuels during times of nutrient abundance (fed state) and nutrient deficiency (fasting). Insulin is secreted in the fed state and is called the "hormone of nutrient abundance." By contrast, glucagon is secreted in response to an overall deficit in nutrient supply. These two hormones play an important role in directing the flow of metabolic fuels.

Insulin Affects the Metabolism of Carbohydrates, Lipids, and Proteins in Liver, Muscle, and Adipose Tissues

The primary targets for insulin are liver, skeletal muscle, and adipose tissues. Insulin has multiple individual actions in each of these tissues, the net result of which is fuel storage.

Mechanism of Insulin Action. Although insulin was one of the first peptide hormones to be identified, isolated, and characterized, its exact mechanism of action remains elusive. The **insulin receptor** is a heterotetramer, consisting of a pair of α/β subunit complexes held together by disulfide bonds (Fig. 35.3). The α subunit is an extracellular protein containing the insulin-binding component of the receptor. The β subunit is a transmembrane protein that couples the extracellular event of insulin binding to its intracellular actions.

Activation of the β subunit of the insulin receptor results in autophosphorylation, involving the phosphorylation of a few selected tyrosine residues in the intracellular portion of the receptor. This event further activates the tyrosine kinase portion of the β subunit, leading to tyrosine phosphorylation of specific intracellular substrates. A cascade of events follows, leading to the pleiotropic actions of insulin in its target cells. While tyrosine phosphorylation events appear to be the early steps in insulin action, serine/threonine phosphorylation or dephosphorylation is involved in many of the final steps of insulin action.

Insulin and Glucose Transport. Perhaps one of the most important functions of insulin is to promote the uptake of glucose from blood into cells. Glucose uptake into many cell types is by facilitated diffusion. A specific cell membrane carrier is involved but no energy is required, and the process cannot move glucose against a concentration gradient. The carriers shuttle glucose across the membrane faster than would occur by diffusion alone. Considerable recent work has revealed not just one transporter, but a family of about seven different glucose transporters (GLUT), commonly called GLUT 1 to GLUT 7. These transporters are expressed in different tissues and, in some cases, at different times during fetal development.

GLUT 4, the insulin-stimulated glucose transporter, is the primary form of the transporter present in skeletal muscle tissue and adipose tissue. It is present in plasma membranes and in intracellular vesicles of the smooth ER. In target cells, the effect of insulin is to promote the translocation of GLUT 4 transporters from the intracellular pool into plasma membranes. As a result, more transporters are available in the plasma membrane, and glucose uptake by target cells is, thereby, increased.

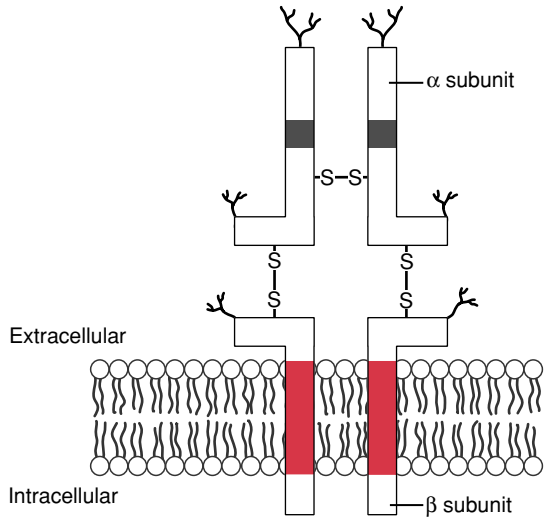

FIGURE 35.3 **The structure of the insulin receptor.** The insulin receptor is a heterotetramer consisting of two extracellular insulin-binding α subunits linked by disulfide bonds to two transmembrane β subunits. The β subunits contain an intrinsic tyrosine kinase that is activated upon insulin binding to the α subunit.

Insulin and the Synthesis of Glycogen. Besides promoting glucose uptake into target cells, insulin promotes its storage. Glucose carbon is stored in the body in two primary forms: as glycogen and (by metabolic conversion) as triglycerides. Glycogen is a short-term storage form that plays an important role in maintaining normal blood glucose levels. The primary glycogen storage sites are the liver and skeletal muscle; other tissues, such as adipose tissue, also store glycogen but in quantitatively small amounts. Insulin promotes glycogen storage primarily through two enzymes (Fig. 35.4). It activates **glycogen synthase** by promoting its dephosphorylation and concomitantly inactivates **glycogen phosphorylase**, also by promoting its dephosphorylation. The result is that glycogen synthesis is promoted and glycogen breakdown is inhibited.

Insulin and Glycolysis. Insulin also enhances glycolysis. In addition to increasing glucose uptake and providing a mass action stimulus for glycolysis, insulin activates the enzymes glucokinase and hexokinase and phosphofructokinase, pyruvate kinase, and pyruvate dehydrogenase of the glycolytic pathway (see Fig. 35.4).

Lipogenic and Antilipolytic Effects of Insulin. In adipose tissue and liver tissue, insulin promotes lipogenesis and inhibits lipolysis (Fig. 35.5). Insulin has similar actions in muscle, but since muscle is not a major site of lipid storage, the discussion here focuses on actions in adipose tissue and the liver. By promoting the flow of intermediates through glycolysis, insulin promotes the formation of α-glycerol phosphate and fatty acids necessary for triglyceride formation. In addition, it stimulates fatty acid synthase, leading directly to increased fatty acid synthesis. Insulin inhibits the breakdown of triglycerides by inhibiting hormone-sensitive lipase, which is activated by a variety of counterregulatory hormones, such as epinephrine and adrenal glucocorticoids. By inhibiting this enzyme, insulin promotes the accumulation of triglycerides in adipose tissue.

In addition to promoting *de novo* fatty acid synthesis in adipose tissue, insulin increases the activity of lipoprotein lipase, which plays a role in the uptake of fatty acids from the blood into adipose tissue. As a result, lipoproteins synthesized in the liver are taken up by adipose tissue, and fatty acids are ultimately stored as triglycerides.

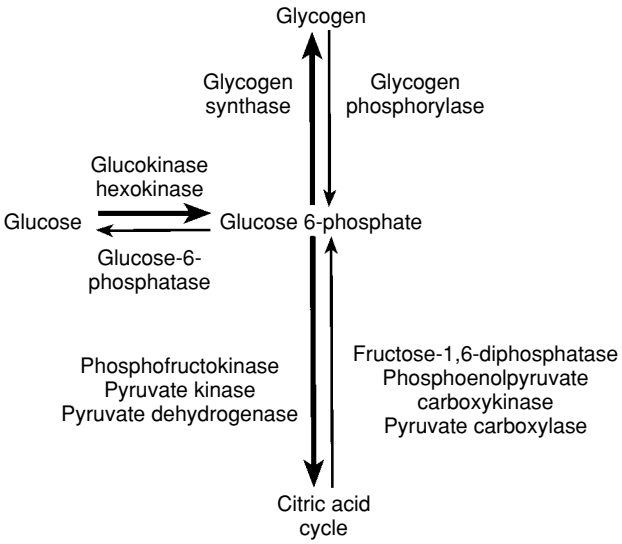

FIGURE 35.4 **Insulin stimulation of glycogen synthesis and glucose metabolism.** Insulin promotes glucose uptake into target tissues, stimulates glycogen synthesis, and inhibits glycogenolysis. In addition it promotes glycolysis in its target tissues. Heavy arrows indicate processes stimulated by insulin; light arrows indicate processes inhibited by insulin.

Effects of Insulin on Protein Synthesis and Protein Degradation. Insulin promotes protein accumulation in its primary target tissues—liver, adipose tissue, and muscle—in three specific ways (Fig. 35.6). First, it stimulates amino acid uptake. Second, it increases the activity of several factors involved in protein synthesis. For example, it increases the activity of protein synthesis initiation factors, promoting the start of translation and increasing the efficiency of protein synthesis. Insulin also increases the amount of protein synthesis machinery in cells by promoting ribosome synthesis. Third, insulin inhibits protein degradation by reducing lysosome activity and possibly other mechanisms as well.

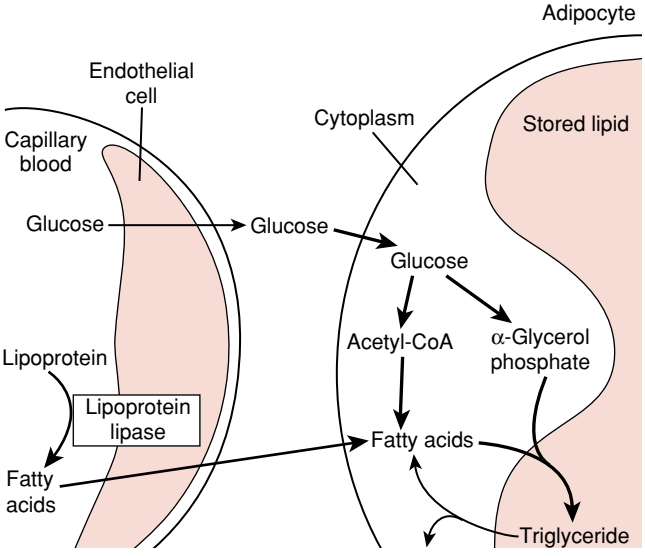

FIGURE 35.5 **Effects of insulin on lipid metabolism in adipocytes.** Insulin promotes the accumulation of lipid (triglycerides) in adipocytes by stimulating the processes shown by the heavy arrows and inhibiting the processes shown by the light arrows. Similar stimulatory and inhibitory effects occur in liver cells.

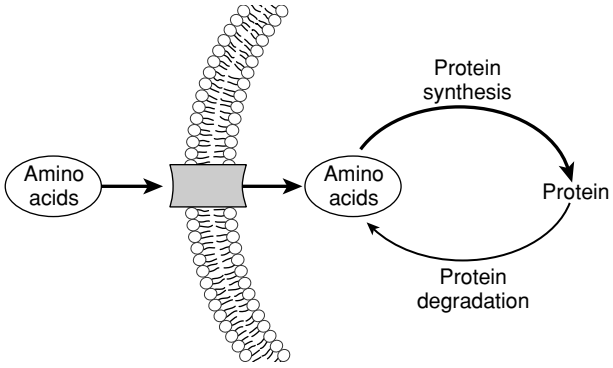

FIGURE 35.6 **Effects of insulin on protein synthesis and protein degradation.** Insulin promotes the accumulation of protein by stimulating (heavy arrows) amino acid uptake and protein synthesis and by inhibiting (light arrows) protein degradation in liver, skeletal muscle, and adipose tissue.

Glucagon Primarily Affects the Liver Metabolism of Carbohydrates, Lipids, and Proteins

The primary physiological actions of glucagon are exerted in the liver. Numerous effects of glucagon have been documented in other tissues, primarily adipose tissue, when the hormone has been added at high, nonphysiological concentrations in experimental situations. While these effects may play a role in certain abnormal situations, the normal daily effects of glucagon occur primarily in the liver.

Mechanism of Glucagon Action. Glucagon initiates its biological effects by interacting with one or more types of cell membrane receptors. **Glucagon receptors** are coupled to G proteins and promote increased intracellular cAMP, via the activation of adenylyl cyclase, or elevated cytosolic calcium as a result of phospholipid breakdown to form IP_3.

Glucagon and Glycogenolysis. Glucagon is an important regulator of hepatic glycogen metabolism. It produces a net effect of glycogen breakdown by increasing intracellular cAMP levels, initiating a cascade of phosphorylation events that ultimately results in the phosphorylation of phosphorylase b and its activation by conversion into phosphorylase a. Similarly, glucagon promotes the net breakdown of glycogen by promoting the inactivation of glycogen synthase (Fig. 35.7).

Glucagon and Gluconeogenesis. In addition to promoting hepatic glucose production by stimulating glycogenolysis, glucagon stimulates hepatic gluconeogenesis (Fig. 35.8). It does this principally by increasing the transcription of mRNA coding for the enzyme phosphoenolpyruvate carboxykinase (PEPCK), a key rate-limiting enzyme in gluconeogenesis. Glucagon also stimulates amino acid

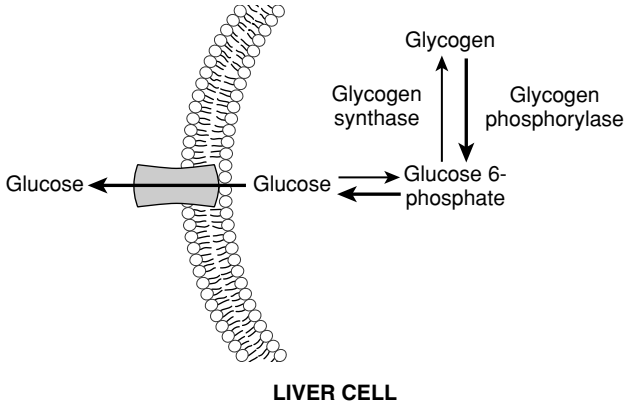

FIGURE 35.7 **The role of glucagon in glycogenolysis and glucose production in liver cells.** Heavy arrows indicate processes stimulated by glucagon; light arrows indicate processes inhibited by glucagon.

transport into liver cells and the degradation of hepatic proteins, helping provide substrates for gluconeogenesis.

Glucagon and Ureagenesis. The glucagon-enhanced conversion of amino acids into glucose leads to increased formation of ammonia. Glucagon assists in the disposal of ammonia by increasing the activity of the urea cycle enzymes in liver cells (see Fig. 35.8).

Glucagon and Lipolysis. Glucagon promotes lipolysis in liver cells (Fig. 35.9), although the quantity of lipids stored in liver is small compared to that in adipose tissue.

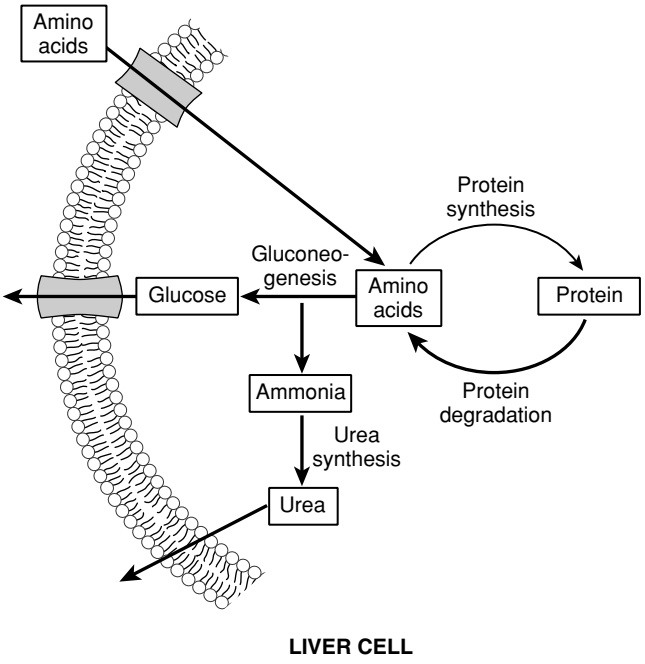

FIGURE 35.8 **The role of glucagon in gluconeogenesis and ureagenesis in liver cells.** Heavy arrows indicate processes stimulated by glucagon; light arrow indicates processes inhibited by glucagon.

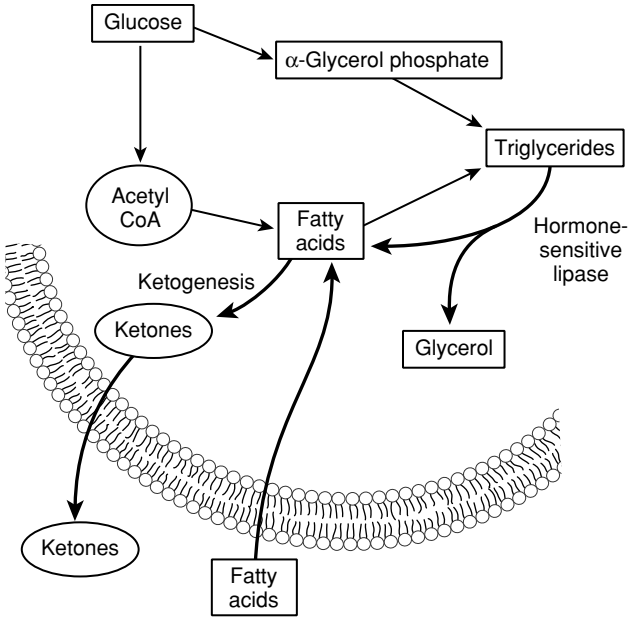

FIGURE 35.9 **The role of glucagon in lipolysis and ketogenesis in liver cells.** Heavy arrows indicate processes stimulated by glucagon; light arrows indicate processes inhibited by glucagon.

Glucagon and Ketogenesis. Glucagon promotes ketogenesis, the production of ketones, by lowering the levels of malonyl CoA, relieving an inhibition of palmitoyl transferase and allowing fatty acids to enter the mitochondria for oxidation to ketones (see Fig 35.9). Ketones are an important source of fuel for muscle cells and heart cells during times of starvation, sparing blood glucose for other tissues that are obligate glucose users, such as the central nervous system. During prolonged starvation, the brain adapts its metabolism to use ketones as a fuel source, lessening the overall need for hepatic glucose production (see Chapter 34).

The Insulin-Glucagon Ratio Determines Metabolic Status

In most instances, insulin and glucagon produce opposing effects. Therefore, the net physiological response is determined by the relative levels of both hormones in the blood plasma, the **insulin-glucagon ratio** (I/G ratio).

I/G Ratio in the Fed and Fasting States. The I/G ratio may vary 100-fold or more because the plasma concentration of each hormone can vary considerably in different nutritional states. In the fed state, the molar I/G ratio is approximately 30. After an overnight fast, it may fall to about 2, and with prolonged fasting, it may fall to as low as 0.5.

Inappropriate I/G Ratios in Diabetes. A good example of the profound influence of the I/G ratio on metabolic status is in insulin-deficient diabetes. Insulin levels are low, so pathways that insulin stimulates operate at a reduced level.

However, insulin is also necessary for alpha cells to sense blood glucose appropriately; in the absence of insulin, the secretion of glucagon is inappropriately elevated. The result is an imbalance in the I/G ratio and an accentuation of glucagon effects well above what would be seen in normal states of low insulin, such as in fasting.

DIABETES MELLITUS

Diabetes mellitus is a disease of metabolic dysregulation—most notably a dysregulation of glucose metabolism—accompanied by long-term vascular and neurological complications. Diabetes has several clinical forms, each of which has a distinct etiology, clinical presentation, and course. Insights into diabetes and its complications have been gleaned from extensive metabolic studies, the use of radioimmunoassays for insulin and glucagon, and the application of molecular biology strategies. Diabetes is the most common endocrine disorder. Some 16 million people may have the disease in the United States; the exact number is not known because many people have a borderline, subclinical form of the disorder. Many deaths attributed to cardiovascular disease are in fact the result of complications from diabetes.

Diagnosing diabetes mellitus is not difficult to do. Symptoms usually include frequent urination, increased thirst, increased food consumption, and weight loss. The standard criterion for a diagnosis of diabetes is an elevated plasma glucose level after an overnight fast on at least two separate occasions. A glucose value above 126 mg/dL (7.0 mmol/L) is often used as the diagnostic value.

Diabetes mellitus is a heterogeneous disorder. The causes, symptoms, and general medical outcomes are variable. Generally, the disease takes one of two forms, **type 1 diabetes** or **type 2 diabetes**. Other forms of diabetes, such as **gestational diabetes**, are also well known.

Most Forms of Type 1 Diabetes Mellitus Involve an Autoimmune Disorder

Type 1 diabetes is characterized by the inability of beta cells to produce physiologically appropriate amounts of insulin. In some instances, this may result from a mutation in the preproinsulin gene. However, the most common form of type 1 diabetes results from destruction of the pancreatic beta cells by the immune system. The initial pathological event is **insulitis,** involving a lymphocytic attack on beta cells. Antibodies to beta cell cell-surface antigens have also been found in the circulation of many persons with type 1 diabetes, but this is not a primary causative factor and probably results from the initial cellular damage.

Studies of identical twins have provided important information regarding the genetic basis of type 1 diabetes. If one twin develops type 1 diabetes, the odds that the second will develop the disease are much higher than for any random individual in the population, even when the twins are raised apart under different socioeconomic conditions. In addition, individuals with certain cell-surface HLA antigens bear a higher risk for the disease than others.

Environmental factors are involved as well because the development of type 1 diabetes in one twin predicts only a 50% or less chance that the second will develop the disease. The specific environmental factors have not been identified, although much evidence implicates viruses. Therefore, it appears that a combination of genetics and environment are strong contributing factors to the development of type 1 diabetes.

Because the primary defect in type 1 diabetes is the inability of beta cells to secrete adequate amounts of insulin, these patients must be treated with injections of insulin. In an attempt to match insulin concentrations in the blood with the metabolic requirements of the individual, various formulations of insulin with different durations of action have been developed. Patients inject an appropriate amount of these different insulin forms to match their dietary and lifestyle requirements.

The long-term control of type 1 diabetes depends on maintaining a balance between three factors: insulin, diet, and exercise. To strictly control their blood glucose, patients are advised to monitor their diet and level of physical activity, as well as their insulin dosage. Exercise per se, much like insulin, increases glucose uptake by muscle. Diabetic patients must take this into account and make appropriate adjustments in diet or insulin whenever general exercise levels change dramatically.

Type 2 Diabetes Mellitus Primarily Originates in the Target Tissue

Type 2 diabetes mellitus results primarily from impaired ability of target tissues to respond to insulin. There are multiple forms of the disease, each with a different etiology. In some cases, it is a permanent, lifelong disorder; in others, it results from the secretion of counterregulatory hormones in a normal (e.g., pregnant) or pathophysiological (e.g., Cushing's disease) state. **Gestational diabetes** occurs in 2 to 5% of all pregnancies but usually disappears after delivery. Women who have had gestational diabetes have an increased risk of developing type 2 diabetes later in life.

Insulin Resistance in Type 2 Diabetes. In most cases of type 2 diabetes, normal or higher-than-normal amounts of insulin are present in the circulation. Therefore, there is no impairment in the secretory capacity of pancreatic beta cells but only in the ability of target cells to respond to insulin. In some instances, it has been demonstrated that the fundamental defect is in the insulin receptor. In most cases, however, receptor function appears normal, and the impairment in insulin action is ascribed to a postreceptor defect. Since the exact mechanism of insulin action has not been determined, it is difficult to explore the causes of insulin resistance in much greater depth.

Genetics, Environment, and Type 2 Diabetes. As with type 1 diabetes, key information on the influence of genetics and environmental factors in type 2 diabetes comes from studies of identical twins. These studies indicate that there is a strong genetic component to the development of type 2 diabetes and that environmental factors, including diet, play a considerably lesser role. If one identical twin develops type 2 diabetes, chances are nearly 100% that the

second will as well, even if they are raised apart under entirely different conditions.

Many persons with type 2 diabetes are overweight, and often the severity of their disease can be lessened simply by weight loss. However, no strict cause-and-effect relationship between these two conditions has been established. Clearly, not all persons with type 2 diabetes are obese, and not all obese individuals develop diabetes.

Treatment Options for Type 2 Diabetes. In milder forms of type 2 diabetes, dietary restriction leading to weight loss may be the only treatment necessary. Commonly, however, dietary restriction is supplemented by treatment with one of several orally active agents, most often of the sulfonylurea class. These drugs appear to act in two ways. First, they promote insulin action in target cells, lessening insulin resistance in tissues. Second, they correct or reverse a somewhat sluggish response of pancreatic beta cells often seen in type 2 diabetes, normalizing insulin secretory responses to glucose. The exact mechanisms of these effects are unknown. In some cases, persons with type 2 diabetes may also be treated with insulin, although in the most of cases a regimen of oral agents and dietary manipulation is sufficient.

Diabetes Mellitus Complications Present Major Health Problems

If left untreated or if glycemic control is poor, diabetes leads to acute complications that may prove fatal. However, even with reasonably good control of blood glucose, over a period of years, most diabetics develop secondary complications of the disease that result in tissue damage, primarily involving the cardiovascular and nervous systems.

Acute Complications of Diabetes. The nature of acute complications that develop in type 1 and type 2 diabetics differs. Persons with poorly controlled type 1 diabetes often exhibit hyperglycemia, glucosuria, dehydration, and **diabetic ketoacidosis**. As blood glucose becomes elevated above the renal plasma threshold, glucose appears in the urine. As a result of osmotic effects, water follows glucose, leading to polyuria, excessive loss of fluid from the body, and dehydration. With fluid loss, the circulating blood volume is reduced, compromising cardiovascular function, which may lead to circulatory failure.

Excessive ketone formation leads to acidosis and electrolyte imbalances in persons with type 1 diabetes. If uncontrolled, ketones may be elevated in the blood to such an extent that the odor of acetone (one of the ketones) is noticeable on the breath. Production of the primary ketones, β-hydroxybutyric acid and acetoacetic acid, results in the generation of excess hydrogen ions and a metabolic acidosis. Ketones may accumulate in the blood to such a degree that they exceed renal transport capacities and appear in the urine. As a result of osmotic effects, water is also lost in the urine. In addition, the pK of ketones is such that, even with the most acidic urine, a normal kidney can produce about half of the excreted ketones in the salt (or base) form. To ensure electrical neutrality, these must be accompanied by a cation, usually either sodium or potassium. The loss of ketones in the urine, therefore, also results in a loss of important electrolytes. Excessive ketone production in type 1 diabetes results in acidosis, a loss of cations, and a loss of fluids. Emergency department procedures are directed toward immediate correction of these acute problems and usually involve the administration of base, fluids, and insulin.

The complex sequence of events that can result from uncontrolled type 1 diabetes is shown in Figure 35.10. If left unchecked, many of these complications can have an additive effect to further the severity of the disease state.

Persons with type 2 diabetes are generally not ketotic and do not develop acidosis or the electrolyte imbalances characteristic of type 1 diabetes. Hyperglycemia leads to fluid loss and dehydration. Severe cases may result in hyperosmolar coma as a result of excessive fluid loss. The initial objective of treatment in these individuals is the administration of fluids to restore fluid volumes to normal and eliminate the hyperosmolar state.

Chronic Secondary Complications of Diabetes. With good control of their disease, most persons with diabetes can avoid the acute complications described above; however, it is rare that they will not suffer from some of the chronic secondary complications of the disease. In most instances, such complications will ultimately lead to reduced life expectancy.

Most lesions occur in the circulatory system, although the nervous system is also often affected. Large vessels often show changes similar to those in atherosclerosis, with the deposition of large fatty plaques in arteries. However, most of the circulatory complications in diabetes occur in microvessels. The common finding in affected vessels is a

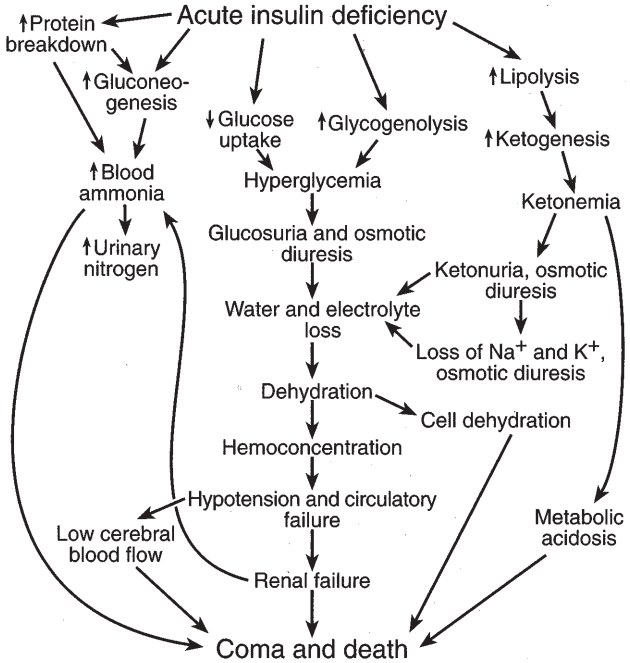

FIGURE 35.10 **Events resulting from acute deficiency in type 1 diabetes mellitus.** If left untreated, insulin deficiency may lead to several complications, which may have additive or confounding effects that may ultimately result in death.

CLINICAL FOCUS BOX 35.1

The Diabetic Foot

Despite efforts to control their disease and maintain a normal glycemic state, most persons with diabetes eventually develop one or more secondary complications of the disease. These complications may be somewhat subtle in onset and slow in progression; however, they account for the high rates of morbidity and mortality. While the specific mechanisms involved remain areas of debate and research activity, most secondary complications are vascular or neural in nature.

Vascular complications may involve atherosclerotic-like lesions in the large blood vessels or impaired function in the microcirculation. Damage to the basement membrane of capillaries in the eye (**diabetic retinopathy**) or kidney (**diabetic nephropathy**) is commonly seen. Although there is no satisfactory direct treatment for diabetic vascular disease, its progression is often monitored closely as an indirect indicator of the overall diabetic state.

Diabetic neuropathy typically involves symmetric sensory loss in the distal lower extremities or autonomic neuropathy, leading to impotence, GI dysfunction, or anhidrosis (lack of sweating) in the lower extremities. The **diabetic foot** is an example of several complicating factors exacerbating one another. About 50 to 70% of nontraumatic amputations in the United States each year are due to diabetes. Breakdown of the foot in persons who are diabetic is commonly due to a combination of neuropathy, vascular impairment, and infection. In a typical scenario, small lesions on the foot result from dryness of the skin due to a combination of neural and vascular complications. Impairments in sensory nerve function may result in these small lesions going unnoticed by the patient until a severe infection or gangrene has become well established.

Loss of the affected foot or limb often can be avoided with patient and physician education. The focus in managing patients with diabetes is the maintenance of normal blood glucose levels; avoiding primary complications, such as diabetic ketoacidosis or hyperosmolar coma; and initial secondary complications, such as diabetic retinopathy. There is an increasing awareness of the importance of assessing the feet of a diabetic patient at each visit. The results of one study show that the likelihood of amputation is reduced by half if patients with diabetes simply remove their shoes for foot inspection during every outpatient clinic visit. Therefore, while the underlying physiological mechanisms of the problem may be complex, the problem can be relatively easily avoided.

thickening of the basement membrane. This condition leads to impaired delivery of nutrients and hormones to the tissues and inadequate removal of waste products, resulting in irreparable tissue damage.

Some of the more disabling consequences of diabetic circulatory impairment are deterioration of blood flow to the retina of the eye, causing retinopathy and blindness; deterioration of blood flow to the extremities, causing, in some cases, the need for foot or leg amputation; and deterioration of glomerular filtration in the kidneys, leading to renal failure.

Diabetic peripheral neuropathy is also a common complication of long-standing diabetes. This disorder usually involves sensory nerves and those of the autonomic nervous system. Many persons with diabetes experience diminished sensation in the extremities, especially in the feet and legs, which compounds the problem of diminished blood flow to these areas (see Clinical Focus Box 35.1). Often, impaired sensory nerve function results in lack of awareness of severe ulcerations of the feet caused by reduced blood flow. Men may develop impotence, and both men and women may have impaired bladder and bowel function.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. Which of the following stimulate the secretion of *both* insulin and glucagon from the pancreas?
   (A) Epinephrine
   (B) Amino acids
   (C) Acetylcholine
   (D) Both amino acids and acetylcholine
2. The effects of insulin include
   (A) Inhibition of amino acid uptake into skeletal muscle
   (B) Stimulation of glucose uptake into all tissues in the body
   (C) Inhibition of protein degradation in skeletal muscle
   (D) Stimulation of hormone-sensitive lipase in adipose tissue
3. The effects of glucagon include
   (A) Inhibition of insulin secretion by pancreatic beta cells
   (B) Primary actions in adipose tissue
   (C) Promotion of gluconeogenesis and urea synthesis in liver cells
   (D) Indirect stimulation of ketogenesis in liver cells by the inhibition of pancreatic somatostatin secretion
4. A 55-year-old man was diagnosed with type 1 diabetes at the age of 8. Which would be most characteristic of his form of the disease?
   (A) Insulin resistance
   (B) Treatment with exogenous insulin
   (C) Sulfonylurea treatment
   (D) Virtual absence of secondary complications
5. Type 2 diabetes
   (A) Has a strong genetic component to the development of the disease
   (B) Is characterized by low or negligible circulating insulin
   (C) Occurs only in obese individuals
   (D) Is treated in the same manner as type 1 diabetes
6. Which of the following would you least likely see in a person with long-standing type 2 diabetes?

(continued)

(A) Neuropathy
(B) Nephropathy
(C) Retinopathy
(D) Ketoacidosis

7. Delta cells of the islets of Langerhans produce which hormone?
(A) Insulin
(B) Glucagon
(C) Acetylcholine
(D) Somatostatin

8. The insulin-glucagon ratio would be expected to be lowest
(A) Immediately after a high-carbohydrate meal
(B) Immediately after a high-protein meal
(C) After an overnight fast
(D) After a 3-day fast

SUGGESTED READING

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