The Pancreas

Located partially behind the stomach in the abdomen, the soft, triangular pancreas is a mixed gland composed of both endocrine and exocrine gland cells (Figure 17.15). Like the thyroid and parathyroids, it develops as an outpocketing of the embryonic endoderm, which forms the epithelial lining (and glands) of the gastrointestinal and respiratory tracts. Acinar cells, forming the bulk of the gland, produce an enzyme-rich juice that is ducted into the small intestine during food digestion. This exocrine product is discussed in Chapter 24.

Scattered among the acinar cells are approximately a million pancreatic islets (islets of Langerhans), minute cell clusters that produce pancreatic hormones. The islets contain two major populations of hormone-producing cells, the glucagon-synthesizing alpha (α) cells and the more numerous insulin-producing beta (β) cells. Insulin and glucagon are intimately but independently involved in the regulation of blood glucose levels. Their effects are opposite: Insulin is a hypoglycemic hormone, whereas glucagon is a hyperglycemic hormone (Figure 17.16). Islet cells also synthesize other peptides in small amounts. These include somatostatin (secreted by the delta [δ] cells), which inhibits the release of insulin and glucagon; pancreatic polypeptide (PP) secreted by the F cells, which plays a role in regulating the exocrine (enzyme-secreting) function of the pancreas; and amylin, a hormone cosecreted with insulin by the beta cells that appears to antagonize some of insulin’s effects.

FIGURE 17.16
Regulation of blood sugar levels by insulin and glucagon. When blood sugar levels are high, the pancreas releases insulin. Insulin stimulates sugar uptake by cells and glycogen formation in the liver, which lowers blood sugar levels: that is, insulin exerts hypoglycemic effects. Glucagon, released when blood sugar levels are low, stimulates glycogen breakdown and thereby raises blood sugar; that is, glucagon is a hyperglycemic hormone.

Glucagon

Glucagon (gloo'kah-gon), a 29-amino-acid polypeptide, is an extremely potent hyperglycemic agent: One molecule of this hormone can cause the release of 100 million molecules of glucose into the blood! The major target of glucagon is the liver, where it promotes (1) breakdown of glycogen to glucose (glycogenolysis); (2) synthesis of glucose from lactic acid and from noncarbohydrate molecules such as fatty acids and amino acids (gluconeogenesis); and
(3) release of glucose to the blood by the liver cells, which causes blood sugar levels to rise. A secondary effect is a fall in the concentration of amino acids in the blood as the liver cells sequester them to make new glucose molecules.

Secretion of glucagon by the α cells is prompted by humoral stimuli, most importantly declining blood sugar levels. However, increasing amino acid levels (as might follow a protein-rich meal) are also stimulatory. Glucagon release is suppressed by rising blood sugar levels and somatostatin. Because glucagon is such an important hyperglycemic agent, it has been speculated that people with persistently low blood sugar levels (hypoglycemics) are deficient in glucagon.

**Insulin**

**Insulin** is a small (51-amino-acid) protein consisting of two amino acid chains linked by disulfide bonds. As shown in Figure 17.17, it is initially synthesized as part of a larger polypeptide chain called proinsulin. The middle portion of this chain is then excised by enzymes, releasing functional insulin. This “clipping” process occurs in the secretory vesicles just before insulin is released from the beta cell.

Insulin’s effects are most obvious when we have just eaten. Insulin’s main effect is to lower blood sugar levels, but it also influences protein and fat metabolism. Circulating insulin lowers blood sugar levels by enhancing membrane transport of glucose (and other simple sugars) into body cells, especially muscle cells. (It does not accelerate glucose entry into liver, kidney, and brain tissue, all of which have easy access to blood glucose regardless of insulin levels.) Insulin inhibits the breakdown of glycogen to glucose and conversion of amino acids or fatty acids to glucose: thus, it counters any metabolic activity that would increase plasma levels of glucose. Insulin’s mechanism of action is still being investigated but, as noted earlier (p. 550), its receptor is a tyrosine kinase enzyme that is activated when insulin binds to it.

After glucose enters the target cells, insulin binding triggers enzymatic activities that (1) catalyze the oxidation of glucose for ATP production, (2) join glucose together to form glycogen, and (3) convert glucose to fat (particularly in adipose tissue). As a rule, energy needs are met first, then glycogen deposit occurs. Finally, if excess glucose is still available, fat deposit occurs. Insulin also induces amino acid uptake and protein synthesis in muscle tissue. In summary, insulin sweeps glucose out of the blood, causing it to be used for energy or converted to other forms (glycogen or fats), and it promotes protein synthesis and fat storage.

The β cells are stimulated to secrete insulin chiefly by elevated blood sugar levels, but rising plasma levels of amino acids and fatty acids also trigger insulin release. As the cells avidly take up sugar and other nutrients, and plasma levels of these substances drop, insulin secretion is suppressed. Other hormones also influence insulin release directly or indirectly. For example, any hyperglycemic hormone (such as glucagon, epinephrine, growth hormone, thyroxine, or glucocorticoids) called into action as blood sugar levels drop indirectly stimulates insulin release by promoting glucose entry into the bloodstream. Somatostatin depresses insulin release. Thus, blood sugar levels ultimately reflect a balance of both humoral and hormonal influences. Insulin and (indirectly) somatostatin are the hypoglycemic factors that
counter and counterbalance the many hyperglycemic hormones.

**Diabetes mellitus** (DM) results from hyposecretion or hypoactivity of insulin. When insulin activity is absent or deficient, blood sugar levels remain high after a meal because glucose is unable to enter most tissue cells. Ordinarily, when blood sugar levels rise, hyperglycemic hormones are not released, but when hyperglycemia becomes excessive, the person begins to feel nauseated, which precipitates the fight-or-flight response. This results, inappropriately, in all the reactions that normally occur in the hypoglycemic (fasting) state to make glucose available—that is, glycolysis, lipolysis, and gluconeogenesis. Thus, the already high blood sugar levels rise even higher, and excesses of glucose begin to be lost from the body in the urine (glycosuria).

When sugars cannot be used as cellular fuel, more fats are mobilized resulting in lipidemia (high fatty acid levels in the blood). In severe cases of diabetes mellitus, blood levels of fatty acids and their metabolites (acetoacetic acid, acetone, and others) rise dramatically. The fatty acid metabolites, collectively called **ketones** (keˈtōnz) or **ketone bodies**, are strong organic acids. When they accumulate faster than they can be used or excreted, the blood pH drops, resulting in **ketoacidosis**, and ketones begin to spill into the urine /ketonuria/. Severe ketoacidosis is life-threatening. The nervous system responds by initiating rapid deep breathing to blow off carbon dioxide from the blood and increase blood pH. (The physiological basis of this mechanism is explained in Chapter 23.) If untreated, ketoacidosis disrupts virtually all physiological processes, including heart activity and oxygen transport. Severe depression of the nervous system leads to coma and, finally, death.

The three cardinal signs of diabetes mellitus are polyuria, polydipsia, and polyphagia. The excessive glucose in the kidney filtrate acts as an osmotic diuretic, i.e., it inhibits water reabsorption by the kidney tubules, resulting in **polyuria**, a huge urine output that leads to decreased blood volume and dehydration. Serious electrolyte losses also occur because of the need to rid the body of excess ketones. Since ketones are negatively charged, they carry positive ions out with them; as a result, sodium and potassium ions are also lost from the body. Because of the electrolyte imbalance, the person gets abdominal pains and may vomit, and the stress reaction spirals even higher. Dehydration stimulates hypothalamic thirst centers, causing **polydipsia**, or excessive thirst. The final cardinal sign, **polyphagia**, refers to excessive hunger and food consumption, a sign that the person is “starving in the land of plenty.” That is, although plenty of glucose is available, it cannot be used, and the body starts to utilize its fat and protein stores for energy metabolism. Figure 17.18 summarizes the consequences of insulin deficiency.

Two major forms of diabetes mellitus have been distinguished: type I and type II. **Type I diabetes mellitus**, or **insulin-dependent diabetes mellitus** (IDDM), was formerly known as **juvenile-onset diabetes**. The symptoms of type I diabetes appear suddenly, usually before the age of 15 years. However, a long asymptomatic period during which the beta cells are systemically destroyed by an autoimmune response precedes these symptoms.

It is likely that type 1 diabetes has several causes. Some investigators believe that molecular mimicry is the problem: Some foreign substance that has entered the body and has been recognized as an alien (and provoked an immune response) is so similar to some beta cell proteins that those self (β cell) proteins are also attacked by the immune system. A prime suspect for an environmental trigger is exposure to a specific fragment of albumin in cow’s milk during the first few months of life in genetically susceptible infants. This albumin fragment is a look-alike of the p69 protein that beta cells display on their surface when they are infected by viruses.

Elegant studies on mice have demonstrated that T cells have at least one other target, a specific enzyme called glutamate decarboxylase (GAD) present in the beta cells. GAD converts the amino acid glutamate into GABA, a key messenger between neurons and, to a lesser extent, between pancreatic cells. Because most of the body’s GAD is in the brain, essentially hidden from the immune system, these researchers suggest that the immune system may not recognize GAD as a self-protein. Like the albumin fragment described above, a piece of GAD closely resembles a virus that has been associated with diabetes. GAD is probably not the whole answer either, but it appears to be an important part of it, because when mice prone to develop diabetes were injected with doses of GAD before the autoimmune attack on the pancreas began, all mice treated escaped developing diabetes.

Type I diabetics totally lack insulin activity, and their disease is difficult to control. Because of the early onset of their disease, type I diabetics typically exhibit long-term vascular and neural problems. The lipidemia and high blood cholesterol levels typical of the disease lead to vascular complications including atherosclerosis, strokes, heart attacks, renal shutdown, gangrene, and blindness. Consequences of neuropathies include loss of sensation, impaired bladder function, and impotence. Previously, the protocol was insulin injections once or twice daily to manage ketoacidosis and, to a lesser extent, hyperglycemia. Currently, the recommendation is for more intense control to reduce vascular and renal complications via more frequent insulin injections (up to four times daily) or insulin infusion delivered continuously by an insulin pump worn externally. Although pancreatic islet cell transplants have been somewhat successful in helping type I diabetics,
<table>
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<tr>
<th>Organ response to insulin deficiency</th>
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<th>Signs and symptoms</th>
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<td>Blood</td>
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<td>Decreased glucose uptake and utilization</td>
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<td>Protein catabolism and gluconeogenesis</td>
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<td>Acetone breath - Hyperpnea - Nausea/vomiting/abdominal pain</td>
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<td>Cardiac irregularities</td>
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<td>Central nervous system depression; coma</td>
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*FIGURE 17.18
Symptomatic results of insulin deficit (diabetes mellitus).*

the requirement for immunsuppression is a problem, particularly in young patients. Immune system manipulation to prevent the initial sensitization to the cross-reacting fragment now seems more promising.

Type II diabetes, or non-insulin-dependent diabetes mellitus (NIDDM) was formerly called mature-onset diabetes because it occurs mostly after the age of 40 years and is increasingly common with age. Heredity or a familial predisposition is particularly striking in this diabetic group. If an identical twin has type II diabetes mellitus, the probability that the other twin will have the disease is 100%. Most type II diabetics produce insulin, but the amount is inadequate or the insulin receptors are unable to respond to insulin, a phenomenon called insulin resistance. Type II diabetics are almost always overweight and account for over 90% of the known cases of diabetes mellitus. The link between obesity and DM has been obscure until recently. It now appears that adipose cells of obese people overproduce a hormonelike chemical called tumor necrosis factor-alpha, which depresses synthesis of a protein (glut4). Since glut4 enables glucose to pass through insulin-primed plasma membranes, cells cannot take up glucose in its absence. Ketosis is not a major problem for this group, and in many cases the symptoms can be managed solely by exercise and diet (weight loss).

Hyperinsulinism, or excessive insulin secretion, results in low blood sugar levels, or hypoglycemia. Hypoglycemia triggers the release of hyperglycemic hormones, which cause anxiety, nervousness, tremors, and a feeling of weakness. Insufficient glucose delivery to the brain causes disorientation, progressing to convulsions, unconsciousness, and even death. In rare cases, hyperinsulinism results from an islet cell tumor. More commonly, it is caused by an overdose of insulin and is easily treated by ingesting some sugar.

The Gonads

The male and female gonads (see Figure 17.1) produce steroidal sex hormones, identical in every way to those produced by adrenal cortical cells. The major distinction is the source and relative amounts produced. The paired ovaries are small, oval organs located in the female’s abdominopelvic cavity. Besides producing ova or eggs, the ovaries produce estrogens and progesterone (pro-jes’te-rön). The estrogens are alone responsible for maturation of the reproductive organs and the appearance of the secondary sex characteristics of females at puberty. Acting with progesterone, estrogens promote breast development and cyclic changes in the uterine mucosa (the menstrual cycle).

The testes, located in an extra-abdominal skin pouch called the scrotum, produce sperm and male sex hormones, primarily testosterone (tes-tos’te-rön). During puberty, testosterone initiates the maturation of the male reproductive organs and the appearance of secondary sex characteristics and sex drive. In addition, testosterone is necessary for normal sperm
Disorders of the Parathyroid Glands  Surgical removal of the parathyroid glands sometimes unintentionally occurs when the thyroid is removed because of a tumor or the presence of Graves' disease. The resulting fall in parathyroid hormone (PTH) causes a decrease in plasma calcium levels, which can lead to severe muscle tetany. Hyperparathyroidism is usually caused by a tumor that secretes excessive amounts of PTH. This stimulates demineralization of bone, which makes the bones soft and raises the blood levels of calcium and phosphate. As a result of these changes, bones are subject to deformity and fracture, and stones (renal calculi) composed of calcium phosphate are likely to develop in the urinary tract.

Disorders of the Pancreatic Islets

Diabetes Mellitus  Diabetes mellitus is characterized by fasting hyperglycemia and the presence of glucose in the urine. There are two forms of this disease. Type I, or insulin-dependent diabetes mellitus, is caused by destruction of the beta cells and the resulting lack of insulin secretion. Type II, or noninsulin-dependent diabetes mellitus (which is the more common form) is caused by decreased tissue sensitivity to the effects of insulin, so that increasingly large amounts of insulin are required to produce a normal effect. Both types of diabetes mellitus are also associated with abnormally high levels of glucagon secretion. Diabetes mellitus is discussed in more detail in chapter 27.

Reactive Hypoglycemia  People with a genetic predisposition for type II diabetes mellitus often first develop reactive hypoglycemia. In this condition, the rise in blood glucose that follows the ingestion of carbohydrates stimulates excessive secretion of insulin, which in turn causes the blood glucose levels to fall below the normal range. This can result in weakness, changes in personality, and mental disorientation.
Inadequate ADH Secretion  A dysfunction of the neurohypophysis results in a deficiency in ADH secretion, causing a condition called diabetes insipidus. Symptoms of this disease include polyuria (excessive urination), polydipsia (excessive thirst), and severe ionic imbalances. Diabetes insipidus is treated by injections of ADH.

Disorders of the Adrenal Glands

Tumors of the Adrenal Medulla  Tumors of the chromaffin cells of the adrenal medulla are referred to as pheochromocytomas (fē-ō-kro-mō-si-to-maz). These tumors cause hypersecretion of epinephrine and norepinephrine, which produce an effect similar to continuous sympathetic nervous stimulation. The symptoms of this condition are hypertension, elevated metabolism, hyperglycemia and sugar in the urine, nervousness, digestive problems, and sweating. It does not take long for the body to become totally fatigued under these conditions, making the patient susceptible to other diseases.

Addison’s Disease  This disease is caused by inadequate secretion of both glucocorticoids and mineralocorticoids, which results in hypoglycemia, sodium and potassium imbalance, dehydration, hypotension, rapid weight loss, and generalized weakness. A person with this condition who is not treated with corticosteroids will die within a few days because of the severe electrolyte imbalance and dehydration. Another symptom of this disease is darkening of the skin. This is caused by excess secretion of ACTH and possibly MSH (because MSH is derived from the same parent molecule as ACTH) as a result of lack of negative feedback inhibition of the pituitary by corticosteroids.

Cushing’s Syndrome  Hypersecretion of corticosteroids results in Cushing’s syndrome. This is generally caused by a tumor of the adrenal cortex or by oversecretion of ACTH from the adenohypophysis. Cushing’s syndrome is characterized by changes in carbohydrate and protein metabolism, hyperglycemia, hypertension, and muscular weakness. Metabolic problems give the body a puffy appearance and can cause structural changes characterized as “buffalo hump” and “moon face.” Similar effects are also seen when people with chronic inflammatory diseases receive prolonged treatment with corticosteroids, which are given to reduce inflammation and inhibit the immune response.

Disorders of the Thyroid and Parathyroid Glands

Hypothyroidism  The infantile form of hypothyroidism is known as cretinism (kret’i-niz’em). The clinical symptoms of cretinism are stunted growth, thickened facial features, abnormal bone development, mental retardation, low body temperature, and general lethargy. If cretinism is diagnosed early, it may be successfully treated by administering thyroxine.

Myxedema  Hypothyroidism in an adult causes myxedema (mik’se-de’ma). This disorder affects body fluids, causing edema and increasing blood volume, hence increasing blood pressure. Symptoms of myxedema include a low metabolic rate, lethargy, and a tendency to gain weight. This condition is treated with thyroxine or with triiodothyronine, which are taken orally (as pills).

Endemic Goiter  A goiter is an abnormal growth of the thyroid gland. When this condition results from inadequate dietary intake of iodine, it is termed endemic goiter (fig. 19.26). In this case, growth of the thyroid is due to excessive TSH secretion, which results from low levels of thyroxine secretion. Endemic goiter is thus associated with hypothyroidism.

Graves’ Disease  Graves’ disease, also called toxic goiter, involves growth of the thyroid associated with hypersecretion of thyroxine. This hyperthyroidism is produced by antibodies that act like TSH and stimulate the thyroid; it is an autoimmune disease. As a consequence of high levels of thyroxine secretion, the metabolic rate and heart rate increase, the person loses weight, and the autonomic nervous system induces excessive sweating. In about half of the cases, exophthalmos (ek’of-thal’mos) (bulging of the eyes) also develops (fig. 19.27) because of edema in the tissues of the eye sockets and swelling of the extrinsic eye muscles.

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diabetes: Gk. diabetes, to pass through a siphon
Addison’s disease: from Thomas Addison, English physician. 1792–1860
Cushing’s syndrome: from Harvey Cushing, American physician. 1869–1939
myxedema: Gk. myx, mucus; odema, swelling
Graves’ disease: from Robert James Graves, Irish physician, 1796–1853
exophthalmos: Gk. ex, out; opthalmos, eyeball