decreased serum calcium levels. The symptoms range from circumoral numbness or paresthesias (tingling) of the distal extremities and carpopedal spasm, to life-threatening laryngospasm and generalized seizures. The classic findings on physical examination are *Chvostek sign* and *Trousseau sign*. Chvostek sign is elicited in subclinical disease by tapping along the course of the facial nerve, which induces contractions of the muscles of the eye, mouth, or nose. Trousseau sign refers to carpal spasms produced by occlusion of the circulation to the forearm and hand with a blood pressure cuff for several minutes.

- *Mental status changes* include emotional instability, anxiety and depression, confusional states, hallucinations, and frank psychosis.
- *Intracranial manifestations* include calcifications of the basal ganglia, parkinsonian-like movement disorders, and increased intracranial pressure with resultant papilledema. The paradoxical association of hypocalcemia with calcifications may be because of an increase in phosphate levels, resulting in tissue deposits with calcium that exists in local extracellular milieu.
- *Ocular disease* takes the form of calcification of the lens and cataract formation.
- *Cardiovascular manifestations* include a conduction defect that produces a characteristic prolongation of the QT interval in the electrocardiogram.
- *Dental abnormalities* occur when hypocalcemia is present during early development. These findings are highly characteristic of hypoparathyroidism and include dental hypoplasia, failure of eruption, defective enamel and root formation, and abraded carious teeth.

Pseudohypoparathyroidism

In this condition, hypoparathyroidism occurs because of end-organ resistance to the actions of PTH. Indeed, serum PTH levels are normal or elevated. In one form of pseudohypoparathyroidism, there is end-organ resistance to TSH and FSH/LH as well as PTH. All of these hormones signal via G-protein–coupled receptors, and the disorder results from genetic defects in components of this pathway that are shared across endocrine tissues. PTH resistance is the most obvious clinical manifestation. It presents as hypocalcemia, hyperphosphatemia, and elevated circulating PTH. TSH resistance is generally mild, while LH/FSH resistance manifests as hypergonadotropic hypogonadism in females.

THE ENDOCRINE PANCREAS

The endocrine pancreas consists of about 1 million clusters of cells, the *islets of Langerhans*, which contain four major and two minor cell types. The four main types are β, α, δ, and PP (pancreatic polypeptide) cells. They can be differentiated by the ultrastructural characteristics of their granules, and by their hormone content (Fig. 24-27). *The β cells produce insulin*, which regulates glucose utilization in tissues and reduces blood glucose levels, as will be detailed in the discussion of diabetes. *α cells secrete glucagon*, which stimulates glycogenolysis in the liver and thus increases blood sugar. *δ cells secrete somatostatin*, which suppresses both insulin and glucagon release. *PP cells secrete pancreatic polypeptide*, which exerts several gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes and inhibition of intestinal motility. These cells not only are present in islets but also are scattered in the exocrine pancreas. The two rare cell types are *D1 cells* and *enterochromaffin cells*. D1 cells elaborate vasoactive intestinal polypeptide (*VIP*), a hormone that induces glycogenolysis and hyperglycemia; it also stimulates gastrointestinal fluid secretion and causes secretory diarrhea. *Enterochromaffin cells synthesize serotonin* and are the source of pancreatic tumors that cause the carcinoid syndrome (Chapter 19).

The following discussion focuses on the two main disorders of islet cells: diabetes mellitus and pancreatic endocrine tumors.

Diabetes Mellitus

Diabetes mellitus is a group of metabolic disorders sharing the common feature of hyperglycemia. Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both. The chronic hyperglycemia and attendant metabolic dysregulation may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves, and blood vessels. **In the United States, diabetes is the leading cause of end-stage renal disease, adult-onset blindness and non-traumatic lower extremity amputations resulting from atherosclerosis of the arteries**.

Diabetes and related disorders of glucose metabolism are extremely common. According to the American Diabetes Association, diabetes affects more than 25 million children and adults, or more than 8% of the population, in the United States, nearly a third of whom are currently unaware that they have hyperglycemia. Approximately 1.9 million new cases of adult diabetes are diagnosed each year in the United States. Furthermore, a staggering 79 million adults in this country have impaired glucose tolerance or "prediabetes," which is defined as elevated blood sugar that does not reach the criterion accepted for an outright diagnosis of diabetes (see later), and individuals with prediabetes are at high risk for developing frank diabetes. Compared to non-Hispanic whites, Native Americans, African Americans, and Hispanics are 1.5 to 2 times more likely to develop diabetes in their lifetimes. The World Health Organization estimates that as many as 346 million people suffer from diabetes worldwide, with India and China being the largest contributors to the world's diabetic load. Increasingly sedentary life styles and poor eating habits have contributed to the simultaneous escalation of diabetes and obesity, which some have called the *diabesity epidemic*. Sadly, obesity and diabetes have now extended even to