genes that code for the two subunits of the ATP-sensitive K^+-channel, defects in mitochondrial DNA (which can impede ATP synthesis), and mutations of the insulin gene itself.

Genetic Defects that Impair Tissue Response to Insulin. Rare *insulin receptor mutations* that affect receptor synthesis, insulin binding, or receptor tyrosine kinase activity can cause severe insulin resistance, accompanied by hyperinsulinemia and diabetes (type A insulin resistance). Such patients often show a velvety hyperpigmentation of the skin, known as *acanthosis nigricans*. Females with type A insulin resistance frequently have polycystic ovaries and elevated androgen levels. *Lipoatrophic diabetes*, as the name suggests, is hyperglycemia accompanied by loss of adipose tissue, the latter occurring selectively in the subcutaneous fat. This rare group of genetic disorders has in common insulin resistance, diabetes, hypertriglyceridemia, acanthosis nigricans, and abnormal fat deposition in the liver (hepatic steatosis). Multiple subtypes of lipoatrophic diabetes, each ascribed to a different causal mutation, have been reported.

Diabetes and Pregnancy

Pregnancy can be complicated by diabetes in one of two settings: when women with preexisting diabetes become pregnant ("pregestational" or overt diabetes), or women who were previously euglycemic develop impaired glucose tolerance and diabetes for the first time during pregnancy ("gestational" diabetes). Approximately 5% of pregnancies occurring in the United States are complicated by hyperglycemia, and the incidence of both pregestational and gestational diabetes is rising in parallel with the rising incidence of obesity and diabetes in the general population. Pregnancy is a "diabetogenic" state in which the prevailing hormonal milieu favors a state of insulin resistance. In a previously euglycemic woman who is otherwise susceptible due to concurrent genetic and environmental factors, the consequence may be gestational diabetes. Women with pregestational diabetes (where hyperglycemia is already present in the periconception period) have an increased risk of *stillbirth* and *congenital malformations* in the fetus. Poorly controlled diabetes that arises later in pregnancy, regardless of prior history, can lead to excessive birth weight in the newborn (*macrosomia*), as well as long-term sequelae for the child exposed to a diabetic environment in utero, including obesity and diabetes later in life. Gestational diabetes typically resolves following delivery; however, the majority of women with this condition will develop overt diabetes over the next 10 to 20 years.

Clinical Features of Diabetes

It is difficult to sketch with brevity the diverse clinical presentations of diabetes mellitus. We will discuss the most common initial presentation or mode of diagnosis for each of the two major subtypes, followed by a discussion of acute, and then chronic (long-term) complications of diabetes.

Type 1 diabetes was formerly thought to occur primarily in persons younger than age 18 but is now known to occur at any age. In the initial 1 or 2 years following the onset of overt type 1 diabetes, the exogenous insulin requirements may be minimal because of ongoing endogenous insulin secretion (referred to as the *honeymoon period*). Thereafter, any residual β-cell reserve is exhausted and insulin requirements increase dramatically. Although β-cell destruction is a prolonged process, the transition from impaired glucose tolerance to overt diabetes may be abrupt and is often brought on by an event, such as infection, that is also associated with increased insulin requirements.

In contrast to type 1 diabetes, patients with **type 2 diabetes** are typically older than 40 years and frequently obese. However, with the increase in obesity and sedentary lifestyle in this society, type 2 diabetes is being seen in children and adolescents with increasing frequency. In some cases, medical attention is sought because of unexplained fatigue, dizziness, or blurred vision. **Most frequently, however, the diagnosis of type 2 diabetes is made after routine blood testing in asymptomatic persons.** In fact, in light of the large number of asymptomatic individuals with undiagnosed hyperglycemia in the United States, routine glucose testing is recommended for everyone older than 45 years of age.

The Classic Triad of Diabetes

The onset of type 1 diabetes is usually marked by the triad of polyuria, polydipsia, polyphagia, and, when severe, diabetic ketoacidosis, all resulting from metabolic derangements. Because insulin is a major anabolic hormone, its deficiency results in a *catabolic* state that affects not only glucose metabolism but also fat and protein metabolism. Unopposed secretion of counterregulatory hormones (glucagon, growth hormone, epinephrine) also plays a role in these metabolic derangements. The assimilation of glucose into muscle and adipose tissue is sharply diminished or abolished. Not only does storage of glycogen in liver and muscle cease, but also reserves are depleted by glycogenolysis. The resultant hyperglycemia exceeds the renal threshold for reabsorption, and glycosuria ensues. The glycosuria induces an osmotic diuresis and thus *polyuria*, causing a profound loss of water and electrolytes (Fig. 24-33). The obligatory renal water loss combined with the hyperosmolarity resulting from the increased levels of glucose in the blood tends to deplete intracellular water, triggering the osmoreceptors of the thirst centers of the brain. In this manner, intense thirst (*polydipsia*) appears. With a deficiency of insulin the scales swing from insulin-promoted anabolism to catabolism of proteins and fats. Proteolysis follows, releasing gluconeogenic amino acids that are removed by the liver and used as building blocks for glucose. The catabolism of proteins and fats tends to induce a negative energy balance, which in turn leads to increasing appetite (*polyphagia*), thus completing the classic triad of diabetes: polyuria, polydipsia, and polyphagia. Despite the increased appetite, catabolic effects prevail, resulting in weight loss and muscle weakness. The combination of polyphagia and weight loss is paradoxical and should always raise the suspicion of diabetes.

Acute Metabolic Complications of Diabetes

Diabetic ketoacidosis is a severe acute metabolic complication of type 1 diabetes, but may also occur in type 2 diabetes, though not as commonly and not to as marked an