- ***Diabetic nephropathy* is a leading cause of end-stage renal disease in the United States**. Approximately 30% to 40% of all diabetics develop clinical evidence of nephropathy, but a considerably smaller fraction of patients with type 2 diabetes progress to end-stage renal disease. However, because of the much greater prevalence of type 2 diabetes, these patients constitute slightly over half the diabetic patients starting dialysis each year.

  The frequency of diabetic nephropathy is greatly influenced by the genetic makeup of the population in question; for example, Native Americans, Hispanics, and African Americans have a greater risk of developing end-stage renal disease than do non-Hispanic whites with type 2 diabetes. The earliest manifestation of diabetic nephropathy is the appearance of low amounts of albumin in the urine (>30 mg/day, but <300 mg/day), that is, *microalbuminuria*. Notably, microalbuminuria is also a marker for greatly increased cardiovascular morbidity and mortality for persons with either type 1 or type 2 diabetes. Therefore, all patients with microalbuminuria should be screened for macrovascular disease, and aggressive intervention should be undertaken to reduce cardiovascular risk factors. Without specific interventions, approximately 80% of type 1 diabetics and 20% to 40% of type 2 diabetics will develop *overt nephropathy with macroalbuminuria* (>300 mg of urinary albumin per day) over 10 to 15 years, usually accompanied by the appearance of hypertension. The progression from overt nephropathy to end-stage renal disease is highly variable, but by 20 years, more than 75% of type 1 diabetics and approximately 20% of type 2 diabetics with overt nephropathy will develop end-stage renal disease, requiring dialysis or renal transplantation.
- ***Visual impairment*, sometimes even total blindness, is one of the more feared consequences of long-standing diabetes**. Approximately 60% to 80% of patients develop some form of *diabetic retinopathy* approximately 15 to 20 years after diagnosis. The fundamental lesion of retinopathy—neovascularization—is attributable to hypoxia-induced overexpression of VEGF in the retina. Current treatment for this condition includes administration of antiangiogenic agents. As stated earlier, diabetics also have an increased propensity for *glaucoma* and *cataract formation*, both of which contribute to visual impairment in diabetes.
- *Diabetic neuropathy* can elicit a variety of clinical syndromes, afflicting the central nervous system, peripheral sensorimotor nerves, and the autonomic nervous system. **The most frequent pattern of involvement is a *distal symmetric polyneuropathy* of the lower extremities that affects both motor and sensory function**. Over time the upper extremities may be involved as well, thus approximating a "glove and stocking" pattern of polyneuropathy. Other forms include *autonomic neuropathy*, which produces disturbances in bowel and bladder function and sometimes erectile dysfunction, and *diabetic mononeuropathy*, which may manifest as sudden footdrop, wristdrop, or isolated cranial nerve palsies.
- **Diabetics are plagued by enhanced susceptibility to infections of the skin and to tuberculosis, pneumonia, and pyelonephritis**. Such infections cause the deaths of about 5% of diabetics. In an individual with diabetic neuropathy, a trivial infection in a toe may be the first event in a long succession of complications (gangrene, bacteremia, pneumonia) that may ultimately lead to death. The basis of enhanced susceptibility is multifactorial, and includes decreased neutrophil functions (chemotaxis, adherence to the endothelium, phagocytosis, and microbicidal activity), and impaired cytokine production by macrophages. The vascular compromise also reduces delivery of circulating cells and molecules that are required for host defense.

The staggering numbers and the societal and economic impact of diabetes have already been discussed. For the most part, diabetes remains a lifelong diagnosis, although pancreatic islet cell transplantation has the potential to ameliorate type 1 diabetes for many patients. For some individuals with type 2 diabetes, dietary modifications, exercise and weight loss regimens can reduce insulin resistance and hyperglycemia at least early in the disease. However, all patients will ultimately require some form of therapeutic intervention to maintain glycemic control.

KEY CONCEPTS

Diabetes Mellitus: Pathogenesis and Long-Term Complications

- Type 1 diabetes is an *autoimmune disease* characterized by progressive destruction of islet β cells, leading to absolute insulin deficiency. The fundamental immune abnormality in type 1 diabetes is a failure of self-tolerance in T cells, and circulating autoantibodies to islet cell antigens (including insulin) often are detected in affected patients.
- Type 2 diabetes has no autoimmune basis; instead, features central to its pathogenesis are *insulin resistance* and *β-cell dysfunction*, resulting in relative insulin deficiency.
- *Obesity* has an important relationship with insulin resistance (and hence type 2 diabetes), mediated through multiple factors including excess free fatty acids, cytokines released from adipose tissues (adipocytokines), and inflammation.
- Monogenic forms of diabetes are uncommon and are caused by single-gene defects that result in primary β-cell dysfunction (e.g., *glucokinase* mutation) or lead to abnormalities of insulin-insulin receptor signaling (e.g., insulin receptor gene mutations).
- The long-term complications of diabetes are similar in both types and involve four potential mechanisms resulting from sustained hyperglycemia: formation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), disturbances in the polyol pathways leading to oxidative stress, and overload of the hexosamine pathway.
- Long term complications of diabetes include both large vessel disease (*macroangiopathy*), such as atherosclerosis, ischemic heart disease and lower extremity ischemia, as well as small vessel disease (*microangiopathy*), the latter manifesting mainly as retinopathy, nephropathy and neuropathy.