Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia arising as a consequence of a relative or absolute deficiency of insulin secretion, resistance to insulin action, or both. Although diabetes mellitus is recognized by its characteristic hyperglycemia, the metabolic rearrangements are more pervasive, involving altered metabolism of carbohydrates, fats, and proteins. As a function of time and consequent to the metabolic disruption, diabetic patients may suffer the tragic ravages of long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Although several pathogenic processes may be involved in the development of diabetes (Table 2.1), the vast majority of cases fall into two main categories: type 1 diabetes, usually due to an immune-mediated destruction of pancreatic islet β-cells with consequent insulin deficiency; and type 2 diabetes, the more common type, usually due to resistance to insulin action in the setting of inadequate compensatory insulin secretory response. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues resulting from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action.

The criteria used for diagnosis of diabetes mellitus and for prediabetes—"impaired glucose tolerance" (IGT) and "impaired fasting glucose" (IFG)—are listed in Table 2.2.1 The pathogenetic sequence in immune-mediated type 1 diabetes involves, first, a genetic predisposition, conferred principally by "diabetogenic" genes in the major histocompatibility complex (MHC) on the short arm of chromosome 6, although multiple other genetic loci modulate disease risk; second, nongenetic (environmental) factors that appear to act as triggers in genetically susceptible people; and third, activation of cell-mediated immune mechanisms targeted against pancreatic islet β-cells (Fig 2.1). The initial immune response engenders secondary and tertiary immune responses, which collectively result in progressive destruction of pancreatic islet β-cells and consequent development of type 1 diabetes. The process is insidious and may evolve over a period of years. During this time, there appear a number of immune markers that indicate the presence of ongoing β-cell damage, including islet cell autoantibodies (ICAs) detected by immunofluorescence, insulin autoantibodies (IAAs), autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to inactive transmembrane tyrosine phosphatases IA-2 (also called ICA512) and IA-2β. This is accompanied by a progressive decline of β-cell function and mass, with a recognizable metabolic defect, e.g., loss of first-phase insulin response (FPIR) during an intravenous glucose tolerance test (IVGTT). When the vast majority of β-cells have been damaged or destroyed, hyperglycemia supervenes with the overt...
Table 2.1. Classification of diabetes mellitus and other categories of glucose regulations.

**Type 1 diabetes**: β-cell destruction, usually leading to absolute insulin deficiency
- A. Immune-mediated diabetes
- B. Idiopathic diabetes

**Type 2 diabetes**: combined insulin secretory defect and insulin resistance

**Prediabetes**: a metabolic stage intermediate between normal glucose homeostasis and diabetes
- IGT
- IFG

**Gestational diabetes mellitus (GDM)**: any degree of glucose intolerance with onset or first recognition during pregnancy

**Other specific types of diabetes**
- Genetic defects of the β-cell
  - Maturity-onset diabetes of the young (MODY)
    - MODY1: mutation in hepatic nuclear factor 4α gene on chromosome 20
    - MODY2: mutation in glucokinase gene on chromosome 7
    - MODY3: mutation in hepatic nuclear factor 1α gene on chromosome 12
    - MODY4: mutation in insulin promoter factor 1 gene on chromosome 13
    - MODY5: mutation in hepatocyte nuclear factor 1β gene on chromosome 17
    - MODY6: mutation in neurogenic 1/β-cell E-Box transactivator 2 gene on chromosome 2
- Point mutations in mitochondrial DNA—associated with deafness
- Genetic abnormalities that result in the inability to convert proinsulin to insulin

**Genetic defects in insulin action**: rare causes of diabetes
- Type A insulin resistance
- Insulin receptor gene mutations
- Leprechaunism
- Rabson–Mendenhall syndrome

**Diseases of the exocrine pancreas**
- Pancreatitis
- Trauma
- Infection
- Pancreatectomy
- Pancreatic carcinoma
- Cystic fibrosis
- Hemochromatosis
- Fibrocystic pancreatitis

**Endocrinopathies**
- Acromegaly
- Cushing’s syndrome
- Glucagonoma
- Pheochromocytoma
- Somatostatinoma
- Aldosteronoma

**Drug- or chemical-induced diabetes**

**Uncommon forms of immune-mediated diabetes**
- Stiff-man syndrome
- Anti-insulin receptor antibodies ("type B insulin resistance")

**Genetic syndromes sometimes associated with diabetes**

Expression of clinical symptoms becoming apparent. Ultimately, when all β-cells have been destroyed residual endogenous insulin secretion is lost (i.e., absence of C-peptide) and "total" diabetes is said to be present. Figure 2.1 depicts this progressive nature of the disease process.

Type 1 diabetes may be distinguished from type 2 diabetes by virtue of one and usually more of the above autoantibodies (ICA, IAA, GAD65, IA-2) being present in 85% to 90% of individuals when fasting hyperglycemia is initially detected.

**Histopathology**

The immune reaction is seen as a mononuclear cell infiltration of islets ("insulitis") and is a pathognomonic lesion seen in pancreases examined near time of onset of type 1 diabetes. However, at the time of diagnosis of type 1 diabetes only a few islets show the insulitis lesion. Some normal islets can be seen, and rarely a hyperplastic islet. Most islets are "pseudonutrophic" small islets, devoid of β-cells and without mononuclear infiltration, but with intact glucagon-secreting α-cells and somatostatin-secreting δ-cells. Presumably, these islets already have had their β-cells destroyed and the immunologic attack has abated. Type 1 diabetes appears when enough β-cells are damaged or destroyed that glucose tolerance can no longer be maintained.

**Genetics**

The specific mode of genetic transmission is not yet established. There is a wide ethnic variation in disease incidence and prevalence. The empirical risk of type 1 diabetes is increased in first-degree relatives of probands with the disease. In US Caucasians, who have an overall risk is 0.2% to 0.4%, the risk in siblings is about 5%, whereas offspring of diabetic parents have a 3% risk when the mother is the one with diabetes but a 6% risk when the father is the one with diabetes.

The best characterized genetic locus for type 1 diabetes is IDDM1, which is within or in close proximity to the class II HLA region on the short arm of chromosome 6 and confers about 50% of genetic predisposition for type 1 diabetes. Because class II MHC genes regulate the immune response, IDDM1 alleles could be involved in antigen presentation of