As with most autoimmune diseases, the pathogenesis of type 1 diabetes involves an interplay of genetic and environmental factors.

### *Genetic Susceptibility*

Epidemiologic studies, such as those demonstrating higher concordance rates for disease in monozygotic vs dizygotic twins, have convincingly established a genetic basis for type 1 diabetes. More recently, genome-wide association studies have identified multiple genetic susceptibility loci for type 1 diabetes, as well as for type 2 diabetes (see later). More than 30 susceptibility loci for type 1 diabetes are now known. **Of these, the most important locus is the *HLA* gene cluster on chromosome 6p21, which according to some estimates contributes as much as 50% of the genetic susceptibility to type 1 diabetes**. Ninety percent to 95% of Caucasians with this disease have either an HLA-DR3 or HLA-DR4 haplotype, in contrast to about 40% of normal subjects; moreover, 40% to 50% of patients with type 1 diabetes are combined DR3/DR4 heterozygotes, in contrast to 5% of normal subjects. Individuals who have either DR3 or DR4 concurrently with a DQ8 haplotype (which corresponds to *DQA1*0301-DQB1*0302* alleles) demonstrate one of the highest inherited risks for type 1 diabetes in sibling studies. Predictably, the polymorphisms in the HLA molecules are located in or adjacent to the peptide-binding pockets, consistent with the notion that disease-associated alleles code for molecules that have the capacity to display particular antigens. However, as discussed in Chapter 6, it is still not known if these HLA-disease associations reflect the ability of specific HLA molecules to present self islet antigens or if they are related to the role of HLA molecules in T-cell selection and tolerance.

Several *non-HLA genes* also confer susceptibility to type 1 diabetes. The first disease-associated non-MHC gene to be identified was *insulin*, with variable number of tandem repeats (VNTRs) in the promoter region being associated with disease susceptibility. The mechanism underlying this association is unknown. It is possible that these polymorphisms influence the level of expression of insulin in the thymus, thus affecting the negative selection of insulin-reactive T cells (Chapter 6). The association between polymorphisms in *CTLA4* and *PTPN22* and autoimmune thyroiditis was mentioned earlier; not surprisingly, these genes have also been linked with susceptibility to type 1 diabetes. The relationship of type 1 diabetes to altered T-cell selection and regulation is also underscored by the striking prevalence of this disease in individuals with rare germline defects in genes that code for immune regulators, such as *AIRE*, mutations of which cause autoimmune polyendocrinopathy syndrome, type 1 (APS, type 1) (see Adrenal Gland later).

### *Environmental Factors*

As in other autoimmune diseases, genetic susceptibility contributes to only a part of diabetes risk, and environmental factors must play a role. The nature of these environmental influences remains an enigma. Although antecedent *viral infections* have been suggested as triggers for development of the disease, neither the type of virus nor how it promotes islet-specific autoimmunity is established. Some studies suggest that viruses might share epitopes with islet antigens, and the immune response to the virus results in cross-reactivity and destruction of islet tissues, a phenomenon known as *molecular mimicry*. On the other hand, infections are also known to be protective against type 1 diabetes.

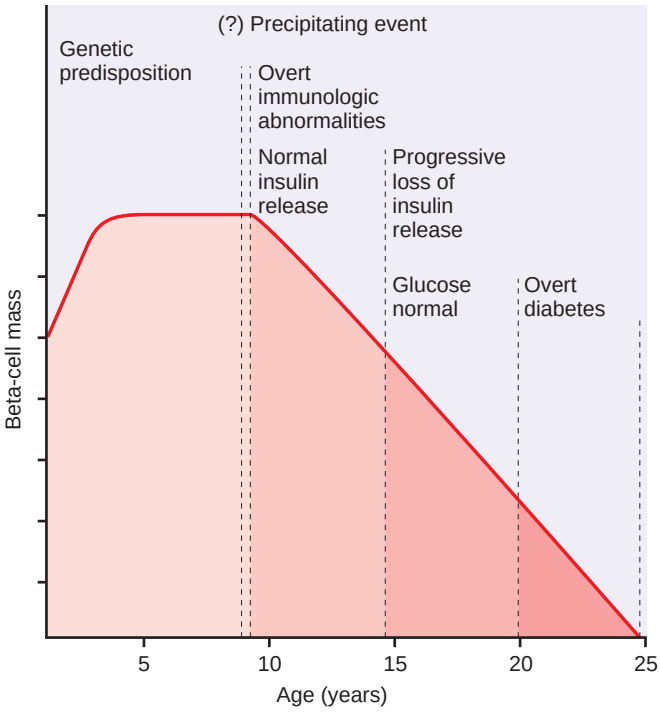


**Figure 24-31** Stages in the development of type 1 diabetes mellitus. The stages are listed from left to right, and hypothetical β-cell mass is plotted against age. (From Eisenbarth GE: Type 1 diabetes: a chronic autoimmune disease. N Engl J Med 314:1360, 1986. Copyright © 1986, Massachusetts Medical Society. All rights reserved.)

### *Mechanisms of β Cell Destruction*

Although the clinical onset of type 1 diabetes is often abrupt, there is a lengthy lag period between initiation of the autoimmune process and the appearance of disease, during which there is progressive loss of insulin reserves (Fig. 24-31). The classic manifestations of the disease (hyperglycemia and ketosis) occur late in its course, after more than 90% of the β cells have been destroyed.

**The fundamental immune abnormality in type 1 diabetes is a failure of self-tolerance in T cells specific for islet antigens.** This failure of tolerance may be a result of some combination of defective clonal deletion of self-reactive T cells in the thymus, as well as defects in the functions of regulatory T cells or resistance of effector T cells to suppression by regulatory cells. Thus, autoreactive T cells not only survive but are poised to respond to self-antigens. The initial activation of these cells is thought to occur in the peripancreatic lymph nodes, perhaps in response to antigens that are released from damaged islets. The activated T cells then traffic to the pancreas, where they cause β-cell injury. Multiple T-cell populations have been implicated in this damage, including $T_H1$ cells (which may secrete cytokines, including IFN-γ and TNF, that injure β cells), and CD8+ CTLs (which kill β cells directly). The islet autoantigens that are the targets of immune attack may include insulin, the β cell enzyme glutamic acid decarboxylase (GAD), and islet cell autoantigen 512 (ICA512).