INSULIN-DEPENDENT (TYPE 1) DIABETES MELLITUS

Part of "CHAPTER 136 - CLASSIFICATION, DIAGNOSTIC TESTS, AND PATHOGENESIS OF TYPE 1 DIABETES MELLITUS"

Type 1 diabetes mellitus is characterized by an insulin deficiency secondary to B-cell destruction. In the absence of insulin therapy, the resulting metabolic abnormalities eventually lead to death. In the preinsulin era, patients were treated with the Allen starvation diet and sometimes lived without insulin therapy for 5 or more years after diagnosis. Despite this, these patients actually were insulin dependent because they ultimately were dependent on insulin for survival. Although the terms *insulin-dependent diabetes* and *type 1 diabetes* commonly were used synonymously in the past, the author prefers to use the term *type 1A* to signify the autoimmune disease associated with IDDM, because any process that destroys enough B cells will cause IDDM, including extensive pancreatectomy, the ingestion of toxins such as the rodenticide pyriminil (Vacor), and certain genetic disorders such as Wolfram syndrome. The typical pancreatic lesion of type 1A diabetes is a selective loss of almost all B cells, whereas other islet cell types (A, D, and PP cells) are intact.13 Such “end-stage” islets are characterized by an absence of the inflammatory infiltrate (insulitis) that is present in many islets in children who die shortly after the onset of type 1A diabetes. Significantly, islet inflammation and B-cell destruction are a spotty process, in many ways resembling the lesions of early vitiligo, in which melanocytes in seemingly random regions of the skin are destroyed, and normal and vitiliginous skin are interspersed. Insulitis is not seen in the islets of patients with type 2 diabetes, but B-cell mass appears to be ~50% lower than in the pancreases of weight-matched control subjects.14 Not all spontaneous type 1 diabetes is the result of autoimmune mechanisms.15 In db/db mice, after a period of hyperin-sulinemia, B-cell destruction occurs. Introduction of a gene for severe combined immunodeficiency into mice with the db/db mutation blocks the production of several autoantibodies but has no influence on the loss of B cells. Conversely, in nonobese diabetic (NOD) mice, an animal model of type 1 diabetes, the introduction of an immunodeficiency gene prevents diabetes, as would be expected for an autoimmune disease.16 Selective B-cell destruction in humans also can occur in the absence of known immunologic pathogenesis. For example, persons with Wolfram syndrome inherit an autosomal recessive gene that

leads to extensive B-cell destruction as well as to numerous neurologic

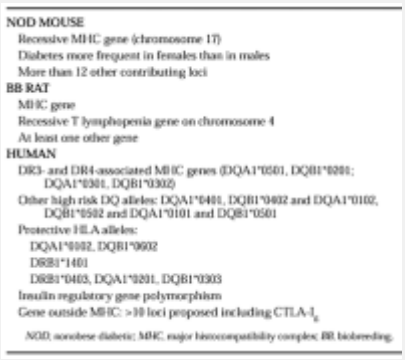
deficits.17 This constellation is designated by the acronym *DIDMOAD syndrome* (*d*iabetes *i*nsipidus, *d*iabetes *m*ellitus, *o*ptic *a*trophy, and nerve *d*eafness). No HLA-DR3 or HLA-DR4 association with this syndrome is seen, and no autoantibodies can be detected. In addition, in animals, strepto-zotocin, alloxan, and several viruses selectively destroy B cells.18 Clinically, Vacor poisoning often leads to transient insulin dependence, as well as to severe neuropathy.19

The number of pathologic processes whose result is selective B-cell destruction is remarkable. Whether this reflects the ability to detect B-cell destruction more easily than a loss of, for instance, A cells, or whether it reflects a unique metabolic sensitivity of B cells is unknown.

ROLE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX

AUTOIMMUNITY IN PATHOGENESIS OF TYPE 1A DIABETES

A large body of information indicates that autoimmune mechanisms lead to B-cell destruction in most persons in whom insulin dependence develops. In humans with type 1A diabetes and in the two animal models of this disease (the NOD mouse and the BB [biobreeding] rat), this destruction is associated with a gene within the major histocompatibility complex15,20 (MHC) (Table 136-3). The MHC is ~2 ×10^6 nucleotide base pairs long and presumably contains more than 100 different genes.21,22 Included in this region of the human genome are three classes of genes that profoundly affect immune function.



NOD MOUSE
Recessive MHC gene (chromosome 17)
Diabetes more frequent in females than in males
More than 12 other contributing loci
BB RAT
MHC gene
Recessive T lymphopenia gene on chromosome 4
At least one other gene
HUMAN
DR3- and DR4-associated MHC genes (DQA1*0501, DQB1*0201; DQA1*0301, DQB1*0302)
Other high risk DQ alleles: DQA1*0401, DQB1*0402 and DQA1*0102, DQB1*0502 and DQA1*0101 and DQB1*0501
Protective HLA alleles:
DQA1*0102, DQB1*0602
DRB1*1401
DRB1*0403, DQA1*0201, DQB1*0303
Insulin regulatory gene polymorphism
Gene outside MHC: >10 loci proposed including CTLA-I_g

NOD, nonobese diabetic; MHC, major histocompatibility complex; BB, biobreeding.

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TABLE 136-3. Genetics of Type 1 Diabetes Mellitus in Humans and Rodent Models

Class I genes (HLA-A, HLA-B, and HLA-C) are the classic strong transplantation antigens. The class I genes code for single-chain glycoproteins. These molecules also are recognized by cytotoxic T lymphocytes when they destroy virus-infected cells.

In humans, at least three expressed class II molecules are found, termed *DP, DQ*, and *DR*.[23] These molecules are dimeric glycoproteins and also are termed *Ia* (immune-associated) or *Ir* (immune-response) molecules. Once thought to be restricted in their tissue distribution, these molecules now are known to be expressed on many cells at different stages of development or in response to various stimuli. In particular, nondividing human macrophages and B lymphocytes express Ia antigens, whereas T lymphocytes express Ia antigens only after activation. Fibroblasts, thyrocytes, and many epithelial cells express Ia antigens if exposed to γ-interferon (a T-lymphocyte product). Erythroid precursor cells and some other bone marrow cells express DR early in their life cycles. Myoblasts within atheromas express Ia antigens. In type 1A human diabetes after extensive B-cell destruction, but not in early lesions of BB rats and NOD mice, a small proportion of the B cells may express Ia. This is a controversial area, because such cells may represent dead B cells ingested by macrophages.

The class III genes code for components of the complement cascade. This subject is discussed in Chapter 194.

In addition to class I, II, and III genes, other genes are found within the MHC, such as the gene coding for the enzyme 21-hydroxylase. A defect of this gene leads to congenital adrenal hyperplasia. Although the specific gene within the MHC associated with type 1A diabetes is unknown, it is most likely a class II or Ir gene. Ninety-five percent of white patients with IDDM express the HLA alleles DR3 or DR4. Although ~40% of normal persons express DR3 or DR4, this huge excess of DR3/DR4 heterozygotes in patients with IDDM indicates that >90% of persons with type 1A diabetes have a histocompatibility-related gene contributing to the disease.[24,25]

The different alleles of the histocompatibility genes also are nonrandomly associated with each other (i.e., in linkage disequilibrium).[21] Thus, many different histocompatibility genes are associated with diabetes. For example, because DR3 is associated with type 1 diabetes, and alleles A1 and B8 are associated with DR3, alleles A1 and B8 also are associated with type 1 diabetes.

Several alleles appear to be protective (e.g., DQB1*0602, DRB1*1401). Persons heterozygous for both DR3 and DR4 are at highest risk for the development of type 1A diabetes. The excess risk of DR3 and DR4 heterozygotes extends even to identical twins. Almost 70% of monozygotic

twins expressing both DR3 and DR4 alleles are concordant for type 1A diabetes, compared with 30% to 40% of twins not expressing both DR3 and DR4. This synergistic effect suggests that more than one gene within the MHC contributes to the development of type 1 diabetes.

Persons who have inherited the same HLA haplotypes as a sibling with type 1A diabetes are at increased risk for the development of diabetes (Fig. 136-1). Thus, persons who are HLA-identical to a sibling with diabetes have approximately a 1:10 to 1:20 chance of developing diabetes, whereas siblings sharing neither HLA haplotype have less than a 1:100 chance of developing diabetes. The excess of persons who are HLA-identical to a diabetic sibling suggests that one diabetogenic gene in the MHC functions in a recessive manner. Not all diabetic siblings express identical HLA haplotypes, however. This may be explained by the relatively large number of parents (e.g., 20%) who are potentially homozygous for diabetogenic MHC genes. Such a high percentage of homozygous parents is suggested by the observations that 5% of parents of children with type 1A

diabetes develop overt type 1A diabetes, and that penetrance even in HLA-identical siblings is <1:4.

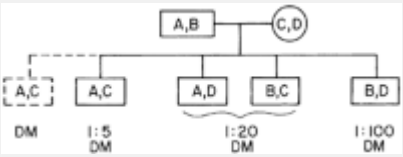

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FIGURE 136-1. HLA haplotype sharing versus approximate concordance for type 1 diabetes mellitus (*DM*) in a family in which neither parent has type 1A diabetes. Letters refer to four major histocompatibility complex (*MHC*) haplotypes in the family, with each parent passing on one of the two sixth chromosomes to each child (MHC region marked by HLA typing). Siblings HLA-identical to the proband have the highest risk of type 1 diabetes (1:10 to 1:5) and siblings sharing neither HLA haplotype have the lowest risk (1:100). (From Eisenbarth GS. Autoimmune beta cell insufficiency. Triangle 1984; 24:111.)

Although DR alleles are associated with risk for type 1A diabetes, DQ molecules appear to be more important in determining diabetes susceptibility,24 DR and DQ molecules are closely linked, and both function to bind peptides for presentation to CD4-positive T lymphocytes. Each DQ

molecule has two chains, α and β. For DQ molecules, both chains are polymorphic. Each different amino-acid sequence (polymorphism) of these chains is assigned a number. With DNA-based technology, small amounts of blood can be typed rapidly (within hours) for DQ alleles. One hypothesis related the presence of aspartic acid at position 57 on the DQ β chain to diabetes risk (DQ alleles lacking aspartic acid at position 57 are frequently associated with diabetes[26]). Too many exceptions exist to this rule, however, for it to be useful (e.g., DQB1*0402),[26] given the ease of typing for specific alleles with current technology.

Certain DQ molecules appear to provide almost complete protection from type 1A diabetes, such as DQA1*0102/DQB1*0602.[27,28] This molecule is usually associated with DR2, but when DR2 is associated with other DQ molecules (e.g., DR2, DQB1*0502, which is found among patients with type 1 diabetes on the island of Sardinia), the haplotype is diabetogenic. Of >800 patients with type 1A diabetes, the author and his associates have typed five who have had DQB1*0602, and one 0602 patient had the polyendocrine autoimmune type I syndrome with its coexistent mucocutaneous candidiasis. The manner in which this DQ molecule protects against type 1A diabetes is unknown.

The highest-risk DQ alleles associated with type 1A diabetes are DQA1*0501/DQB1*0201 associated with DR3, and DQA1*0301/DQB1*0302 associated with DR4. Persons in the general population heterozygous for these two alleles have a risk of diabetes similar to that of an offspring of a parent with type 1 diabetes (~1:16). Such persons make up ~2% of the U.S. population, but account for 40% of patients with type 1A diabetes. A research program to identify these persons at birth is under way. Subsequent studies will define the timing and sequence of the appearance of autoantibodies, with the long-term goal of predicting type 1A diabetes in the general population.

The fact that the incidence of diabetes in HLA-identical siblings (16%) is less than that in identical twins (40–50%) strongly suggests that another gene outside the MHC contributes to diabetes susceptibility. This is similar to the genetics of diabetes susceptibility of BB rats and NOD mice. When either of these animals is crossed with normal-strain animals, only offspring inheriting a “diabetogenic” MHC gene and other autosomal genes develop diabetes. Multiple other genes influence the susceptibility of NOD mice, and a gene on chromosome 4 influences susceptibility associated with a T-cell immunodeficiency of BB rats (see Table 136-3).

Too many false-positive results occur with HLA typing (30– 40% of the general population express DR3 or DR4) for this study to aid in clinical decision making. Moreover, HLA typing is relatively expensive and can never indicate a risk for diabetes greater than that of DR3/4 HLA-identical siblings (25–40%).

(Within a family, nondiabetic siblings who are HLA-identical by serologic typing to a sibling with type 1A diabetes are usually [>99% of the time] identical at all HLA loci; nevertheless, their risk of developing diabetes is only ~17%.) The imprecision of HLA typing for predicting diabetes even within families probably results in part from the inability to identify another genetic linkage group for type 1A diabetes. Even when such a linkage group is discovered, genetic prediction of the risk of type 1A diabetes cannot exceed the concordance rate of identical twins (50%).

In addition to alleles within the MHC on chromosome 6, alleles of the insulin gene on chromosome 11 contribute to diabetes susceptibility.[29] Approximately 90% of persons with type 1A diabetes are homozygous for a common allele compared with 60% of the general population. Some controversy exists regarding whether this insulin-gene polymorphism shows “imprinting” (i.e., a differential influence on diabetes susceptibility depending on whether it is inherited from the father or the mother). These insulin alleles differ not in their coding sequence but in the 5' region of the gene. Thus, differential regulation of expression of insulin, particularly for expression in the thymus, may have an important influence on diabetes risk.

In addition to genes within the MHC and insulin alleles, other genes probably influence diabetes risk. With molecular and computational tools provided by the Genome Project, and shared national repositories of cell lines and DNA from families with multiple affected members, the search for these additional genes is under way and has identified multiple loci that may be associated with diabetes risk. Environmental factors may not be necessary for the triggering of type 1A diabetes. As in many cancers, somatic mutations may randomly trigger disease expression. Testing of this hypothesis will likely depend on the localization of major susceptibility genes.

GENETIC AND ENVIRONMENTAL FACTORS

The lack of 100% concordance for type 1A diabetes in identical twins has been used to argue that environmental factors must contribute to the development of this disease.[30,31] One environmental factor known to increase the incidence of type 1A diabetes is congenital rubella. After prenatal infection with this virus, as many as 20% of children later develop diabetes. As in those who spontaneously develop type 1A diabetes, individuals with congential rubella who later develop diabetes express HLA alleles DR3 and DR4.[32] These children often also have thyroiditis and other immunologic disorders (e.g., agammaglobulinemia) in association with an abnormal T-lymphocyte phenotype that differs from that in both normal persons and usual patients with type 1A diabetes.

No epidemiologically defined environmental factors other than congenital rubella have been clearly associated with type 1A diabetes. Viral infections, in particular those that occur close to the time of onset of overt diabetes, are known to precipitate hyperglycemia (secondary to insulin resistance associated with infection), but they are unlikely to play a primary pathogenic role. Although coxsackievirus B4 has been isolated from the pancreas of a child with recent-onset diabetes,[33] the pancreas had multiple pseudoatrophic islets (islets with no B cells but abundant A and D cells) with no inflammation, indicating chronic B-cell destruction preceding the viral infection. Any search for environmental factors that may trigger autoimmunity, such as drugs, unknown viruses, or dietary components (e.g., milk proteins), must focus on factors that act months to years before the onset of diabetes rather than on acutely diabetogenic factors.

ISLET CELL ANTIBODIES AND OTHER IMMUNOLOGIC MARKERS

Approximately 5% of first-degree relatives of patients with type 1A diabetes also develop diabetes. Immunologic and endocrinologic assays capable of identifying those relatives most likely to develop diabetes and predicting approximately when overt diabetes will occur include the immunofluorescence assay for cytoplasmic islet cell antibody, the results of which are positive in 70% to 80% of patients with new-onset type 1A diabetes. Some assays for islet cell antibodies[34],[35] and [36] and a few radioimmunoassays for antiinsulin autoantibodies[37],[38] have the requisite specificity to identify persons at high risk. Examples are the complement-fixation tests for cytoplasmic islet cell antibodies, variants of the standard cytoplasmic islet cell antibody assays, fluid-phase antiinsulin autoantibody assays, and autoantibodies to a 64-kDa islet protein (predominantly antibodies to glutamic acid decarboxylase [GAD]) and antibodies to a molecule termed ICA512(IA-2).[38] Autoantibody assays using defined

islet autoantigens (GAD65, ICA512, or insulin) have improved so much (Fig. 136-2) that for most clinical settings the difficult-to-standardize cytoplasmic islet cell antibody assay should be abandoned.

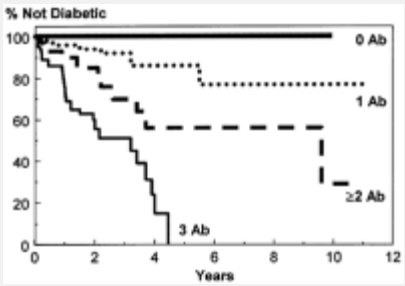

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FIGURE 136-2. Progression to type 1A diabetes of first-degree relatives of patients with diabetes based on the number of defined antiislet autoantibodies (*Ab*; of GAD65 [glutamic acid decarboxylase], ICA512, and insulin). One relative (of ~500) lacking autoantibodies progressed to diabetes. (From Verge CF, Gianani R, Kawasaki E, et al. Prediction of type 1 diabetes in first-degree relatives using a combination of insulin, GAD and ICA512bdc/IA-2 autoantibodies. Diabetes 1996; 45:926.)

The presence of antiislet cell antibodies can precede the development of overt diabetes by more than a decade[34,39] (Fig. 136-3). HLA typing of antibody-positive relatives and even antibody-positive “normal” persons indicates that they have the same HLA distribution as do patients with type 1A diabetes, and within 7 years, ~50% develop overt diabetes.

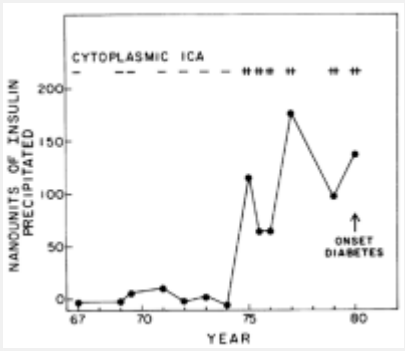

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FIGURE 136-3. Development of insulin autoantibodies and cytoplasmic islet cell antibodies (*ICA*) in overt diabetes. (Adapted from Soeldner JS, Tuttleman M, Srikanta S, et al. Insulin dependent diabetes mellitus and initiation of autoimmunity: islet cell autoantibodies, insulin autoantibodies and beta cell failure. N Engl J Med 1985; 313:893.)

The appearance of autoantibodies to human insulin also can precede by years the development of type 1A diabetes.[40] Anti-insulin antibodies are present in both cytoplasmic antibody– positive and antibody–negative persons who develop diabetes; these antibodies provided the first radioimmunoassay aid for predicting type 1A diabetes. Antiinsulin autoantibodies are found in ~60% of persons who develop diabetes. When this test is combined with assays for

cytoplasmic islet cell antibodies, 90% of patients with new-onset type 1A diabetes are found to have evidence of autoimmune disease.

In addition to the presence of cytoplasmic islet cell antibodies and insulin autoantibodies, many immunologic abnormalities are present in patients with type 1A diabetes and their relatives.41 Many of these abnormalities (e.g., presence of antithyroglobulin and microsomal antibodies, antibodies to single-stranded DNA, antibodies to the surface of rat islet cells and a rat insulinoma cell line) are inherited independently of the HLA susceptibility to type 1A diabetes and are present in as many as 30% of first-degree relatives. Such abnormalities provide relatively little prognostic information but appear to be related to the autoimmune background of type 1A diabetes.

A major advance in the past several years has been the biochemical characterization of a series of islet autoantigens, including insulin, GAD (a major component of the 64-kDa autoantigen),42 carboxypeptidase H,43 a milk-related islet protein (ICA69),44 ICA512,45 and ganglioside GM2-1.46 Biochemical assays are now available that use recombinant human proteins to measure antibodies to insulin, GAD, and ICA512. When just these three assays are used, >98% of patients with new-onset type 1A diabetes and prediabetes express at least one antibody, and >80% express two or more. Specificity and sensitivity are much higher with these biochemical assays than with cytoplasmic islet cell antibody testing. In contrast to cytoplasmic islet cell antibody testing, with its inherent problems of reproducibility, biochemical determination of autoantibodies is remarkably stable in the prediabetic phase. International workshops to standardize insulin and GAD radioassays are under way. Such assays should rapidly replace standard cytoplasmic islet cell antibody testing in both the diagnosis and prediction of type 1A diabetes.

FIRST-PHASE INSULIN SECRETION AS AN INDEX OF EARLY TYPE 1 DIABETES MELLITUS

Approximately 3% of nondiabetic relatives of patients with type 1A diabetes have positive results on screening assays for islet cell autoantibodies. When such antibodies are detected, intravenous glucose-tolerance testing can be used to assess first-phase insulin release as a measure of subclinical B-cell dysfunction (Fig. 136-4). The loss of first-phase insulin secretion, as well as its rate of fall, aids in predicting the time of onset of overt diabetes.47,48 At the time of initial detection of islet cell antibodies, one of four patients has first-phase insulin secretion below the first percentile of normal persons. Almost all persons who develop type 1A diabetes lose first-phase insulin secretion before they develop overt diabetes. For patients with initially normal insulin release, intravenous glucose-tolerance testing is performed again in 3 to 6 months and,

depending on its stability, at subsequent 3- to 12-month intervals. Immunologically and endocrinologically, persons with abnormal results may be alerted to the risk of type 1A diabetes and advised concerning routine home monitoring for glucosuria or capillary blood glucose determination.

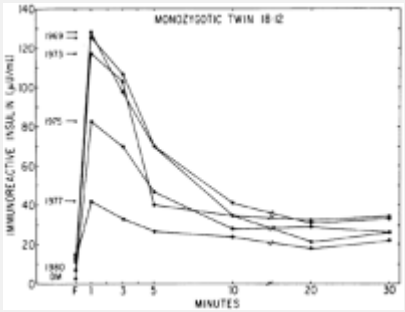

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FIGURE 136-4. Loss of first-phase insulin secretion in a prediabetic twin with islet cell antibody. The y-axis gives insulin concentrations at the times indicated after the intravenous injection of glucose. Initial phase of insulin release (1 and 3 minutes) is progressively lost. (DM, diabetes mellitus; F, fasting.) (Adapted from Srikanta S, Ganda OP, Eisenbarth GS, Soeldner JS. Islet cell antibodies and beta cell function in monozygotic triplets and twins initially discordant for type I diabetes. N Engl J Med 1983; 308:322.)

To aid in predicting the time of onset of type 1A diabetes among antibody-positive relatives of persons with type 1A diabetes, the following mathematic formula has been developed: years to diabetes = -0.12 + 1.35 ×$\log_e$ (insulin secretion) -0.59 $\log_e$ (insulin autoantibody concentration). This simple formula appears to account for ~50% of the variance in the time of diabetes onset.[48] Immunologic assays also are being used to aid in the classification of patients with diabetes. Insulin dependence is a physiologic state that can evolve slowly, even in type 1A diabetes, from a stage in which hyperglycemia is controlled with diet or oral medication to a stage in which death occurs in the absence

of insulin therapy (Fig. 136-5). Antiislet antibodies are found in as many as 10% of patients with classic type 2 diabetes at the time of diagnosis, and over the ensuing 5 years, many of these patients become insulin dependent.[35] Epidemiologic data from Japan, Pittsburgh, the Netherlands, and Poland indicate that 1 in 200 children die of ketoacidosis at the time of diagnosis of their diabetes. Such deaths probably could be prevented by early detection and treatment of diabetes.

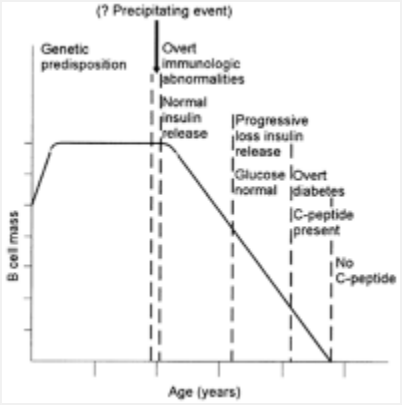

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FIGURE 136-5. Stages in the development of type 1 diabetes, beginning with genetic predisposition and ending with insulin-dependent diabetes with essentially complete B-cell destruction. (Adapted from Eisen-barth GS. Type I diabetes mellitus: a chronic autoimmune disease. N Engl J Med 1986; 314:1360.)

IMPLICATIONS FOR PREVENTIVE THERAPY

The newer immunologic knowledge concerning type 1A diabetes and the success of a wide variety of immunotherapies in preventing the diabetes of BB rats and NOD mice have led to trials of immunotherapy in patients with recent-onset type 1A diabetes, and to a few trials in persons at high risk for the development of type 1A diabetes. These trials indicate that limiting B-cell destruction is possible. Toxic side effects of the most powerful (and most effective) drugs are a serious problem, however. For example, cyclosporine A is nephrotoxic at the dosages that appear to be required to induce remissions of type 1A diabetes,[49,50] and azathioprine may be associated with epithelial malignancies. Prednisone given after the onset of type 1A diabetes is ineffective, and a series of other therapies, such as plasmapheresis and treatment with antithymocyte globulin or monoclonal antibody T12, produce no long-term benefit.

A series of new agents that are not significantly immunosuppressive yet are able to limit B-cell destruction in animal models of type 1A diabetes are being studied. All immunologic attempts to limit B-cell destruction are considered investigational and should be used only under the oversight of a human investigation committee.[51]

Trials investigating the prevention of type 1A diabetes and the amelioration of further B-cell loss after diabetes onset are concentrating on nonimmunosuppressive therapies. Such trials include administration of the vitamin nicotinamide,[52] which modestly delays diabetes onset in NOD mice; vaccination with bacille Calmette-Guérin[53]; administration of oral insulin[54]; and therapy with parenteral insulin.[55] Nicotinamide may have an effect by limiting free radical damage to B cells. In the NOD mouse model, a single

injection of bacille Calmette-Guérin (BCG) prevents diabetes but not insulitis. Such therapy may limit B-cell destruction by altering cytokines produced by infiltrating T cells. A completed German trial of nicotinamide found no benefit, but a larger European trial is continuing. In randomized trials, BCG had no beneficial effect. Oral administration of insulin delays or prevents type 1 diabetes in NOD mice. Its effect is likely due to the generation of T cells (by peptides of insulin present in the intestinal mucosa) that suppress inflammation. The most dramatic prevention of diabetes in both the NOD mouse and the BB rat has been obtained with parenteral administration of insulin. Such therapy prevents not only diabetes, but also infiltration of islets by T cells and destruction of B cells. A small pilot trial[53] of intravenous insulin and low-dose subcutaneous insulin for the prevention of diabetes in high-risk relatives of patients with diabetes suggests that such therapy may delay the onset of type 1 diabetes, and a large U.S. prevention trial (DPT-1 [Diabetes Prevention Trial-1]) is under way.

AUTOIMMUNE POLYGLANDULAR FAILURE

Approximately 20% of patients with type 1A diabetes develop other organ-specific autoimmune diseases (see Chap. 197), such as celiac disease, Graves disease, hypothyroidism, Addison disease, and pernicious anemia.[56,57] Some patients develop multiple disorders as a part of two inherited polyendocrine autoimmune syndromes (type I and type II). The type I syndrome usually has its onset in infancy, with hypoparathyroidism, mucocutaneous candidiasis, and, somewhat later, Addison disease and other organ-specific disorders. Fifteen percent of these children develop type 1A diabetes. This disorder is inherited in an autosomal recessive manner with no HLA association due to mutations of a gene (*AIRE*) located on chromosome 21. This mutated gene codes for a DNA-binding protein that is expressed in the thymus. The type II polyendocrine autoimmune syndrome (Addison disease, type 1 diabetes [50% of patients], Graves disease, hypothyroidism, myasthenia gravis, and other organ-specific diseases) is strongly HLA-associated

and has an onset from late childhood to middle age. In these families, a high prevalence of undiagnosed organ-specific auto-immune disease is seen, and, at a minimum, thyroid function tests should be performed in the first-degree relatives of these patients. Biochemical evaluation for adrenal insufficiency and pernicious anemia should be performed if any suggestive symptom or sign is present (e.g., decreasing insulin requirements can herald the development of Addison disease in a patient with type 1 diabetes before electrolyte abnormalities or hyperpigmentation develop). Excellent autoantibody tests can

facilitate the detection of Addison disease (21-hydroxylase autoantibodies) or celiac disease (transglutaminase autoantibodies) in patients with type 1A diabetes. As many as 1 in 200 patients with type 1A diabetes develop Addison disease, and 1 in 20 develop celiac disease.