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Insulin-Dependent Diabetes Mellitus

Review

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Introduction

Insulin-dependent diabetes mellitus (IDDM) is a multifactorial autoimmune disease for which susceptibility is determined by environmental and genetic factors. Inheritance is polygenic, with the genotype of the major histocompatibility complex (MHC) being the strongest genetic determinant. However, even in monozygotic twins, the concordance rate is only 50% (Barnett et al., 1981), indicating the importance of a number of as yet unidentified environmental factors (Castano and Eisenbarth, 1990). There is a north–south gradient in incidence of the disease with the highest incidence (1%–1.5% in Finland) being in northern Europe, with decreasing incidence in more southerly and tropical locations. Although this suggests the effect of infectious agents, in the nonobese diabetic (NOD) mouse, germ-free NOD mice have the highest incidence (nearly 100%) that has been seen in any NOD colony.

While MHC class II genotype is one of the strongest factors determining susceptibility to IDDM, it has long been apparent that susceptibility at MHC class II is a necessary but not sufficient predisposing genetic factor. Microsatellite analyses of genome-wide polymorphisms in multiplex IDDM families and in NOD crosses with nonsusceptible strains have identified many other genetic regions that also influence susceptibility. Thus, in the NOD mouse there are at least 15 other regions on 11 other chromosomes that contribute to genetic predisposition (Vyse and Todd, 1996 [this issue of *Cell*]). In man, linkage studies have suggested an even larger number (as many as 19) genetic regions determining IDDM susceptibility. For the most part, the genes determining susceptibility in each of these chromosomal regions have yet to be identified. Several of these regions also influence susceptibility to a murine counterpart of systemic lupus erythematosus and to a murine model of multiple sclerosis (Vyse and Todd, 1996).

IDDM in animal models is T cell mediated and requires the participation of both $CD8^+$, class I MHC restricted and $CD4^+$, class II MHC restricted T cells (Wicker et al., 1995). Extensive studies in rodent models have failed to identify the origins of the autoreactivity in IDDM, but demonstrate the importance of a number (8–10) of islet β cell–expressed proteins that are the targets of the autoimmune process in this disease (Table 1). Other studies have shown the important roles of several regulatory and proinflammatory cytokines, including interferon-γ (IFNγ), tumor necrosis factor α (TNFα), interleukin-4 (IL-4), and IL-10, as well as the importance of a number of accessory molecules (B7.1, B7.2) (Lenschow et al., 1995) and adhesion molecules (very late antigen 4) (Yang et al., 1993).

Studies of rodent models and preliminary studies in man have shown that the completion of β cell destruction can be considerably delayed or prevented by parenteral administration of β cell autoantigens—including insulin, glutamic acid decarboxylase (GAD), and heat shock protein 60 (HSP60). A number of studies have also shown that manipulation of cytokine networks by administration of specific cytokines or their antagonists can delay or prevent diabetes.

Together, these advances have set the stage for developing a complete molecular understanding of the pathogenesis of this autoimmune disease and for the design of rational and effective means of prevention. Prevention could then replace insulin therapy, which is effective but associated with long term renal, vascular, and retinal complications.

The Role of the Major Histocompatibility Complex

Extensive sequencing of MHC class II alleles in man, the NOD mouse, and the Bio-breeding rat, as well as the use of NOD mice transgenic for several MHC class II molecules, has revealed a complex interplay between alleles of the two major isotypes of MHC class II molecules (HLA [human leukocyte antigen] DR and DQ in man, and I-A and I-E in the mouse]) (Wicker et al., 1995). Susceptibility to type I diabetes is most strongly determined by DQ and I-Aβ chain alleles that encode serine, alanine, or valine at position 57 on both chromosomes (Acha-Orbea and McDevitt, 1987; Todd et al., 1987). DQβ and I-Aβ position 57 aspartic acid positive alleles mediate resistance to IDDM, which varies in degree with the sequence of other residues in the DQα and β chains. Expression of I-E (β chain position 57 aspartic acid positive) in the NOD mouse, and of DR B1 chains expressing aspartic acid at position 57, also mediates varying degrees of resistance to type I IDDM. Thus, HLA DR B1 alleles lacking aspartic acid at position 57 in Japanese patients are associated with a higher degree of susceptibility than Asp-57(+) HLA-DR B1 alleles (Ikegami et al., 1989, Diabetes, abstract). There is also evidence that MHC class I genotype may have a similar modifying effect (Ikegami et al., 1993).

These associations have now been extensively tested in many studies (Nepom and Erlich, 1991) and several exceptions have been noted. (Ikegami et al., 1989, Diabetes, abstract; Erlich et al., 1993). Results from these studies indicate that polymorphisms in the DQα chain, elsewhere in the DQβ chain, and in the DR B1 chain play an important modifying role. In some populations this can be shown to be due to similar sequence polymorphisms at DR B1 position 57, with aspartic acid negative alleles mediating susceptibility while aspartic acid positive alleles mediate resistance. (Ikegami et al., 1989, Diabetes, abstract; Cucca et al., 1995). There is

Table 1. Targets of the Autoimmune Response in IDDM

Autoantigen	Antibody	T Cell Responses[a]
Insulin	+	+
GAD65/67	+	+
ICA 105 (IA-2)	+	?
Carboxypeptides H	+	+
Peripherin	+	+
HSP60	+	+
p69	+	?
ICA 512	+	?
52 kDa Ag	+	?
Gangliosides	+	?
38 kDa secretory granule antigen	?	+

[a] For specific references, see Atkinson and Maclaren, 1993.

also evidence that a polymorphism at HLA-DR B1 position 74 can have a strong modifying affect on susceptibility (Cucca et al., 1995) (Table 2, this study).

Peptide elution studies by Ramensee et al. (1995) and Reich et al. (1994) have provided indirect support for the concept that HLA-DQ ,-DR, and I-A polymorphisms affect susceptibility to IDDM by selectively affecting the nature of the peptides presented to T cells by these class II molecules. These authors showed that peptides eluted from HLA-DR alleles that have or lack aspartic acid at HLA-DRβ57 bind overlapping but distinct sets of peptides. Thus HLA DR B1-04 alleles lacking aspartic acid at position 57 bind peptides with glutamic acid or aspartic acid at position P9 in the peptide (Table 3). This is presumably because the absence of aspartic acid at DR β1 position 57 leaves a conserved arginine at DRα79 free to interact with a negative charge at the carboxyl terminus of the peptide (Stern et al., 1994; Wucherpfennig and Strominger, 1995). In position 57 aspartic acid positive alleles, Asp-57 forms a salt bridge with α-Arg-79, and peptides with a negative charge at or near the carboxyl terminus of the peptide are not bound to any appreciable degree. (These data are derived from amino acid sequence studies of complex mixtures of peptides eluted from the respective alleles. It is likely that both types of allele, which are nearly identical in sequence elsewhere in the DR β1 chain, will also bind many of the same peptides).

Table 2. MHC Class II Sequence Polymorphisms in IDDM

Locus	Allele	Susceptible	Resistant
DQ B1	0201	Ala-57	
DQ B1	0302	Ala-57	
DQ B1	0303[a]		Asp-57
DQ B1	0301[a]		Asp-57
DQ B1	0502	Ser-57	
DQ B1	0602[c]		Asp-57
DR B1	0405	Ser-57	
DR B1	0403		Asp-57, Glu-74
DR B1	0401[b]	Asp-57	
I-Eβ	g7[c]		Asp-57
I-A	g7	Ser-57	
I-A	b[c]		Asp-57

[a] Neutral or weakly negative with respect to IDDM.
[b] Less susceptible than DRB1 0405.
[c] Strongly resistant to IDDM.

Table 3. Peptides Bound by DR4 Subtypes

DR4 Allele	Amino Acid(s) at Peptide Position 9
0401 β-Asp-57	Ala, Ser, Gln
0405 β-Ser-57	Asp, Glu

Considerable evidence (see below) indicates that islet β cell damage and destruction is mediated by islet antigen specific T helper type 1 (Th1) lymphocytes. The results cited above suggest that, while susceptible and resistant alleles can present many of the same peptides, susceptible alleles also present a distinct subset of peptides with a negative charge at position P9. These peptides, when bound by susceptible DQ and I-A alleles, may preferentially induce a Th1 response. In contrast, resistant alleles would be expected to present peptides that would elicit a predominant Th2 response. NOD mice expressing transgenic I-A alleles (I-A^d, I-A^k, I-Ag^7) with a mutation to aspartic acid at position 57 in A_β have a decreased or zero incidence of IDDM (see references in Quartey-Papafio et al., 1995). Cell transfer studies suggest this decreased incidence is the result of a predominant Th2 response to islet cell antigens (Singer, et al., 1993), but definitive proof for this interpretation is yet to be published. Competition between susceptible and resistant alleles for binding a critical diabetogenic peptide has been postulated as an alternative explanation for these data (Nepom, 1990; Quartey-Papafio et al., 1995). Support for the former hypothesis is seen in studies of IDDM families (Thai and Eisenbarth, 1993). Although DQB1 0602 (an IDDM-resistant allele) positive siblings of diabetics rarely develop diabetes, they can produce high titers of autoantibodies to several islet cell antigens. This indicates that resistant alleles do not cause resistance by inducing more complete self-tolerance to islet cell antigens than do the susceptible DQβ1 alleles. (Nepom, 1990; Erlich et al., 1993).

The results cited above bring us tantalizingly close to understanding how susceptible and resistant alleles mediate their effects. The issues raised can only be resolved when peptide epitopes derived from critical islet cell autoantigens have been identified and characterized with respect to their ability to elicit insulitis and IDDM-inducing T cells. The long list of antigens that are the target of an autoimmune response in both mouse and man (see below) means that the peptide epitopes derived from a number of islet cell autoantigens will have to be identified and characterized to achieve this goal.

The Autoantigens Targeted in IDDM

The strong association that exists between specific MHC class II alleles and disease susceptibility implies that the diabetogenic response is antigen driven. This is supported by the observation that T cells obtained from NOD mice in which the β cells have been ablated at an early age no longer have the capacity to adoptively transfer disease (Larger et al., 1995). Studies in the NOD mouse from the neonatal period until disease onset suggest that the diabetogenic response can be viewed as a series of stages culminating in massive β cell destruction and the establishment of overt diabetes. Peri-insulitis, first seen at 4–6 weeks of age, is characterized by

an accumulation of macrophages, dendritic cells, and B and T lymphocytes that enter the periductal areas but remain outside of the islet proper. At later time points, intra-insulitis develops and is characterized by the direct invasion of the islets by infiltrating cells, and is dependent on the recognition of β cell antigen(s) (Wicker et al., 1992). A temporal analysis of β cell reactivity in NOD mice suggests that only a few autoantigens are targeted in the early stages (Kaufman et al., 1993; Tisch et al., 1993). As intra-insulitis progresses, additional β cell destruction occurs, apparently resulting in the sensitization and recruitment of other β cell–specific T cells found in the periphery. Intra-insulitis per se, however, does not appear to be sufficient to drive the response to an overt diabetic state. This is suggested by studies in NOD mice transgenic for a pathogenic T cell receptor (TCR) that exhibit a highly aggressive form of intra-insulitis beginning abruptly at 3–4 weeks of age, yet the time of onset (18–20 weeks) and the frequency of overt diabetes in these animals is only marginally enhanced (Katz et al., 1993a). These 3 week and 18–20 week checkpoints may reflect the requirement for additional events in order to initiate insulitis and then to progress to overt diabetes. These events may depend on the outcome of interactions occurring between effector and regulatory T cells (see below) or sequential targeting of specific β cell autoantigens, or both.

Only in the past 5–7 years has the identity of most of the β cell autoantigens been determined. Despite this progress, little is known about the role these autoantigens may play in the disease process, i.e. whether they are in fact pathogenic. At present, conclusions regarding the possible role/importance of a given β cell autoantigen in IDDM are based upon two sources: first, observed correlations between autoantibody reactivity (and more recently T cell reactivity) and disease progression in man and in NOD mice, and second, studies determining whether the diabetogenic response in NOD mice can be modulated following treatment with the autoantigen or transfer of specific T cell clones, or both.

Using the above criteria, glutamic acid decarboxylase (GAD) is one of only three critical β cell autoantigens. GAD is an enzmye with two isoforms, GAD65 and GAD67, that catalyze the biosynthesis of the neurotransmitter γ-aminobutyric acid. The presence of anti-GAD antibodies in the sera of prediabetic individuals has proven to be a reliable predictive marker for progression to overt diabetes (Baekkeskov et al., 1990; Hagopian et al., 1993). T cell reactivity in IDDM patients can be detected to a region of GAD that contains homology to the Coxsackie B P2-C viral protein (Atkinson et al., 1994). The fact that Coxsackie B viral infections have been implicated in cases of IDDM has led to the intriguing hypothesis that recognition of GAD may be stimulated in some instances by a response to the virus.

NOD mice also exhibit antibody reactivity to GAD (and to insulin). Responses to GAD and insulin (but not to other β cell autoantigens such as HSP60, peripherin, and carboxypeptidase H) can be detected in animals at an age when minimal histological signs of islet inflammation are observed (Kaufman et al., 1993; Tisch et al., 1993). Anti-GAD reactivity is seen in some NOD mice that exhibit extensive intra-insulitis, yet remain diabetes free (Tisch et al., 1993). These observations suggest that recognition of GAD (and insulin, see below) occurs early in the disease process, and that anti-GAD reactivity may mediate initial events associated with intra-insulitis. NOD mice remain protected from diabetes when treated with GAD either at an age preceding islet inflammation or when exhibiting extensive intra-insulitis, providing functional evidence that GAD may have a critical role in the disease process (Kaufman et al., 1993; Tisch et al., 1993; Elliott et al., 1994). In these studies protection, at least in part, appears to be mediated through the induction of GAD-specific regulatory T cells that secrete lymphokines that nonspecifically suppress the diabetogenic response. To determine the relative contribution and precise role of anti-GAD reactivity in the disease process, experiments need to be done in which GAD-specific T cells are selectively tolerized by clonal deletion/anergy induction, to detect the effect this has on development of insulitis and IDDM.

Insulin is another β cell autoantigen that appears to have a critical role in the diabetogenic response. Anti-insulin autoantibodies can be detected in ~50% of recent-onset IDDM subjects and are most frequent in younger children who exhibit an enhanced rate of β cell destruction (Castano and Eisenbarth, 1990). Insulin is a key T cell target in that insulin B chain–specific $CD4^+$ T cell clones can accelerate diabetes in young NOD mice or adoptively transfer disease in NOD-*scid* mice (Daniel et al., 1995). Furthermore, oral or parenteral treatment of young NOD mice with whole insulin or insulin B chain, respectively, can protect animals from diabetes (Zhang et al., 1991; Muir et al., 1995). This protection again appears to be partially mediated through the induction of immunoregulatory T cells, so that the relative contribution of anti-insulin reactivity to the disease process is still not clear. In contrast to young NOD mice treated with GAD, animals receiving insulin or insulin–B chain continue to exhibit intra-insulitis, suggesting that anti-insulin reactivity may be necessary for more distal events in disease progression.

Additional autoreactivity seen during the development of human diabetes includes antibodies to two tryptic fragments with molecular masses of 37 and 40 kDa, derived from a β cell antigen. Autoantibodies against these fragments have been detected in 60% of newly diagnosed individuals and appear to identify a subgroup of IDDM patients who rapidly progress to diabetes (Christie et al., 1994). The recent discovery that the two tryptic fragments are derived from the putative tyrosine phosphatase IA-2 should aid in assessing T cell reactivity to the autoantigen and its possible role in the diabetogenic response (Passini et al., 1995). A protein designated as p69 has been shown to be an additional target of autoantibodies found in IDDM patients (Pietropaolo et al., 1993).

Autoantibodies and T cell reactivity specific for HSP60 have also been detected in NOD mice. Whether HSP60 is targeted in the human diabetogenic response remains unclear. However, treatment of NOD mice with HSP60 protects animals from disease (Elias et al., 1991). Moreover, it has been reported that treatment of hyperglycemic NOD mice with an HSP60-specific peptide can reestablish euglycemic blood levels (Elias and Cohen, 1994). Finally, HSP60-specific $CD4^+$ T cell lines have been shown to accelerate or block disease in NOD recipients (Elias et al., 1991).

Undefined components of the β cell secretory granule have been shown to be targeted by pathogenic $CD4^+$ T cell clones established from NOD mice (Haskins and McDuffie, 1990) and by $CD4^+$ T cell clones from IDDM patients (Roep et al., 1990).

Thus, a number of β cell autoantigens are recognized during the diabetogenic process. The task at hand is to distinguish those antigens that play a primary role in initiating the autoimmune process from those autoantigens that elicit an autoimmune response as a secondary event due to local inflammation. This might be achieved in animal studies in which the T cells specific for a given autoantigen are selectively tolerized, and the effect this has on insulitis and IDDM then determined. A sequential study over time of T cell reactivity in HLA identical siblings of diabetics, and in recent onset IDDM patients, may also provide further insight into the relative importance of a given autoantigen.

The T Cell Response in IDDM

Studies primarily in the NOD mouse have attempted to determine whether the repertoire of infiltrating T cells exhibit Vα or Vβ restriction. To date, there has been no consistent evidence indicating that restriction in Vα or Vβ usage exists among T cells found in the pancreas. However, a recent study has reported that, in two diabetic patients, preferential usage of the Vβ7 gene was detected in the infiltrating T cells (Conrad et al., 1994). This restriction was argued to be the result of T cell activation by an unidentified infectious agent encoding a superantigen within the islets.

Studies with NOD mice deficient in MHC class I or class II expression—and in turn devoid of $CD8^+$ on $CD4^+$ T cells, respectively—have demonstrated that both T cell subsets are required for islet infiltration and subsequent β cell destruction (Katz et al., 1993b; Serreze et al., 1994; Wicker et al., 1994). However, the respective contribution of each subset is presently not clear. Numerous studies have shown that $CD4^+$ T cells alone are far more efficient in the adoptive transfer of disease than $CD8^+$ T cells. The effectiveness of $CD4^+$ T cells in transferring disease is most likely due to the secretion of lymphokines such as IFNγ and TNFα that are directly toxic to β cells and that recruit nonspecific effector cells to amplify the response. $CD8^+$ T cells on the other hand, may have a more restricted role in the disease process. It has been suggested that $CD8^+$ T cells are required to initiate β cell injury, which in turn could lead to the priming of $CD4^+$ T cells and subsequent amplification of the response (Wicker et al., 1994). The lack of insulitis in class I–deficient NOD mice and the appearance of $CD8^+$ T cells in the islets prior to $CD4^+$ T cells (Jarpe et al., 1991) support this notion.

$CD4^+$ T cell dominance in the diabetic process may reflect the critical role this subset has in regulating the immune system. $CD4^+$ T cells can be divided into distinct subsets based on their cytokine profiles. These subsets of Th cells oppose one another through reciprocal down-regulatory effects mediated by their respective cytokines. Th1 cells, which secrete IL-2, IFNγ, and TNFα and predominantly support cell-mediated immunity, are believed to be the primary $CD4^+$ T cells mediating IDDM. This is supported by animal studies showing that administration of cytokines that promote Th1 development exacerbates the development of diabetes and that monoclonal antibodies specific for Th1-derived cytokines block the development of the disease (Rabinovitch, 1994). In addition, murine β cell–specific T cell clones that exhibit a Th1 phenotype can efficiently transfer disease in syngeneic young NOD recipients (Haskins and McDuffie, 1990; Shimizu et al., 1993; Katz et al., 1995). Th2 cells, which are characterized by the secretion of IL-4, IL-5, IL-6, IL-10, and IL-13 and primarily support humoral mediated immunity, appear to have a down-regulatory role in IDDM. Administration of IL-4 (Rapoport et al., 1993) or IL-10 (Pennline et al., 1994), both of which promote Th2 development and function, protects NOD mice from diabetes. In addition, purified T cells with a $CD45RC^{lo}$ (Th2-like) phenotype prevent an induced form of diabetes in rats (Fowell and Mason, 1993).

Several studies indicate that a functional imbalance between the two Th cell subsets is a key determinant in establishing islet pathology. A high ratio of IFNγ/IL-4 producing T cells can normally be detected in infiltrates leading to the destruction of islets grafted under the kidney capsule in NOD mice (Shehadeh et al., 1993). In contrast, grafted islets in NOD mice containing infiltrates with a lower ratio of IFNγ/IL-4 producing T cells (as a result of receiving Freund's adjuvant) remain intact. Furthermore, a recent study has suggested that an inverse relationship exists between humoral reactivity to GAD and risk for IDDM in prediabetic patient populations (Harrison et al., 1993).

The events that modulate the balance between the two Th subsets in IDDM are still a matter of speculation. Factors that may have quantitative or qualitative effects on T cell activation such as the density of MHC/peptide complexes on the surface of APCs (Pfeiffer et al., 1995), TCR affinity/avidity for the binary complex, or interactions between costimulatory molecules (Lenschow et al., 1995) may lead to preferential development of Th1 cells in IDDM. It is also conceivable that one or more of the several non-MHC genes that confer IDDM susceptibility may be associated with some aspect of Th cell subset development (Scott et al., 1994).

To view the regulation of the disease process strictly in terms of Th1 and Th2 subsets is undoubtly an oversimplification. For example, $CD4^+$ Th1 autoreactive T cell clones have been established from NOD mice that secrete an unknown factor which can suppress the adoptive transfer of diabetes (Akhtar et al., 1995). In addition, T cells expressing a diabetogenic TCR and cultured under conditions to promote Th2 development are unable to mediate protection in NOD recipients (Katz et al., 1995). $CD8^+$ T cells have also been shown to exhibit Th1- and Th2-like phenotypes, and the contribution of cytokines secreted by non–T cells must certainly be considered. The development of a given Th cell subset and, in turn, the outcome of the diabetogenic response undoubtedly involve the interplay of a number of cell types and factors.

Immunotherapy

Early attempts to prevent IDDM typically relied on immunosuppressive drugs (cyclosporine) or drugs that indiscriminantly inhibit cell proliferation (imuran), often leading to serious side effects. Therefore, a great deal of

effort has focused on selectively targeting those T cells involved in the disease process. One general approach has been to employ monoclonal antibodies specific for molecules expressed by the effector T cell population. Monoclonal antibodies specific for CD4 (Shizuru et al., 1988) and CD3, a component of TCRs (Chatenoud et al., 1993), have been shown to be effective in the prevention and treatment, respectively, of diabetes in NOD mice. Similarly, prediabetic NOD mice are protected from disease when treated with antibodies that interfere with antigen recognition (anti-class II, Boitard et al., 1988; anti-TCR, Sempe et al., 1991), cellular activation (anti-B7; Lenschow et al., 1995), and homing to the pancreas (anti–L selectin and anti-VLA-4; Yang et al., 1993). Finally, antibodies targeting cytokines associated with Th1 activity (anti-IFNγ, anti-TNFα, and anti-IL-12; Rabinovitch, 1994) have been able to prevent disease in prediabetic NOD mice. In general, however, the applicability of antibodies specific for these "immune–related molecules" to human IDDM is limited by the side effects of chronic administration, such as immunogenicity, and the lack of selectivity.

An alternative approach is to devise protocols in which immunomodulation can be selectively applied through the use of a specific antigen/peptide. Recently, it has been demonstrated that insulin, when adminstered prior to the onset of diabetes, can delay or prevent disease in individuals at high risk for IDDM (Keller et al., 1993). The precise mechanism by which protection is mediated is not known. Both metabolic and immunologic factors may contribute to the effectiveness of this form of therapy. Nevertheless, multicenter trials of subcutaneous insulin prophylaxis to individuals at high risk for developing diabetes have recently been initiated.

In general, antigen-specific tolerance can be induced via two distinct processes: clonal deletion/anergy and induction of regulatory T cells. Clonal deletion/anergy has been shown to be effective in acute experimental autoimmune diseases where the inciting autoantigen/peptide is known. However, the high degree of specificity associated with this approach might be limiting in IDDM, in which the inciting autoantigen is not known, and where spreading of the autoimmune response to a number of epitopes within a single autoantigen and targeting of other autoantigens occur. Despite these reservations, administration of GAD, insulin, or HSP60 (but not carboxypeptidase H or peripherin) to NOD mice appears to result in the induction of antigen-specific regualtory T cells (Th2) that effectively suppress the disease. These regulatory T cells are thought to suppress the effects of nearby diabetogenic T cells through the antigen-stimulated secretion of IL-4, IL-10, and TGFβ. The advantage of this approach is that knowledge of the inciting β cell autoantigen (if only one such antigen truly exists) is not required. However, it is still unclear whether regimens can be devised that effectively induce a long lasting form of active suppression with no deleterious side effects in a clinical setting. For example, oral administration of antigen appears to be nontoxic, but its effects are variable and dose specific. This does not appear to be the case with systemically administered antigen. However, the possibility exists that systemic administration of antigen might have an immunizing effect and exacerbate disease.

Although antigen-specific immunotherapy appears to be a promising method to prevent IDDM, it is most likely that a combination of approaches may prove to be more generally effective. Thus, active suppression by antigen-induced regulatory T cells may be enhanced in concert with antibodies targeting cytokines required for Th1 development and function. Furthermore, as additional β cell autoantigens are identified and shown to have a role in the disease process, therapy might employ a number of autoantigens to target the polyclonal population of autoreactive T cells, thereby increasing the likelihood of successful treatment.

Even if safe, effective, and long lasting immunotherapies are developed, their application is a formidable challenge. Only 15% of new cases of IDDM occur in families with a previous case in the kindred. Overt diabetes develops only when β cell destruction is nearly complete, and the patient is asymptomatic for months or years until that point is reached. Immunotherapy thus must be preventive, which requires inexpensive, accurate genetic, autoantibody, and T cell screening techniques. Given the large number of islet cell autoantigens now available and the rapid progress in identifying genetic susceptibility markers, such screening techniques should soon be feasible. Hopefully, effective methods of prevention will promote widespread population screening and the application of preventive therapy.

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