This article presents a model for the HLA effect in insulin-dependent diabetes mellitus (IDDM) that is almost the mirror image of a model suggested by Nepom (1). In the Nepom model, the products of certain HLA alleles are associated with IDDM because they bind and present a specific peptide or peptides so as to induce an immune response to pancreatic β-cells; certain other alleles can protect against IDDM if they compete strongly for binding of the diabetogenic peptide. My model focuses instead on the failure of the immune system to maintain tolerance to pancreatic β-cells. I suggest that the HLA alleles negatively associated with IDDM (e.g., DR2 and DQw1) produce products with high affinity for certain β-cell peptide or peptides needed to establish and maintain tolerance to β-cells, whereas the alleles that are common in IDDM (e.g., DR3, DR4, and DQw8) produce products that have low affinity for the tolerogenic peptide or peptides or that bind the peptide or peptides in the wrong orientation or configuration for establishing tolerance. I also discuss the multiplicity of HLA loci, alleles, and amino acids contributing to IDDM and the fact that the associations of specific loci, alleles, and even genotypes with IDDM depend not only on their intrinsic properties but also on various population parameters. Diabetes 41:123–29, 1992.

Most cases of insulin-dependent diabetes mellitus (IDDM) are caused by an autoimmune process that destroys pancreatic β-cells. Like other autoimmune diseases, autoimmune β-cell destruction is influenced by HLA genes. IDDM susceptibility seems to be significantly affected by at least three HLA class II genes: DQA1, DQB1, and DRB1, and probably by the DPB1 locus as well.

In an earlier Perspective, Nepom (1) suggested a model wherein HLA class II alleles affect IDDM susceptibility as follows. 1) The array of class II dimers, encoded by any individual's HLA complex, vary in their affinities for a specific peptide that can induce autoimmunity to β-cells. 2) Only certain class II dimers, the products of "susceptibility genes," actually promote autoimmunity to β-cells after binding that peptide. 3) An individual is susceptible if the product of a susceptibility gene binds the peptide more strongly than the products of the nonsusceptibility genes present in that individual. An unstated assumption is that the concentration of the diabetogenic peptide is limiting. The mechanism whereby susceptibility and nonsusceptibility gene products differ was not specified.

In this article, I argue for an alternative model in which immunological tolerance is the primary determinant of IDDM susceptibility. This is almost the mirror image of the Nepom model (1). In the model proposed herein, a specific peptide or peptides can potentially induce tolerance to β-cells, and β-cell tolerance actually occurs if the individual has one or more class II dimers that can bind the tolerogen strongly and in the proper orientation. Susceptible HLA genotypes would be those that "tolerate" ineffectively because of weak or otherwise ineffective binding of tolerogen.

HETEROGENEITY OF DQw8 HAPLOTYPES WITH REGARD TO IDDM SUSCEPTIBILITY

This article originated with an attempt to explain why DQw8+ haplotypes differ greatly in their effects on IDDM susceptibility (2). Generally, in whites, DR4 haplotypes with DQw8 are associated with IDDM susceptibility, whereas DR4 haplotypes with DQw7 are not (3). DR4 haplotypes also vary at the DRB1 locus, however,
with different allelic subtypes of DR4: DRB1*0401–0405 (formerly Dw4, Dw10, and Dw13–15, respectively). The DR4 subtypes also differ in their degree of association with IDDM. These associations are less well documented because the DR4 subtypes cannot be distinguished by serology or restriction-fragment–length polymorphism analysis. Until the advent of oligonucleotide typing, they could be distinguished only by reactions of bulk or cloned T lymphocytes, sophisticated biochemistry, or protein or DNA sequencing. Although the relative associations of the DR4 subtypes have varied from study to study (4–11), by combining the available data, they appear to rank, from most to least associated with IDDM: 0402 > 0401 > 0404 and 0405 > 0403. It is least clear where allele 0405 fits into this sequence because there are relatively few data comparing this to DR4 subtypes other than 0403.

Although it was speculated that certain DR4 subtypes are associated with IDDM because of linkage disequilibrium with DQw8, this was found not to be the case (2). Among DR4* subjects, DRB1*0401 correlated positively with IDDM but negatively with DQw8 (2). Therefore, the DR4 subtypes are or serve as a marker for an IDDM risk factor distinct from DQw8. At least for the DR4 haplotypes, high susceptibility to IDDM seems to require a combination of IDDM-associated alleles at both DR and DQ β-chain loci (2). In that study, the DR and DQ β-chain alleles had nearly identical degrees of association with IDDM, with the DR effect actually being slightly stronger by most measures of association. Moreover, DQw8 was associated with increased risk for diabetes only when the linked DRB1 allele was DRB1*0401 or 0402 (relative risk [RR] = 12), whereas DQw8 haplotypes carrying other DRB1 alleles did not correlate with IDDM (RR = 0.7). Likewise, DRB1*0401 in combination with DQw7 did not correlate with IDDM (RR = 0.2) (2). Similarly, Nepom et al. (12) found a much lower risk for DQw8 haplotypes with DRB1*0401 or 0402.

The large study (164 patients and 200 control subjects) by Owerbach et al. (9) has been interpreted as showing a minimal role for the DRB1 alleles on DR4 haplotypes (3,9). However, the highest RR in that study was for DRB1*0402, followed by DQw8. RR values in Owerbach et al. are not directly comparable with our RR values from an earlier study (2), because Owerbach et al. calculated RR values with only the DR4* subjects as the population base. To reflect the importance of the various alleles in the population and to allow direct comparison with our results, we recalculated their RR values in the conventional manner, using all patients and control subjects as the population base. The recalculated RR values were 63.3 for DRB1*0402, 11.7 for DQw8, and 3.1 for DRB1*0401. Therefore, these data do not support the contention of a predominant role for the DQB1 alleles in DR4 haplotypes.

The article by Owerbach et al. (9) did not present data on combinations of DR and DQ alleles, but Owerbach shared those data in a personal communication. In Owerbach et al. (9), among Houston subjects (all control subjects were from Houston but half of diabetic patients were from Boston), the overall RR was 10.5 for DQw8; DQw8 haplotypes with DRB1*0401 or 0402 had an RR of 13, whereas DQw8 haplotypes with DRB1*0403–0405 had an RR of only 1.9. Thus the Houston data (9), like ours (2) and those of Nepom et al. (12), show a strong effect of DRB1 alleles even among DQw8* haplotypes.

**ALTERNATIVE EXPLANATIONS FOR THE APPARENT DR × DQ INTERACTION IN DR4 HAPLOTYPES**

As summarized above, DR4 haplotypes are strongly associated with IDDM (high RR) only if they have high-risk alleles at both DR and DQ β-chain loci. This observation can be explained in several ways. 1) Certain DRB1 alleles (primarily 0401 and 0402) interact positively with DQw8 to promote β-cell destruction. 2) DRB1 alleles 0403–0405, found on the remaining DQw8 haplotypes, are somewhat protective. 3) The different DRB1 alleles mark haplotypes with distinct DQw8 subtypes. 4) The different DRB1 alleles mark haplotypes with distinct alleles at a third locus, probably in the DQ region, that interact with DQw8 to promote or prevent β-cell destruction.

Hypotheses 3 and 4 seemed unlikely because of previously published results. Sequencing has not revealed any microheterogeneity in DQw8 alleles; moreover, all DR4 haplotypes seem to have the same DQA1 allele (13), and DQA2 and DQB2 are nearly monomorphic (see ref. 14). We sequenced additional examples of all these loci (14; C. Emler, M.H. Neme de Gimenez, M.J.S., American Red Cross, Madison, WI, unpublished observations) and, despite some previously undetected heterogeneity in DQA2 (14), found no DQ-region sequences to account for the preferential association of certain DR4 subtypes with IDDM. In testing at the functional level (K. Lundin, K.E.A. Lundin, J.R. Rowe, E. Thorsby, M.J.S. Rikshospitalet, Oslo; American Red Cross, Madison, WI, unpublished observations), DQw8-specific T-lymphocyte clones could not distinguish among the DQw8 alleles on various DR4 haplotypes.

The sequence data do not rule out significant variation in regulatory sequences or posttranslational modification. Moreover, much of the sequencing, including our own, was limited to the second exon, corresponding to the putative peptide-binding pocket. Nevertheless, the existence of DRB1 sequence variation and failure to find differences elsewhere among haplotypes that vary in their association with diabetes (DRB1*0401–0404) turns our attention back to the DRB1 sequences themselves (hypotheses 1 and 2).

I do not favor hypothesis 1 (positive interaction of DRB1*0401 and 0402 with DQw8), because it is not clear how the DR and DQ β-chains would interact to promote diabetes other than to promote immune responses to two distinct antigenic peptides. It seems unlikely that such a mechanism would produce the strong synergy observed between DR and DQ β-chain loci (2; D. Owerbach, unpublished observations).

Hypothesis 2 (varying degrees of protection by the various DR4 subtypes) seems to me the simplest explanation for the DR4-DQw8 haplotype data. Certain haplotypes, such as those bearing DQw8 and DRB1*0402,
may confer maximum risk simply because they have minimally protective alleles at both DR and DQ loci. Dominant immune suppression by MHC class II alleles is well documented (15), and there is good evidence that HLA haplotypes bearing certain subtypes of DR2 and DQw1 protect against IDDM (16,17). I am proposing a lesser degree of protection by certain DR4 subtypes and by DQw7. According to this "protective" hypothesis, any haplotype will be positively associated with IDDM (RR > 1) in a given population if it is less protective than the average haplotype in that population.

**THE "ICEBERG" NATURE OF GENOTYPE-DISEASE ASSOCIATIONS**

By the same reasoning, regardless of the genetic mechanisms involved, a given genotype will appear to be diabetogenic, neutral, or protective if it confers above-average, average, or below-average risk compared with other genotypes that exist in that population. Thus, a genotype that appears neutral in western Europe might appear diabetogenic in Japan, where the population risk for IDDM is low. If one cuts off the tip of the iceberg (the most susceptible genotypes), other genotypes will become the new tip of the iceberg.

**OTHER EVIDENCE THAT PROTECTION FROM IDDM IS FUNCTIONALLY DOMINANT OVER SUSCEPTIBILITY**

Initially I and possibly many other researchers assumed that certain HLA alleles promote IDDM by actively promoting anti-β-cell autoimmunity. However, a "protective" model, wherein certain HLA alleles are associated with IDDM only because they are poorly protective, may be the simplest explanation for many of the data. Functional data, transgenic mouse data, and classical genetic data all reflect the major importance of protection versus lack of protection in determining who develops IDDM.

Several types of functional study suggest that the autoimmunity leading to IDDM is not due to an overly effective immune response but rather to an immune response that is deficient in some way and results in ineffective regulation. For example, humans with IDDM have subnormal rather than supranormal interleukin-2 (IL-2) production (18). Similarly, BB rats are T lymphopenic (19), contrary to what one would expect if their immune response were excessively robust. NOD mice, although having a normal number of T lymphocytes, may be "functionally T lymphopenic" (E. Leiter, Jackson Laboratory, Bar Harbor, ME, personal communication). NOD mice have subnormal autologous mixed-lymphocyte reactions and generate subnormal amounts of suppressor activity in autologous mixed-lymphocyte reactions or in response to concanavalin A (ConA) stimulation (20,21). Thymocytes from young NOD mice are deficient in their response to T-lymphocyte mitogens ConA and anti-CD3 (22; E. Leiter, unpublished observations). Diabetes incidence is reduced in NOD mice and BB rats by injection of tumor necrosis factor α (23,24), and in NOD mice only by injection of IL-2 or poly-IC (25), all of which are expected to upregulate the immune response.

One interpretation of certain transgenic mouse studies is that IDDM is at least partly due to specific holes in the antigen-presenting repertoire. Like several other mouse strains, the NOD mouse lacks I-E expression because its I-Eα gene (DRα homolog) is defective (26). In all reported cases (28–30), an I-Eα transgene was protective. A specific in vitro-modified I-Aβ allele (DQβ homolog) was protective as a transgene (30), although other I-Aβ transgenes were not protective (28,31), perhaps because of inefficient pairing with the endogenous I-Aα. In two reports, protection by I-A was achieved with an ω/β transgene pair (31,32). In each case, the transgenes were protective despite the presence of the endogenous I-Aα and -β alleles of the NOD mouse (i.e., protection was dominant).

I suggest that the protective MHC alleles and ω/β allele pairs actively promote β-cell tolerance. However, these data and the classical genetic and bone marrow transplant data cited below are also compatible with the Nepom model (1), which proposed that the protective H-2 molecules outcompete the NOD mouse's H-2 molecules for limiting amounts of a diabetogenic peptide but present the peptide in a harmless way.

In BB rat (33,34) and NOD mouse (reviewed in ref. 35) breeding studies, non–diabetes-associated MHC and non-MHC alleles were dominant or nearly dominant over the diabetes-associated alleles. Similarly, human DR3 haplotypes behave as recessive in IDDM (36). Recessive inheritance implies a deficiency, not an excess, in the amount or the functional level of a given gene product. In contrast, DR4 haplotypes seem to have additive or dominant effects on IDDM (36). However, the apparent dominance of DR4 haplotypes could possibly be an illusion if, as some studies indicate, the diabetogenic DR4 haplotype is preferentially inherited from the father (reviewed in ref. 37).

NOD mice were protected by bone marrow transplants from NOD.H-2<sup>NON</sup> congenic mice (0 of 10 mice diabetic at 25 wk old) but not from NOD mice (9 of 12 diabetic at 25 wk old) (38). The H-2<sup>NON</sup> congenic cells seem to be functionally dominant, as indicated by transplantation of a 50:50 mixture of NOD and NOD.H-2<sup>NON</sup> congenic cells (1 of 14 diabetic, more like the protective congenic cells than like the nonprotective NOD cells) (38).

**DR β-CHAIN STRUCTURAL FEATURES CORRELATING WITH IDDM SUSCEPTIBILITY/PROTECTION**

Earlier in this article, I attempted to list the five DR4 subtypes in order from most to least correlated with IDDM. To reveal any possible structural correlates, we listed those alleles in that order with their first-domain amino acid sequences (the 1st domain being the most polymorphic and probably the peptide-binding domain [39]). All sequences mentioned can be found in a review by Marsh and Bodmer (40) and other sources.

In our study (2) and that of Rønningen et al. (10), allele 0403 was the only DR4 subtype with an RR < 1. That allele, putatively the most protective DR4 allele, is the only one with glutamic acid instead of alanine at position 74. Thus, within the context of DR4, Glu74 may contribute to protection. The three alleles at the bottom of the list, 0403–0405, are the only ones with arginine at position 71. Therefore, Arg71 may also contribute to protection.
within the context of DR4). Allele 0401 has a relatively conservative substitution of lysine (also basic) at position 71, whereas 0402, with the strongest IDDM association, has a more significant replacement by glutamic acid (acidic). Allele 0402 is also the only DR4 subtype with Ile instead of Leu at position 67 and Asp instead of Gln at position 70.

Thus, of the six amino acid positions where these DR4 subtypes differ, a cluster of four from positions 67–74 correlate with the degree of IDDM susceptibility. These structural features support the concept that DRβ1 alleles directly influence IDDM susceptibility rather than being markers for unknown genetic variation at another locus.

Unlike in white populations, in which DQw8 has consistently been associated with IDDM (3), DQw8 is not diabetes associated in Japan (see refs. cited in ref. 3). The lack of IDDM association with DQw8 in Japan may be due to a protective effect of the linked DRβ1 alleles 0403 and “DwKT2” (11,41).

Like the DR4 subtypes, the DR2 subtypes are easily distinguished by T lymphocytes, are difficult to distinguish serologically, and differ greatly in their effects on IDDM. The correlation of Arg71 with protection from IDDM, discussed above for the DR4 subtypes, is also seen for the DR2 subtypes. Likewise, the correlation of Ile67 with higher susceptibility recurs in the DR2 subtypes. However, these are only two of six amino acid positions where these DR2 subtypes 1501 and 1502 (which correlate with strong protection from IDDM) are alike but differ from DR2 subtype 1601 (not associated with protection). Any or all of the six amino acids could account for the different IDDM associations. Again, however, the structural data are consistent with a direct role for DRβ1 alleles in IDDM susceptibility.

An analogous situation exists for the DQβ1 alleles of the same DR2, DQw1 haplotypes. Asp57 of DQβ1, which roughly correlates with protection from IDDM (42,43), correlates with protection in the DR2 haplotypes, but it is only one of eight amino acids (Met14, Tyr30, Asp57, Thr71, Glu74, Lys75, Arg77, Phe87) that are unique to the putatively more-protective alleles.

Because the alleles at the DQβ1 and DRβ1 loci are in strong linkage disequilibrium on DR2 haplotypes of whites (3), one cannot distinguish between a protective effect of DR, DQ, or a combination of the two. In north India, where these DQ and DR alleles are found on separate haplotypes, both haplotypes appear to be protective (RRs of 0.1 and 0.26, respectively; 44), although less so than when they appear together in whites (RR = 0.04; 44). I suggest that specific DR2 haplotypes of whites may be strongly protective precisely because they have protective alleles at both DR and DQ loci.

Comparing the DR2 alleles as a group (strongly negative to neutral associations with IDDM) with the DR4 alleles as a group (weakly negative to strongly positive associations with IDDM), one finds that the two groups of alleles differ at several sites near the amino terminus (positions 9–37).

Of the sequence features noted for the DR4 and DR2 subtypes, the correlation of Arg71 with relative protection seems to be the most consistent when one looks at the remaining DRβ1 alleles. All in all, this correlation seems to be no better or worse than that described previously for Asp57 of DQB1. It correlates with lower susceptibility in most cases; the exceptions can be rationalized in various ways, it is not an absolute but a relative effect, and other amino acids clearly play important roles as well.

For DQA1, DQB1, and DRB1, the data on IDDM susceptibility are limited to correlations and to analogies with mice. More-direct data may be obtainable if NOD mice are made transgenic with various HLA or H-2-HLA hybrid genes. As described earlier, some experiments have been done for the murine I-A loci (DQ homologs) and I-Ex (DRα homolog). Such experiments will be more difficult for DRB1 or its murine homolog I-Eβ, because the NOD mouse must be made I-Eβ− (its I-Ex gene is nonfunctional [26]), and its endogenous I-Eβ must be eliminated, perhaps by homologous recombination in embryonic stem cells.

A MODEL IN WHICH THE HLA CLASS II GENES AFFECT IDDM SUSCEPTIBILITY MAINLY VIA INDUCTION/MAINTENANCE OF TOLERANCE

From human, rat, and mouse studies summarized in this article, it appears that class II dimers negatively associated or weakly positively associated with IDDM are generally dominant or epistatic over those that are more positively associated with IDDM. (Epistasis is analogous to dominance but acting between alleles at different loci.) Thus, I suggest that, despite the probable role of class II–restricted CD4+ and class I–restricted CD8+ T lymphocytes in β-cell destruction, the genetic effect of class II alleles occurs mainly at the level of induction or maintenance of immunological tolerance. There are several levels at which this could occur.

A priori, the protection could occur 1) in the thymic medulla during negative selection of T lymphocytes reactive with self-MHC; 2) in the thymic cortex during positive selection of T lymphocytes recognizing “modified self” (self-MHC plus foreign antigens); or 3) extrathyroidically, perhaps via “clonal paralysis” or stimulation of regulatory T lymphocytes. Some experimental data argue against the first two possibilities. In a transgenic mouse study, apparently normal I-E expression in thymic medulla was insufficient to prevent IDDM (29). Similarly, in a transplantation study (38), IDDM could not be prevented by transplantation of a thymus from a resistant strain depleted of bone marrow–derived cells, although the positive selection phase seems to be due to class II+ thymic epithelial cells. Thus, an extrathyroidic process seems the most probable. I favor the hypothesis of active suppression by regulatory T lymphocytes for several reasons, including the dominance of nonsusceptibility genotypes.

Thus, the genetic effects of HLA class II dimers on IDDM susceptibility might occur as outlined in Fig. 1. In this model, there is a potential tolerogen, perhaps a fragment of a β-cell–derived protein that is actually tolerogenic only if the individual has one or more MHC class II dimers that can bind and present it effectively. A class II dimer that binds the peptide strongly and in the
**FIG. 1.** A model in which HLA class II alleles affect insulin-dependent diabetes mellitus susceptibility primarily via binding and presentation of a peptide with the potential to induce immunological tolerance to pancreatic β-cells. In this model, class II dimers that bind the tolerogen strongly and in the proper orientation (a) are strongly protective, whereas those that bind it weakly (b) or not at all (c) are correspondingly less protective. Finally, some class II dimers might bind the tolerogen tightly but in the wrong orientation or configuration (d). This last situation (d) would also be nonprotective; competition by such dimers would be of functional significance only if amount of tolerogen is limiting. The text includes a discussion of possible protective mechanisms, as well as a rationale for suggesting that it is a matter of extra-thymic peptide presentation to CD4+ tolerance-maintaining T cells.

proper orientation (Fig. 1a), stimulates the appropriate regulatory T lymphocytes, and is strongly protective. Class II dimers that bind the peptide weakly (Fig. 1b) or not at all (Fig. 1c) offer correspondingly lesser degrees of β-cell protection. The case in Fig. 1d might also exist: a dimer that competes strongly for the tolerogen but presents it in a nontolerogenic orientation or configuration. Even if this occurs, the resulting competition would only be of practical importance if the concentration of tolerogen were limiting.

This model implies a dominance hierarchy among class II dimers: negatively associated (strongly protective) > “neutral” (weakly protective) > positively associated (nonprotective). The various protective effects would likely be cumulative. For example, a person with a protective DR dimer and a protective DQ dimer or with two protective DQ dimers would probably be less susceptible than someone with one protective dimer.

**CAN A “PROTECTIVE” MODEL ACCOUNT FOR THE EXCESS OF DR3/4 HETEROZYGOTES?**

The excess of DR3/4 heterozygosity in IDDM suggests synergistic effects of DR3 and DR4 haplotypes, and the evidence of IDDM-associated DQA1 alleles (45,46) and specific DQA1/DQB1 combinations in cis or trans (10,47, 48) supports the hypothesis of trans complementation between DQα and DQβ chains on DR3 and DR4 haplotypes. It is a bit simpler to explain such trans complementation in terms of autoaggression (effective presentation of a diabetogenic peptide) than in terms of lack of protection. However, in the protective model, one could propose that DR3 and DR4 haplotypes are synergistic because a complementing DQαβ dimer competes strongly for binding of a tolerogenic peptide but presents it in a nontolerogenic manner (Fig. 1d). Another possibility, perhaps less likely, is that DQα and DQβ chains from DR3 and DR4 haplotypes preferentially form trans dimers, and that those are even less protective than the cis dimers.

Rubinstein et al. (37) argued that the excess of DR3/4 heterozygotes need not be interpreted as synergy at all. They pointed out that the DR3/4 excess does not exist in all populations and suggested that an excess of DR3/4 and deficit of DR4/4 patients could be due to the supposed paternal bias whereby patients' DR4 haplotypes more often come from their fathers (refs. cited in ref. 37).
Whatever the mechanism, a paternal bias in DR4 transmission as an explanation for the DR3/4 excess would be equally consistent with various models.

CONCLUDING REMARKS

Current models of the genetics of IDDM must include at least three HLA loci: DQA1, DQB1, and DRB1, and possibly DPB1 as well (49). Considering all available data, DQA1, DQB1, and DRB1 seem to have similar impacts on IDDM susceptibility, although their relative importance varies considerably from population to population and from study to study. In my opinion, the major source of this variation is population structure (differing linkage disequilibria, allele frequencies, and the presence or absence of specific alleles). For example, the influence of DR4 subtypes (DRB1 locus) is quite evident in populations with substantial frequencies of DRB1*0402 and 0403, which have very different effects on IDDM susceptibility, and less evident in populations lacking either or both of those alleles. Similarly, the apparent importance of DQA1 or DQB1 depends on linkage disequilibrium and on the existence in the population of specific alleles at the complementary locus (DQB1 or DQA1, respectively). Some other sources of interstudy variation are sampling error (due to finite sample sizes) and inadequately matched patient and control groups.

A reminder may be warranted to recall why this discussion of HLA and IDDM is biased so heavily toward degrees of protection. Until recently, my own thinking was dominated by susceptibility alleles, with only a rare afterthought to the apparent protection by DR2-DQW1 haplotypes. However, in diverse populations, the negative association of IDDM with DR2 is a more common feature than the positive associations with DR3 and DR4. The shift of focus was precipitated by the DR4 haplotype data discussed earlier. Although both DQ and DR β-chain loci have alleles positively associated with IDDM, in each case, this positive association can be nullified by non-IDDM-associated alleles at the other locus (2): i.e., lack of susceptibility was dominant. In addition, all functional, transgenic, and classical rat and mouse genetic studies, summarized earlier, suggested that protection is functionally dominant. Although CD4+ class II-restricted T lymphocytes seem to be important in the effector phase of β-cell destruction, I suggest that the genetic determination of IDDM susceptibility by class II alleles occurs primarily at an earlier stage, affecting the individual’s success at maintaining β-cell-specific tolerance.

The model presented in this paper is almost certainly an oversimplification but it may suffice to stimulate additional thought and discussion.

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