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The Modes of Inheritance of Insulin-Dependent Diabetes Mellitus
or
The Genetics of IDDM, No Longer a Nightmare but Still a Headache*

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SUMMARY

The discovery of HLA antigen associations with juvenile-type insulin-dependent diabetes mellitus (IDDM) provided strong evidence separating this disorder, or group of disorders, from maturity-type noninsulin-dependent diabetes, as well as adding to the evidence for an immunologic pathogenesis. In addition, it was hoped that the use of these disease-marker associations in appropriate studies might clarify the genetics of IDDM. While these associations have provided a useful tool to further investigate the genetics and pathogenesis of IDDM, the mode or modes of inheritance of this group of disorders remain an area of great controversy. Susceptibility to IDDM is currently being proposed as being inherited as a single autosomal dominant, as a single autosomal recessive, as recessive and some dominant forms, in an intermediate gene dosage model, in a heterogeneous three-allele or two HLA loci model, and as a two-locus disorder. The arguments for each of these proposals is presented, as well as the problems of each. We surmise that the weight of evidence supports the heterogeneity hypothesis but that the modes of inheritance of IDDM will be fully resolved only when we can more reliably identify the diabetogenic genotype, rather than being limited in our investigations to the study of only full-blown clinical disease.

* (with apologies to James Neel)

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INTRODUCTION

There is currently an ongoing, lively (and only occasionally acrimonious) debate regarding the mode(s) of inheritance of insulin-dependent type (juvenile) diabetes (IDDM). Susceptibility to IDDM has been variously proposed to be inherited in autosomal dominant, autosomal recessive, intermediate, and heterogeneous fashion, based on population studies of HLA antigen associations and family studies of HLA haplotypes (see table 1). The population associations of HLA antigens B8, B15, Dw3, and Dw4 with IDDM are now well established, and helped separate IDDM from noninsulin-dependent diabetes mellitus (NIDDM). Studies within families have revealed that siblings who are both affected with IDDM share both HLA haplotypes more often than is expected by chance alone. (A haplotype is the set of alleles at the four closely linked *HLA* loci, *A*, *B*, *C*, and *D*, on one chromosome 6. Each individual inherits two haplotypes, one from each parent.) If there were no linkage-association between the HLA region and IDDM, affected pairs of siblings would be expected to share two haplotypes (HLA identical), one haplotype (HLA haploidentical), and zero haplotypes (HLA nonidentical) in a ratio of 25% to 50% to 25%. Instead, a number of reports indicate that pairs of diabetic siblings share two haplotypes approximately 55%–60% of the time, share one haplotype approximately 40% of the time, and in only a few cases, share zero haplotypes [2, 6, 7, 10, 21–25]. This is between the 100% and 0% for two and one shared haplotypes that would be expected for simple autosomal recessive inheritance (for rare disorders) and the 50% and 50% expected for a rare autosomal dominant. Rubinstein et al. [6] appropriately point out that these expected numbers are a function of gene frequency, and if the disease susceptibility gene is frequent enough, the observed numbers are consistent with recessive susceptibility.

Most investigators have concluded that these data are most easily explained by a susceptibility locus (or loci) closely linked (probably within) the HLA complex. Certain alleles at the susceptibility locus (or loci) would then predispose to IDDM. These alleles are presumed to be in linkage disequilibrium with the respective *HLA B* and *D* alleles since there is such a great deal of linkage disequilibrium within the HLA complex. This is not the only possible explanation. An alternative is that the *HLA* alleles themselves predispose to IDDM (presumably the *HLA D* alleles, since they have the highest population association). Since not all IDDM diabetics have these alleles, and these alleles are frequent in the general nondiabetic population, presumably additional genes at other loci would be required, a model that implicates two or more loci. Such an alternative model can explain much of the population and family observations in HLA-associated diseases in general [26, 27].

Many groups have utilized these observations and proceeded to formal genetic analysis. There are, however, several problems that confound such an analysis. One is the problem of the reduced penetrance of the IDDM diabetic genotype. When the mode of inheritance is unclear, the only estimate we have for this is identical twin concordance data. The largest twin data set is that of the British diabetic twin study, which reports concordance for IDDM of some 50% [28]. However, it is clear that this sample is a biased one, with only a fraction of the twins in the British Isles identified, and thus a presumed bias toward concordant pairs [29, 30].

TABLE 1

PROPOSED MODES OF INHERITANCE OF IDDM SUSCEPTIBILITY

Mode of inheritance	Comments	Problems	Proposers and suggesters
Autosomal dominant	1. Fits racial admixture and prevalence of IDDM in U.S. blacks	1. Does not explain excess sharing of two haplotypes in sibships 2. Does not explain heterogeneity	Svejgaard et al. 1975 [1]; Spielman et al., 1979 [2]; MacDonald, 1980 [3]
Autosomal recessive	1. Explains excess of two shared haplotypes	1. High estimate for gene frequency (implausible, but not impossible) 2. Requires different penetrances in familial cases and the population at large 3. Does not explain U.S. black-Caucasian incidence differences 4. Does not explain heterogeneity	Thomson and Bodmer, 1977 [4]; Rubinstein et al., 1977 [5], 1981 [6]
Some autosomal recessive, some autosomal dominant	1. Uses observed familial aggregation pattern, and assumes mode of inheritance	1. Without further phenotypic differences, different inheritance not demonstrable 2. Both sets of families have high incidence of *HLA*-associated alleles 3. Does not explain immunologic heterogeneity	Barbosa et al., 1977, 1978, 1980 [7–9]
Intermediate, gene-dosage model	1. One dose of the gene is sufficient, but second dose increases susceptibility 2. Explains excess of shared haplotypes	1. Does not explain heterogeneity	Spielman et al., 1980 [10]
Two different susceptibility alleles (and/or two *HLA*-linked loci)	1. Different immunologic forms of IDDM differentially associated with B8-Drw3, and B15-Drw4, and a compound form 2. Accounts for immunologic differences 3. Predicts autoimmunity in U.S. blacks less frequent than in U.S. whites	1. Too many parameters, can't be fully tested on existing data sets (i.e., some parameters such as tight linkage must be assumed)	Svejgaard et al., 1975 [1]; Bottazzo and Doniach, 1976 [11]; Rotter and Rimoin, 1978, 1979 [12, 13]; Cudworth and Festenstein, 1978 [14]; Irvine et al., 1978 [15, 16]; Hodge et al., 1980 [17]; Rotter and Hodge, 1980 [18]
Two unlinked loci	1. Unlinked genes interacting with *HLA* alleles, or *HLA*-linked alleles 2. Evidence for additional non-*HLA*-linked genes in other B8-associated disorders—coeliac and Graves disease.	1. Again, too many parameters, can't be tested without additional assumptions 2. Does not explain heterogeneity unless incorporates different *HLA*-linked alleles	Thomson, 1980 [19]; Rotter and Rimoin, 1981 [20]

NOTE: The proposed modes of inheritance of IDDM susceptibility are propositions made in the "HLA era."

Reports from less biased but much smaller samples report concordances of 20% [31, 32]. This gives us a large gray area, which can cover a multitude of hypotheses (and sins). An equally formidable problem is that most standard linkage technology has as an integral assumption: the finding of no population association. It is unclear what the effect of an association at the population level has on the results of our standard linkage methodology. Simulations of this problem would be a welcome addition to this area. Until this area is adequately explored, we need to accept such analyses in a very guarded light.

GENETICS MODELS OF A SINGLE HLA-LINKED SUSCEPTIBILITY GENE

Nevertheless, many groups of investigators (including the author) have fearlessly braved these uncharted waters and rocky shores and proceeded to perform genetic analyses and linkage studies and to develop models. These efforts have led to a variety of conflicting claims and camps. Many feel the first hypothesis regarding mode of inheritance in the HLA era was made by the Danish group, who argued that the data were most consistent with autosomal dominant inheritance, based primarily on the increased risk of the B8/B15 heterozygote [1]. However, a closer reading of that report indicates that the authors were already supporting the concept of heterogeneity, or as they phrased it at that time, "overdominance." The hypothesis of dominant inheritance of susceptibility was subsequently supported by Spielman et al. [2], based on a detailed analysis of family data available at that time. In a subsequent work, Spielman et al. [10] argue for a gene-dosage effect (i.e., while the carrier of a single diabetogenic gene would have a small but definite susceptibility under this model, the carrier of two such genes would be at a higher risk, that is, more penetrant). This would explain the observed excess, above 50%, of those sib pairs sharing two haplotypes in common. The other advantage of this model is that it does not invoke different penetrances for familial and nonfamilial cases, as does the recessive model proposed by Rubinstein et al. [6]. Most recently, MacDonald [3] has argued from population genetic data that since IDDM in U.S. blacks is associated with the same HLA antigens as in U.S. whites and the relative frequency of IDDM in U.S. blacks is similar to the proposed fraction of gene admixture from the Caucasian population, these two sets of observations are most consistent with dominant inheritance of IDDM susceptibility, and are most inconsistent with recessive susceptibility. Because the gene-dosage model of Spielman et al. [10] has dominant features at a population level, this could also explain the racial observations, as can a heterogeneity model [18].

Thomson and Bodmer [4] were possibly the first to suggest that the observed family data were most consistent with recessive inheritance of an IDDM susceptibility gene tightly linked to HLA, with the alternative hypothesis being that of dominant susceptibility (at that time the only data available were that of Cudworth and Woodrow [21]). Rubinstein et al. [5, 6] have forcefully championed the autosomal recessive hypothesis, and do so again in this issue of the journal [6]. They claim that by appropriately varying the penetrance and gene frequency, which results in a very high value for the latter, they can explain all the observed family data regarding sharing of haplotypes. This does require a rather high gene

frequency. More seriously, it requires that the penetrance varies a great deal between multiple cases in a family and simplex cases in order to resolve the large discrepancy between the estimates of IDDM prevalence predicted by the high gene frequency estimates required by their model and the prevalence actually observed in population studies [10, 25, 33–35] (e.g., the penetrance of "familial cases" would be some 20% or more, while simplex cases would have a corresponding penetrance of 2%–5% [36]). The recessive hypothesis would also seem not to be able to account for the U.S. black-white racial differences [3]. Finally, neither the dominant nor the recessive model can account for the various reports that would suggest immunologic or other phenotypic heterogeneity of the disorder(s) (see below).

EVIDENCE FOR HETEROGENEITY WITHIN IDDM

Various lines of evidence for heterogeneity within insulin-dependent diabetes have been developing for some time. Heterogeneity of IDDM could be inferred when the first detailed argument for heterogeneity within all of diabetes was proposed by Rimoin [37], since frank insulin dependent diabetes was a component of certain defined genetic syndromes, such as the optic atrophy diabetes mellitus syndrome and a syndrome with epiphyseal dysplasia and infantile-onset diabetes [38–40]. More direct evidence came from immunologic studies that suggested that there were forms of insulin-dependent diabetes associated with autoimmunity and those which were not, and that this occurred on a familial basis [41–43].

Additional evidence for heterogeneity was first pointed out by the Danish group in that there was increased relative risk for insulin-dependent diabetes for individuals with two different associated HLA alleles (e.g., B8B15 or Dw3Dw4) as compared with those with only one such allele (B8x or B15x, where x is any nondiabetogenic HLA allele) or those with two identical such alleles (B8B8 or B15B15) [1] [i.e., the risk for individuals with both B8 (Dw3) and B15 (Dw4) antigens was greater than for individuals with only one of these antigens]. In contrast, the relative risk for diabetes was not substantially increased by homozygosity for either B8 or B15 antigens; that is, it made no difference whether an individual had one or two *B8* genes or one or two *B15* genes. These observations have been repeated by many different groups of investigators, and the results remain consistent whether the studies examine the *B* or *D* locus alleles [1, 14, 25, 36, 44–49]. (The *D* locus studies suggest an increased risk for the Dw3 or Dw4 homozygote over the heterozygote, but it is still less than the risk for the individual with both Dw3 and Dw4 antigens.) Falk and Rubinstein have claimed that an excess relative risk for heterozygotes can be demonstrated to occur even if the disorder is due to a single recessive susceptibility gene in linkage disequilibrium with both B8 (Drw3) and B15 (Drw4) [49]. However, a careful reading of their paper reveals that the increased risk for the heterozygote under this model is mild and not of the order of magnitude observed in population studies. Furthermore, even this mildest increase in relative risk is a function of a certain proposed "reasonable" degrees of association between the disease susceptibility and HLA marker alleles, and when instead such association parameters are derived from population considerations of a heter-

ogeneity model, much higher degrees of association are predicted for at least one form [17]. Probably even more telling than these relative risk calculations is the simpler observation that the number of homozygotes (B8/B8 + B15/B15 or Drw3/Drw3 + Drw4/Drw4) is always observed to be considerably less than the number of compound heterozygotes (B8/B15 or Drw3/Drw4) [25, 36, 46, 47, 50].

During this period, Bottazzo and Doniach [11] and later Irvine [51] proposed that insulin-dependent diabetes can be subdivided into autoimmune and viral-induced types, with an intermediate group in the Irvine classification. The autoimmune type would be characterized by pancreatic islet-cell antibodies, which may occur years before the onset of clinical diabetes and persist for years after its onset, by the presence of other associated autoimmune endocrinopathies and antibodies, by an onset at any age, and by a higher incidence in females. In contrast, the hypothesized viral-induced type would have transient islet-cell antibodies at the onset of disease that disappear within the next year, would not be associated with autoimmunity, would tend to have age of onset less than 30 (but may occur later), and have an equal sex incidence. During the same period, Rotter and Rimoin, on the basis of an analysis of published immunologic and metabolic studies, proposed further heterogeneity among the juvenile insulin-dependent form of diabetes based on differential immunologic correlations with different HLA phenotypes, and postulated that the *HLA B8-Dw3* and *B15-Dw4* associated forms of diabetes are distinct diseases—*B8-Dw3*, an autoimmune form, and *B15-Dw4*, an insulin antibody responder type [12, 13, 52].

Several studies now support heterogeneity of the antiinsulin antibody response to exogenous insulin therapy, which appears to differ between the B8 and B15 associated juvenile-onset diabetics (table 2). Individuals who do not develop insulin antibodies have an increased frequency of B8 and a normal frequency of B15, whereas those individuals who form medium or high titers of insulin antibodies have a normal frequency of B8 and an increased frequency of B15. These results, initially reported by Bertrams et al. [53], and by Schernthaner et al. [54], have been confirmed by Irvine et al. [16], examining both *B* and *C* locus alleles, and by Ludvigsson et al. [55] and Schernthaner et al. [56], examining *Dr* locus alleles. The latter group has extended this concept by showing that this association is true regardless of the type of insulin therapy—conventional or monocomponent [57].

The presence or absence of pancreatic islet-cell antibodies also appears to distinguish between the B8 and B15 forms of juvenile onset diabetes, the frequency of islet-cell antibodies being significantly more common among B8 diabetics than among those with other HLA types (table 3). This association of B8 is particularly with persistent islet-cell antibodies and can be obscured if only new onset patients are studied [64], since the frequency of islet-cell antibodies is extremely high among patients with recent onset disease. Initially reported by Nerup et al. [58] and Morris et al. [59], this observation has been confirmed by Irvine's group in two larger studies [15, 60], by Cudworth [23], and by Ludwig et al. [61]. The latter group has also reported a similar association of persistent islet-cell antibodies with Dw3 [63], as would be expected from the linkage disequilibrium (population association and linkage) of B8 and Dw3. B8 juvenile-onset diabetics also have

TABLE 2

HETEROGENEITY OF IDDM, INSULIN ANTIBODIES

Study	Insulin antibody response	B8	B15
Bertrams et al., 1976 [53]	Nonresponder	41%	18%
	Responder	25%	29%
Schernthaner et al., 1976 [54]	Low insulin binding	51%	14%
	High insulin binding	25%	30%
Ludvigsson et al., 1977 [55]	Low insulin binding	45%	0%
	Moderate insulin binding	41%	26%
	High insulin binding	35%	38%
Irvine et al., 1978 [16]	Negative	87%	0%
	Low insulin binding	64%	4%
	Moderate insulin binding	60%	23%
	High insulin binding	43%	43%
		Drw3	Drw4
Schernthaner et al., 1979 [56]	Low and nonresponder	53%	Poor
	Moderate and high	10%	Sera
Schernthaner et al., 1980 [57]	No antibody to monocomponent insulin	56%	56%
	Detectable antibody	29%	92%

evidence of cell-mediated immunity against the pancreatic islets [58]. Thus, the B8-Dw3 form of juvenile-onset diabetes appears to be associated with islet-cell autoimmune disease. The observation is in agreement with previous findings that suggest that other autoimmune endocrine disorders, such as Graves and Addison disease, are also associated with B8 and not with other HLA types [22]. Also supporting this conclusion is the observation that individuals with both insulin-dependent diabetes and thyroid disease or other autoimmune disease have even a higher association with B8 [15, 62]. In addition, the occurrence of IgA deficiency in insulin-dependent diabetics is also a B8-associated phenomenon [65].

This accumulated evidence strongly suggests that genetic heterogeneity exists even within the typical insulin-dependent juvenile-onset type of diabetes. It appears that there are at least two distinct forms of juvenile-onset diabetes, one of which is associated with HLA B8 and the other with B15 [12, 13] (table 4). B8 could be replaced by Dw3 and B15 by Dw4 without any change in concept or conclusion. The HLA-B8 form of the disease (autoimmune form) is characterized by an increased prevalence of the Dw3 allele of the *HLA D* locus, an increased persistence of pancreatic islet-cell antibodies and antipancreatic cell-mediated immunity, and lack of antibody response to exogenous insulin. This form apparently has onset throughout life and probably accounts for a significant fraction of older onset IDDM, which in the older age groups may present for a significant period as treatable without insulin, but in whom the presence of islet-cell antibodies presages eventual insulin dependence [60, 66]. Since such cases have an increased frequency of B8, it would appear that they belong to the general group of IDDM patients. The second form of juvenile-onset-dependent diabetes is associated with

TABLE 3

HETEROGENEITY OF IDDM ISLET-CELL ANTIBODIES

Study	Duration of ICA positivity	B8	B15
Nerup et al., 1976 [58]	ICA positive	72%	50%-other HLA types
Morris et al., 1976 [59]	ICA negative	35%	20%
	ICA positive, < 1 yr	55%	11%
	ICA positive	61%	12%
	ICA positive, > 5 yrs	71%	5%
Irvine et al., 1977 [60]	ICA negative, < 3 mos	32%	18%
	ICA positive	58%	9%
	ICA positive with other endocrine autoimmunity	75%	19%
Ludwig et al., 1977 [61]	ICA negative	36%	23%
	ICA positive	73%	27%
Cudworth, 1978 [23]	ICA negative, > 5 yrs	49%	17%
	ICA positive, > 5 yrs	71%	15%
Bottazzo et al., 1978 [62]	ICA negative, > 5 yrs	50%	18%
	ICA positive, > 5 yrs	69%	17%
	IDDM, thyroid disease	83%	14%
Irvine et al., 1978 [15]	At presentation, < 1 mo	54%	19%
	ICA positive, > 3 yrs	71%	15%
	Associated autoimmune disease	81%	16%
		Drw3	
Ludwig et al., 1979 [63]	ICA negative, > 5 yrs	9%	...
	ICA positive, > 5 yrs	60%	...

the Cw3 allele of the *HLA C* locus and Dw4 of the *D* locus, is not associated with autoimmune disease or islet-cell antibodies, and it is accompanied by an increased antibody response to exogenous insulin. This disorder also appears to have an earlier age of onset than the B8-Dw3 type [25, 36, 67]. Irvine et al. [16] have recently shown a direct relationship between persistent islet antibodies and lower insulin antibody levels, thus directly confirming the differential immunologic features of the two forms.

Not every study will confirm these differential features, nor should every such study be expected to do so. Thus, a few studies have not observed a relationship between islet cell antibodies and B8-Dw3 ([68] and J. Barbosa, personal communication, 1980). Individual studies will be confounded by sampling variation, unrecognized biases, different frequency of the different disease forms in the study population, and sample-size considerations. It is from all the studies in the aggregate that conclusions should be drawn, and they appear to support the differential associations. It is sobering to note that the first reported study of HLA antigens frequencies in IDDM patients was concluded to be a negative study (i.e., against any evidence for an association), because the associations were not significant, due primarily to sample size and population heterogeneity [69].

TABLE 4

HETEROGENEITY WITHIN IDDM

Evidence	B8	B15	B8(Dw3)/B15(Dw4) combined form
Relative risk for diabetes	-Additive-		↑ Relative risk
Linkage disequilibrium	Dw3, Drw3, A1	Cw3, Dw4, Dr4	↑ Occurrence in monozygotic twins
Insulin antibodies	Nonresponder (no antibodies)	High responder (produce antibodies)	↑ Risk to siblings
Islet-cell antibodies	Persistent	Transient	↑ Occurrence in familial cases
Antipancreatic cell-mediated immunity	Increased	Not increased	...
Thyroid autoimmunity in IDDM	Yes	Less frequent	...
Associated with other autoimmune endocrine diseases	Yes	No	...
IgA deficiency in IDDM	Increased	Not increased	...
Isolated pedigrees	Autoimmune disorder	Defect in insulin release	...
Age of onset	Any age	Younger age	Youngest

Not all investigators conclude that these observations indicate genetic heterogeneity. Rubinstein et al. [6] argue that this phenotypic heterogeneity reflects only other linked (in disequilibrium) immune reactivity in the HLA complex, which may not have anything to do with diabetes pathogenesis per se. However, the ability of mathematical models based on these heterogeneity arguments to make accurate population predictions (see below) would seem to be additional evidence in their favor.

It would not be surprising to find even further heterogeneity with insulin-dependent diabetes. There is reasonably good evidence for the existence of a third form, the compound B8-Dw3/B15-Dw4 heterozygote. This form is characterized by an increased relative risk. Evidence hints that it may also have an increased prevalance among concordant twins, an increased prevalance among familial cases, and an increased risk for sibs for diabetes [23, 36, 58]. In addition, this group may have the earliest age of onset and greater islet-cell damage, as indicated by the lowest levels of measurable C-peptide [55].

To further complicate matters, it appears that the recently described Bf-F1/IDDM association identifies a third diabetogenic haplotype, one that carries Bf-F1, HLA B18, and Dw3 [70–74]. In addition, besides the positive HLA associations mentioned, negative associations (i.e., a decreased frequency of certain HLA antigens) have also been noted. Combining data from several centers, Ludwig et al. pointed out that the B7 antigen was decreased in IDDM patients [75]. There are two general explanations for such a finding: a generalized but variable decrease in a number of antigens as a consequence of the increase in others [76], or linkage disequilibrium with a gene that has been hypothesized to be "protective" for IDDM. The latter hypothesis has been most favored from the observations of a marked decrease (to the point of almost complete absence) of the Dw2 and Drw2 alleles in IDDM patients [25, 36, 47, 51, 77, 78]. (The B7 decrease is felt, like most of the *B* locus associations, to be secondary to the stronger *D* locus association).

HETEROGENEITY GENETIC MODELS

This accumulated evidence for heterogeneity, plus the observations regarding the compound form, make the simple autosomal recessive and autosomal dominant hypotheses increasingly less tenable. A more restricted hypothesis would be that at least some forms of juvenile diabetes are due to inheritance of recessive or dominant susceptibility. Barbosa et al. [9] ascertained their patients in order to select two sets of families: those with horizontal and those with vertical aggregation. For the purpose of linkage analysis, they then assumed recessive inheritance for the first set and dominant for the second [7–9]. However, without further phenotypic distinctions, it is not clear whether these different aggregation patterns truly reflect different modes of inheritance (Barbosa et al. are to be thanked for consistently publishing their data in its entirety, thus allowing others to analyze it.) In addition, formal linkage analysis of the multiplex families studied by Barbosa et al. [7], assuming genetic homogeneity and autosomal recessive inheritance, was found to be consistent only with loose linkage to HLA (recombination fraction of 15%–20%) [8, 79]. (Rubinstein et al. [6] point out that these analyses do assume a

low gene frequency.) In the absence of selection, such loose linkage would seem inconsistent with HLA association due to linkage disequilibrium. If the linkage between the HLA alleles and the diabetogenic susceptibility genes was not very tight, we would not expect to see the associations in population (cross-sectional) studies, because the disequilibrium should have disappeared in just a few generations after the appearance of the diabetogenic alleles. More recently, Suarez et al. have shown that this type of genetic analysis is sensitive to assumptions regarding penetrance and gene frequency, hence a variety of conflicting claims would not be unexpected [80].

For the most part, these models ignore the increasingly documented heterogeneity within IDDM. Formal genetic analyses that fail to take this heterogeneity into account and treat IDDM as one entity probably suffer from the same defect as did earlier genetic analyses that failed to distinguish insulin-dependent from noninsulin-dependent diabetes. Other genetic models besides simple autosomal dominant or recessive ones must be developed to take this heterogeneity into account. For example, Hodge et al. [17] have recently developed a three-allele model for a diabetic susceptibility locus tightly linked to the HLA complex that incorporates the immunogenetic heterogeneity observed within IDDM.

Hodge et al. [17] postulated a susceptibility locus S for insulin-dependent diabetes tightly linked to the HLA complex with three alleles: S_1, S_2, and s. S_1 and S_2 would be the diabetogenic alleles for forms 1 and 2, respectively, while s is a normal nondiabetic allele. Genotypes S_1s and S_1S_1 were presumed to be at risk (with penetrance ϕ_1) for the autoimmune B8-associated form of the disease (form 1); S_2S_2 and S_2s were presumed to be at risk (with penetrance ϕ_2) for form 2, characterized by antibodies to exogeneous insulin and associated with B15; S_1S_2 was presumed to be at risk (with penetrance ϕ_3) for form 3, the compound form, which would share the features of both 1 and 2. The normal allelic state ss would not be susceptible to insulin-dependent diabetes. This model therefore takes into account the differential immunologic and HLA associations, and the greatly increased relative risk for the B8/B15 (Dw3/Dw4) heterozygotes. Hodge et al. [17] incorporated the population prevalence of the disease, the HLA relative risks, the concordance rates for sibs and monozygotic twins, and the percentages of *HLA* haplotypes shared in common by affected sib pairs. They then were able to solve for the penetrances of the various forms, and the gene frequencies of the three susceptibility alleles. One solution set that provided a particular good fit to the observations gave gene frequencies of .111, .006, and .883 for S_1, S_2, and s, respectively, and penetrances $\phi_1 = .001$, $\phi_2 = .107$, and $\phi_3 = .436$, respectively. The predicted relative proportions of the three forms among all juvenile diabetics in the Caucasian population were 10%, 60%, and 30% for forms 1, 2, and 3, respectively, a prediction consistent with various reported immunologic studies. The reason form 3 is so frequent among diabetics, even though the underlying genotype frequency is rare compared with the other two forms, is because of its high disease penetrance. This model also predicts, because of the higher penetrance of form 3, that the distribution of the forms of the disease will differ among affected individuals and families with multiple members affected (i.e., of all affect-

ed individuals, approximately 30% will have form 3, but in contrast, almost 50% of all affected sib pairs will have form 3).

There were several predictions and conclusions from this modeling. First, it demonstrates that other models, besides dominant and recessive, can account for the population and HLA observations. Second, in a sense, this model has both dominant and recessive features. Since only one diabetogenic allele is required for susceptibility, genetic transmission mimics dominant inheritance on a population basis. However, the familial forms often involve two alleles, and therefore can mimic recessive inheritance within families.

This heterogeneity model can also account for the racial differences commented upon by MacDonald [3, 18]. In addition, the heterogeneity model makes certain predictions regarding racial differences that would not follow from either simple dominant or recessive susceptibility or the more general one-locus, two-allele gene-dosage model. Given the racial differences and gene admixture proposed by MacDonald [3], the heterogeneity model predicts that the relative incidence of the autoimmune form of the disease would be proportionately less among U.S. black IDDM patients than among U.S. white IDDM patients [18]. This prediction has received direct support from the studies of Maclaren and coworkers [81–83] who have found the prevalence of islet-cell antibodies and adrenal antibodies to be less in U.S. black IDDM patients than in U.S. IDDM whites. The frequency of pancreatic autoimmunity observed in U.S. whites was twice that observed in U.S. blacks, precisely what was predicted by the heterogeneity model [18]. (As a consequence, it would seem that this would also tend to validate MacDonald's assumptions regarding gene admixture and IDDM genes in the U.S. black population, but not his conclusion regarding dominant inheritance.)

This does not mean there are no problems with this model or its solutions [17]. The low penetrance of form 1 is disturbing, meaning it is essentially a sporadic disorder. In addition, if all variables are included in the model (i.e., tight linkage is not assumed), the number of parameters probably becomes unwieldy. In addition, other assumptions were built into the model, again to make it mathematically and computationally tractable. These include: equal penetrances for the form 1 heterozygotes and homozygotes, a similar restriction for form 2, and even the assumption that we were dealing with three alleles at one locus, rather than two different *HLA*-linked diabetic loci, as was originally proposed [12].

EVIDENCE FOR TWO INDEPENDENT GENETIC LOCI

To make an already complicated area even more complex, there are theoretical grounds for considering two independent genetic loci as predisposing to IDDM. The evidence is suggestive but growing. First, the association of B8-Dw3 is not only with IDDM, but with a host of autoimmune disorders such as Graves disease, Addison disease, coeliac disease, chronic active hepatitis, and others [84]. What then provides the specificity? Either a specific disease predisposing gene for each disease must be in linkage disequilibrium with the *B8-Dw3* haplotype, or the *B8-Dw3* haplotype provides some general predisposition to autoimmune disease. Direct evidence for a second non-HLA-linked B-cell alloantigen that specifically

predisposes to coeliac disease has been provided by Pena, Strober, and coworkers [85, 86]. Population genetic analysis also supports a two-locus model for coeliac disease [87]. Equally suggestive is the data regarding Graves disease, in which, besides the HLA B8-Dw3 association, an association with alleles at the *Gm* locus (IgG heavy chain allotypes) has also been identified [88, 89]. In an analogous fashion, we might consider investigating a second locus for IDDM. Specifically, if insulin antibodies have any pathogenetic role in IDDM, then *Gm* locus alleles (or as always, closely linked genes) may be important, as an association between the antibody response to exogenous insulin and certain Gm allotypes has recently been observed by Nakao et al. [90]. Could this be the clue to a second diabetogenic locus in man? A population genetic analysis has been reported to be consistent with a two-locus model for IDDM [19], although the analysis did not take into account the heterogeneity reviewed above. Furthermore, the widely varying estimates of the penetrance of IDDM might make such an analysis rather imprecise, until we have more clues as to the proposed second locus.

Probably the major difficulty in fully resolving the genetics of IDDM remains the problem of identifying those who carry the predisposing diabetic genotype yet do not manifest the disorder (i.e., those individuals who are not fully penetrant). When we don't know the pattern of inheritance, the only estimate of penetrance available is that from identical twin data. Since estimates of monozygotic twin concordance range from 20% to 50%, this means the majority of individuals in the population with the IDDM genetic predisposition are clinically normal. This will continue to confound and bedevil all attempts at rigorous genetic analysis. We must work toward identifying the IDDM genotype in the absence of full-blown clinical disease. In this regard, the recent work of Barbosa et al. [91] is particularly noteworthy. They have demonstrated subtle abnormalities of glucose and insulin levels in HLA identical siblings as opposed to HLA nonidentical siblings of IDDM diabetics. Even more significant was a higher incidence of intense immune fluorescent staining of albumin in the skeletal muscle extracellular membrane in the HLA-identical siblings, those at highest risk, than in nonidentical siblings, who were comparable to controls. Such biological advances provide the hope of eventually identifying those individuals who are genetically susceptible, thus resolving not only the genetics, but providing an invaluable tool in studying the natural history, pathogenesis, and preventive measures, and providing genetic counseling as well. Until that time, the debate over the mode, or modes, of inheritance of insulin-dependent diabetes mellitus is likely to continue.

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