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Review Articles

Type I Diabetes Mellitus

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Summary. The major genetic susceptibility to insulin dependent (Type 1) diabetes is determined by genes in the HLA chromosomal region. An increased relative risk for developing the disease is observed in subjects who are HLA A1, A2, B8, B18, B15, B40, CW3, Bf^s, DW3, DW4, DRW3, DRW4 positive. There is an additive relative risk in subjects who possess two "high risk" HLA B alleles which has an important influence on the prevalence of the disease in sibships and possibly on the concordance rate in diabetic identical twins. There is also suggestive evidence that particular combinations of "high risk" HLA B alleles are associated with increased or persistent antibody production which may reflect enhanced or differential susceptibility. Certain factors (e. g. HLA B7, DW2 and DRW2) are associated with a significantly reduced risk and may exert a "protective" mechanism in Type I diabetes, by linkage disequilibrium with genes which reduce immune responsiveness. The significant increases and decreases in respect of the HLA B antigens are probably secondary to the corresponding HLA D and DRW associations which reflect a stronger linkage disequilibrium between the genes which determine these specificities and the putative genes which control susceptibility. Initial damage to the beta cells probably occurs a considerable time before the onset of symptoms and theoretically modification of the immune response early in the disease process may reduce the rate of beta cell destruction.

Key words: Genetics of diabetes, HLA system, HLA haplotypes, viruses, islet cell antibodies, genetic counselling, retinopathy, identical twins, factor B, 'juvenile-onset' diabetes, 'maturity-onset' diabetes.

At a time when there is considerable interest and speculation into the basic mechanisms underlying the nature and pathogenesis of so-called 'juvenile-onset' diabetes, it seems appropriate to evaluate the evidence that has accumulated so far. Any investigation into the aetiology or pathogenesis of diabetes – and this applies to a number of closely related diseases – should first of all consider the important role of genetic determination, and then, secondly, elucidate how this susceptibility is exploited by environmental factors. The prevalence of the different types of clinical diabetes in families, the possible important role of viruses and immune mechanisms in Type 1 ('juvenile onset' type) disease, and the association of the latter with other auto-immune endocrinopathies strongly suggests the existence of genetic heterogeneity in diabetes.

Previous Genetic Concepts

In a book entitled 'Chances of Morbid Inheritance' R. D. Lawrence (1934) [1] wrote on the genetics of diabetes in which he, in common with geneticists and clinicians of that time, attempted to interpret difficult and complex human pedigree data in terms of simple Mendelian ratios. By 1950, Lawrence quite clearly believed in the existence of two major types of human diabetes characterised by different patterns of age of onset, a tendency to ketosis or obesity, and the dependence or otherwise on insulin [2]. Based on a wealth of clinical experience, he observed that diabetes characterised by absolute insulin deficiency is not entirely confined to the young but may also occur at all ages including the elderly [2]. Although it is generally accepted that diabetes is clinically a heterogeneous disorder, the evidence for genetic

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heterogeneity has taken a long time to become firmly established.

The early studies of pooled pedigree data produced a plethora of conflicting conclusions [3–8]. Several investigators [3, 6] favoured the idea of autosomal recessive inheritance, but found it necessary to postulate that penetrance is markedly reduced such that only about one-fifth of subjects with the genotype actually develop the disease. It has been pointed out that it is unlikely that a clinical entity as common as "diabetes" will be controlled by a single gene, and secondly by invoking incomplete penetrance of this magnitude it is possible to prove that almost everything has a genetic basis [9].

The arguments for polygenic or multifactorial inheritance were based on the concept that an individual's liability is made up of both genetic and environmental influences. Thus, in a population, liability mimics a continuous variable, the dividing line between normality and disease representing the threshold of liability. Estimation of "heritability of liability" is a mathematical expression of the proportion of phenotypic variance that is due to additive genetic variance [10]. This method was applied to two different populations which produced essentially opposite conclusions [11, 12]. The Edinburgh group concluded that early and late onset diabetes have the same genetic predisposition, but one objection to this method of analysis is that it tends to assume from the outset that diabetes is a single disease. Simpson (1964), in an analysis of first degree relatives [13, 14] employed the modified familial/population ratio method [15] (K values). The siblings of propositi with onset of diabetes less than 20 years of age had a much higher K value than would have been expected for multifactorial inheritance and it is of interest that this was interpreted as possibly representing an increase in "high risk alleles" operating in these families.

Genetic Heterogeneity – Clinical Observations

The question of genetic heterogeneity has recently been reviewed [16]. It is noteworthy that some of the early studies [17, 18] indicated that mild late onset diabetes may be consistent with dominant inheritance, whereas Harris (1950) [19] concluded that early onset diabetes and mild late onset diabetes are homozygous and heterozygous states respectively for a gene at the same locus.

For various reasons the concept of genetic heterogeneity receded. However, considerable renewed interest in this hypothesis has resulted predominantly from clinical observations and analyses on the prevalence of different types of diabetes in families [20, 21, 22] and in diabetic identical twins [23]. For example, in the twins study, it was demonstrated that approximately 50% of pairs with insulin dependent diabetes, mostly with an earlier age of onset, are discordant (i.e. only one twin diabetic), whereas nearly all insulin independent pairs are concordant [23]. Another very valuable study was the ascertainment of an equal incidence of maturity-onset type diabetes among the ancestors of juvenile diabetics and non-diabetics [24]. Furthermore, Tattersall and Fajans (1975) have drawn attention to a very mild form of diabetes which is occasionally seen in children and in particular the entirely different pattern of inheritance (? dominant) of this type compared with classical ketosis-prone 'juvenile' diabetes [25]. All these studies have helped to emphasise the existence of genetic heterogeneity, and therefore the probable role of different aetiological and pathogenic mechanisms which operate to produce the clinical syndrome of diabetes mellitus.

Studies of the Major Histocompatibility System (MHS) in Diabetes

1. Genetic and Biological Concepts

Attention has been focussed on the fundamentally important biological role of the MHS in animals and man, and on the factors which control the evolution of the antigenic polymorphisms determined by the multi-allelic systems operating at the closely linked loci (e.g. on chromosome 6 in man – Fig. 1). Many genes in these chromosomal regions probably control differences in immune response and therefore differential susceptibility to a variety of diseases, including in particular perhaps those induced by viruses. The mechanisms by which such genes may operate in association with the major histocompatibility antigens (HLA) have been elegantly reviewed [26, 27]. It is unlikely that the HLA antigens themselves confer susceptibility to particular diseases, and almost certainly they act as inert "markers" for the existence of disease susceptibility or immune response genes which are in linkage disequilibrium with the HLA system. In a random breeding population in genetic equilibrium, alleles operating at two closely linked loci should not show any increase of association any more than the gene frequencies for the respective alleles permits. Thus, if an allele x at locus A has a gene frequency of 0.2, and an allele y at locus B has a gene frequency of 0.3, then the combination of xy will occur with a frequency of 0.06. When the frequency of xy is not equal to the product of the frequencies of the respective alleles, then the two deter-

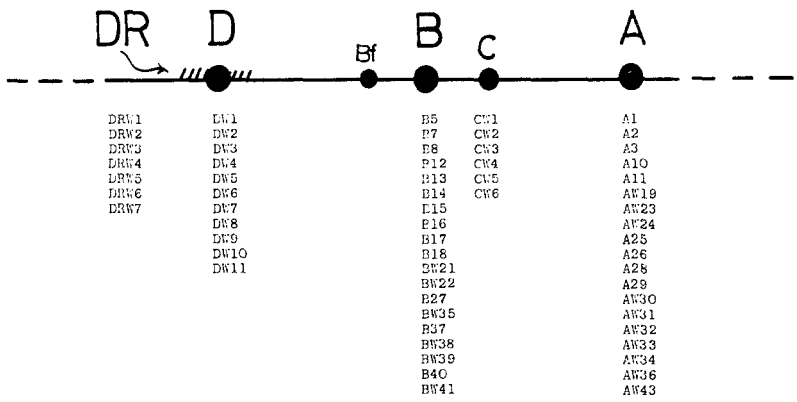

Fig. 1. The major histocompatibility system (MHS) in man

minants are said to be in linkage disequilibrium, and this association will be detected in the population. The association may be positive or negative depending on whether the frequency of xy is greater or less than the expected. An important question is what determines linkage disequilibrium? Theoretically it may be due to a mutant gene not yet having reached equilibrium within the population, or probably more likely, it reflects the pressures of natural selection [27]. Thus, perhaps having adapted and become resistant to one set of diseases, man now finds he is susceptible to a "new" spectrum of pathogenic processes.

It seems likely that specific immune responsiveness is under precise genetic control. Immune response (Ir) genes have been described in both guinea pigs and mice which are closely linked to the MHS of the species [28]. Further examples are the demonstration of major genes controlling susceptibility to Gross virus murine leukaemia, linked to the right-hand part of the H2 locus [29], and the wide variation in susceptibility among murine strains to both acute and chronic infection with lymphocytic choriomeningitis (LCM) virus. In general, those strains producing apparently the greatest amount of virus and the most prolific immune response are more susceptible, whereas strains producing less virus and a weaker immune response are more resistant [30, 31]. Thus, the susceptibility to LCM depends on the host immune response which is determined by an Ir gene(s) closely linked to the H2 locus. A possible working hypothesis is that genes with a similar role exist in the HLA chromosomal region to produce susceptibility to certain types of diabetes.

2. The HLA Specificities

The HLA determinants present on most cell surface membranes, fall into segregant series, each series appearing to behave as though controlled by multiple alleles operating at a single locus. The term locus indicates the position of a gene on the chromosome. An allele is an alternative form of the gene and where there is an appreciable frequency of several genes (or alleles) in the same population, this is referred to as a polymorphism. The remarkable polymorphic nature of the HLA chromosomal region can be seen in Figure 1. The HLA A, B, C loci determinants are most easily detected on lymphocytes using specific antisera which induce lymphocytotoxic effects if the antigen is present. In practice, a number of antisera are used to determine accurate definition of an antigen, because not all sera are monospecific, some exhibiting cross-reactivity with other antigens. The HLA D specificities are determined by mixed lymphocyte culture reactions and the possibility exists that some may be identical to the serologically determined DR (Ia − immune associated) antigens which are present primarily on B lymphocytes [32].

Each individual inherits two alleles of each locus, but as the MHS is extremely polymorphic there are many different pheno- and geno-types in any population. In approximately 0.8 per cent of meiotic divisions, a cross-over or recombination occurs between the A and B loci. The distance from the D locus to the B locus is approximately the same as the A locus is from the B locus and therefore in the vast majority of cases the MHS is inherited 'en bloc' from each parent. Therefore the accurate definition of the HLA determinants in both the parents and the offspring enables identity of the HLA chromosomal region to be firmly established − e. g. by determining the HLA A-B haplotypes or by more extensive investigation, the HLA A-C-B-D(-DR) haplotypes. Thus, the haplotype is a combination of closely linked genes on the same HLA chromosome, and therefore each individual inherits two haplotypes, one from each parent, which constitutes the HLA genotype of that individual. HLA phenotype identity between two siblings does not necessarily imply genotype identity,

Table 1. Spectra of relative risk for HLA A and B antigens in 323 'juvenile-onset' diabetics, age of onset below 30 years, compared with 451 healthy controls

HLA	Relative risk	p value
A1	1.61	0.0017
A2	1.38	0.0330
A29	1.31	0.4260
A9	1.16	0.4543
A28	0.87	0.7728
A3	0.69	0.0037
AW30/31	0.66	0.3898
A10	0.55	0.0533
AW32	0.47	0.1057
A11	0.31	0.0001
	Total $X^2 = 42.40$	
B8	2.63	2.2×10^{-8}
B18	2.26	0.0028
B15	1.85	0.0055
B40	1.30	0.2690
B14	0.84	0.6406
B12	0.82	0.2569
B27	0.67	0.2065
B22	0.62	0.0055
B13	0.61	0.2379
BW35	0.60	0.2226
B17	0.47	0.0222
B5	0.43	0.0072
B7	0.40	1.0×10^{-4}
	Total $X^2 = 104.26$	

and it is therefore imperative in family studies to ascertain the HLA genotypes by typing both parents as well as the offspring.

3. Studies in 'Juvenile-Onset' Diabetes

(i) HLA A locus antigens: The HLA A antigen frequencies in 323 insulin dependent diabetics with an age of onset of below 30 years indicate a spectrum of relative risk ranging from 1.61 ($p = 0.002$) for HLA A1, to 0.31 ($p = 0.0001$) for A11 (Table 1). Analysis has shown that the increase in A1 is entirely explained by the disequilibrium between A1 with B8 in Caucasian populations [33]. A similar explanation applies to the apparent increase in A2 (in disequilibrium with B15). The decrease in A11 remains significant when the data from different centres in Europe are combined [33, 34, 35, 36, 37], and there is also a significant negative combined relative risk (0.44) for AW32 ($p = 0.04$). There is no evidence of heterogeneity between these centres, which indicates a constant pattern of disturbance of A antigen frequencies in 'juvenile-onset' diabetes [33, 34].

(ii) HLA B locus antigens: The HLA B antigen frequencies in 323 insulin dependent diabetics with an age of onset of below 30 years indicate a spectrum of relative risk (Table 1) ranging from 2.63 ($p = 2.2 \times 10^{-8}$) for HLA B8, to 0.40 for HLA B7 ($p = 1.0 \times 10^{-4}$). There are also significantly increased relative risks for B18 (2.26, $p = 0.003$) and B15 (1.85, $p = 0.006$). In addition there is an increase in the relative risk for B40 (1.30) but this is not significant ($p = 0.27$). In a combined analysis of data from different European populations of 'juvenile-onset' diabetics [33, 34, 37], the increases and decreases in relative risks for different antigens have been confirmed. When the logarithms of the relative risks for both the A and B antigens are ranked in order of increasing value, there is a significant concordance value between the three centres [33, 34].

(iii) HLA C locus antigens: In a study of 93 insulin dependent patients [38], a significant increase was found in the frequency of CW3 (34%) compared with 19% in the controls ($p = 0.001$). Thus, CW3 positive subjects have a similar increased relative risk (2.2) for developing this type of diabetes as observed with certain HLA B alleles.

(iv) HLA D locus specificities: A stronger association has been demonstrated between 'juvenile-onset' diabetes and the HLA DW3 and DW4 specificities [39]. Twenty-nine (58%) of 50 patients were found to be DW3 positive and 33 (42%) DW4 positive (relative risk 6.4 and 3.7 respectively). This suggests that the proposed "diabetogenic" gene(s) may be closer to the D locus than the HLA A, B, C and Bf loci.

(v) DR (formerly, immune-associated – Ia) antigens: The Seventh Histo-compatibility Workshop (1977) defined a number of new specificities on B lymphocytes identified by serological techniques which are probably the homologous Ia determinants of the mouse (H2) MHS. They are in general closely related to the HLA D (MLC) specificities and may possibly be the serologically detected determinants of D locus although these relationships require further clarification. Seven DR (D-related) specificities have been provisionally recognised (W), DRW1, DRW2, DRW3 and DRW7 being more clearly defined, each by several sera. Preliminary data from several centres indicate a probable positive association between 'juvenile-onset' diabetes and DRW3 and DRW4 [40, 41, 42, 43, 44, 45], and a negative association with DRW2 [40, 41, 42]. Thus it is now possible to produce a more complete picture of a pattern of 'susceptibility' and 'protection' in relation to the MHS in 'juvenile-onset' diabetes (Fig. 2). It is possible that the significant increases and decreases in respect of the HLA B locus alleles may be entirely secondary to the corresponding HLA D and DR associations.

(vi) Factor B locus specificities: Factor B (Bf) is a glycine rich β-glycoprotein present in serum which

has an important role in the alternative complement pathway. Genetic polymorphism for Bf can be demonstrated by iso-electric focussing in polyacrylamide gel [46]. The genes which determine the different specificities operate at a locus on the HLA chromosome probably to the left of the HLA B locus. The different electrophoretically determined variants were investigated in 156 'juvenile-onset' diabetics and compared with the distribution of Bf phenotypes in 101 healthy controls [47]. Bf^s was detected in 79.5% of diabetics compared with 63.3% in the controls ($p = 0.0068$). The relative risk for developing this type of diabetes in Bf^s positive subjects is 2.23 which is similar to the relative risk observed for those HLA B and C alleles (at loci in close proximity) which have been shown to have a positive association with 'juvenile-onset' diabetes. A significant increase in HLA B8 was observed in Bf^s positive diabetics, compared with the frequency of B8 in Bf^s positive controls ($p < 0.0005$), suggesting that there is linkage disequilibrium between B8 and Bf^s. There was no increase in the frequency of B8 in diabetics with other Bf phenotypes.

4. HLA Frequencies in Late Onset Insulin Dependent Diabetes

In studies of patients with insulin dependent diabetes, age of onset 31–79 years [48], a similar disturbance of HLA B series antigens as seen in insulin-independent diabetics with a younger age of onset is confirmed [33, 49]. The increased relative risk for HLA B8 and B15 (2.19, $p = 0.003$; 2.25, $p = 0.027$) and the reduced relative risk for B7 (0.49, $p = 0.033$) is strikingly similar but there is no increase in B18 and no significant disturbance in the A series antigens. However, as seen in earlier studies [50, 51, 52, 53], the presence or absence of significant associations only becomes apparent with larger numbers.

5. HLA Frequencies in Japanese Diabetics

Although 'juvenile-onset' diabetes is relatively uncommon in Japan, a study of 32 cases [54] has indicated a different pattern of disturbance of HLA antigens, a significant association occurring with BW22J (a Japanese specific BW22 variant) ($p = 0.0005$). This is of great interest because HLA B8 is virtually absent and B15 is common in the Japanese. Thyrotoxicosis is associated with BW35 in this population [55] and this antigen showed some increase in relative risk (1.81) in the diabetic group which may become significant with a larger series.

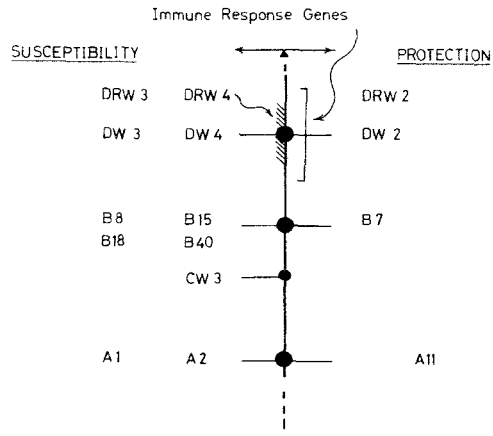

Fig. 2. Pattern of 'susceptibility' and 'protective' HLA factors in Type I diabetes

6. HLA Frequencies in 'Maturity-Onset' (Insulin Independent) Diabetes

In Caucasian insulin independent ('maturity-onset') diabetics, no disturbances in the frequencies of the MHS determinants have been observed [33, 34, 35].

Therefore, the studies of the HLA system in diabetes have provided scientific evidence for the existence of genetic heterogeneity which formed the basis of the new classification of the disease, the HLA linked genetic susceptibility operating irrespective of age of onset (Type I diabetes) [49, 56].

Genetic Interpretation of the HLA Studies in Type I Diabetes

One explanation for the significant concordance of relative risk values for the HLA A, B antigens between different centres is that there is one disease susceptibility gene in Type I diabetes which is in varying disequilibrium with the whole of the HLA system. An important alternative explanation is that there are more than one "diabetogenic" genes (or clusters of genes) operating at loci within the MHS. The main evidence in support of this is the additive relative risk observed in subjects who are both HLA B8 and B15 positive. Data in relation to HLA phenotype combinations are shown in Table 2. In addition to the increased frequency of B8, B15 positive subjects, there is a significant increase in the frequency of B8, B40 phenotypes in Type I diabetes (relative risk 6.87). The data in relation to other phenotype combinations are too small to provide useful information. If the putative disease susceptibility genes in linkage disequilibrium with particular HLA antigens operate at the some locus, this would

Table 2. HLA phenotype combinations in 323 'juvenile-onset' diabetics, age of onset below 30 years, compared with 375 healthy controls

HLA phenotype combinations	Relative risk	p value
B8, B15	5.03	0.0004
B8, B40	6.87	4.5×10^{-5}
B8, B18	2.52	0.2316
B15, B18	1.94	0.8969

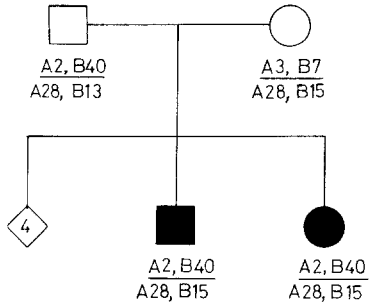

Fig. 3. HLA genotypes in a family with two affected Type I diabetic siblings. The brother also has proven coeliac disease. (The maternal grandmother has pernicious anaemia and a maternal great aunt had insulin dependent diabetes)

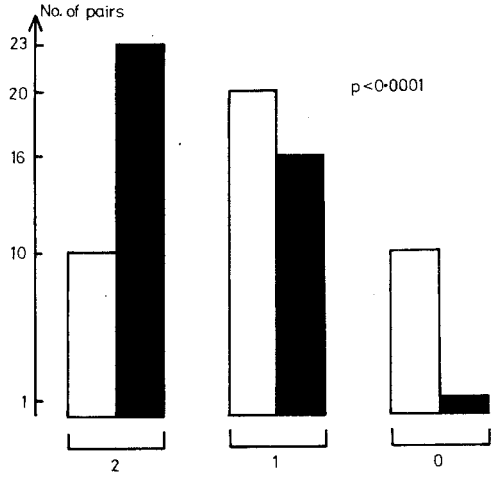

Fig. 4. Zygotic assortment of HLA A-B haplotypes in 40 pairs of Type I diabetic siblings. The expected distribution of identical haplotypes is shown in the open bars: two haplotypes in common = 10 (25%) – one haplotype in common = 20 (50%) – neither haplotype in common = 10 (25%). – The *observed* distribution of identical haplotypes is shown in the solid bars: two haplotypes in common – 23 (57.5%) – one haplotype in common = 16 (40%) – neither haplotype in common = 1 (2.5%)

be indicative of 'overdominance', (or alternatively 'epistasis' if major genes operate at different loci within the MHS). In this context it is important to note that overdominance or epistasis can simulate autosomal recessive inheritance in respect of identical HLA haplotypes in sibship studies and influence the penetrance of the disease in families. Thus the inheritance of two "diabetogenic" genes, whose effect may be mediated by interaction with different environmental agents and/or initiation of different pathogenic processes, may increase the risk of gross islet cell destruction and the development of clinical diabetes. Indirect evidence in support of this concept may be obtained from the studies of families and identical twins.

Family Studies

If in a sibship diabetes is unlikely to occur except where a gene of major effect within the HLA complex is inherited, it is to be expected that affected siblings will have inherited the same HLA chromosomal region from one or both parents. Apart from the occurrence of recombination between the HLA loci, the affected siblings should never inherit two different haplotypes (Fig. 3). Significant evidence in support of this has been provided by the study of families containing two or more siblings with 'juvenile-onset' diabetes [57]. In an analysis of 40 families with a pair of Type 1 diabetic siblings, the striking and significant departure of the pattern of zygotic assortment of HLA haplotypes is confirmed (Fig. 4). There are more pairs possessing two identical HLA A-B haplotypes suggesting a possibility of recessive inheritance, but an important alternative interpretation is the probable role of overdominance. Analysis of the HLA antigen frequencies in 51 probands of families with two or more affected siblings (Table 3) shows a generally similar distribution of relative risks as seen in the population studies (B8 = 2.08; B18 = 4.75; B15 = 2.45; B7 = 0.52). There is also an increase in the frequency of B40 (relative risk 2.21), and in particular there are strikingly increased relative risks in B8, B15 and B8, B40 positive probands. It is of interest that 15 (29%) of the index cases possess two of the antigens showing a significant positive association with the disease. Thus the susceptibility to diabetes within families may be enhanced when there is an aggregation of "high risk" HLA linked genes.

In 96 informative meioses only one A-B crossover was detected which is in perplexing contrast to the findings of Rubinstein et al. [58] who demonstrated eight out of 64 children (12.5%) exhibiting intra HLA recombinations, six occurring between the B locus and the D and/or Bf locus. These workers have suggested that a disease susceptibility gene may invoke chromosomal instability although it is difficult to understand how this might occur. Platz et al. (1977) [40] have reported only one possible B-D

cross-over in 28 diabetic families with 70 informative meioses.

Twin Studies

The study of HLA antigen frequencies in diabetic identical twins [59] demonstrated an increase in HLA B8 and B15 in insulin dependent twins and an absence of any disturbance in HLA antigen frequencies in insulin independent twins. In an extended analysis, the distribution of twin pairs positive for these two antigens according to whether they are concordant or discordant for Type I diabetes is shown in Table 4. There is no evidence of significant heterogeneity in respect of B8 and B15 in concordant pairs compared with discordant twins, but it is of interest that nine (22.5%) concordant pairs had two antigens which have a positive association with Type I diabetes compared with five (10.2%) in the discordant group.

The finding of an association with the HLA system in both concordant and discordant Type I pairs of twins provides evidence that the HLA linked genetic susceptibility is operating in both groups, and supports the idea that whether the second twin develops the disease or not depends on chance environmental events, although the concordance rate may be increased due to a bi-parental contribution of HLA linked "diabetogenic" genes.

Mechanism of Action of HLA Linked Genes

A possible pathogenetic mechanism is that the inheritance of "high risk alleles" (e.g. B8 and B15 linked genes) produces an inappropriate or abnormal immune response to environmental factors (e.g. pancreatotropic viruses), compared with subjects who possess genes which may exert a "protective" effect (e.g. linked with HLA B7) by reducing or modulating the immune response to such agents. Circumstantial evidence in support of this idea may be obtained from the following observations: –

(a) The distribution of particular HLA B phenotypes in 115 Type I diabetics with more than five years duration in relation to the persistence of islet cell antibodies (ICA) is shown in Table 5. There is an increased risk of having persistent ICA of 2.39 ($p = 0.029$) and 3.33 ($p = 0.014$) in HLA B8 and B40 positive diabetics respectively, but in those subjects who possess both antigens the relative risk is increased to 7.25 ($X^2 = 6.34$, $p = 0.008$). There are also increased relative risks for B8, B15 and B8, B18 positive subjects with persistent ICA (2.59 and 4.13 respectively), but these are not significant. It is of interest that all the B15 positive subjects were also B8 positive. This is in marked contrast to the study of ICA in 96 newly diagnosed cases (58.2% positive) in

Table 3. Analysis of HLA phenotypes in 51 probands of families with two or more Type I diabetic siblings

HLA	Relative risk	p value
B5	0.27	0.042
B7	0.52	0.043
B8	2.08	0.012
B15	3.45	9.1×10^{-4}
B18	4.75	3.5×10^{-4}
B35	0.37	0.057
B40	2.21	0.036
B8, B15	9.62	6.4×10^{-4}
B8, B40	7.61	0.022
B15, B18	7.42	0.225
B8, B18	3.16	0.401

Table 4. HLA B phenotypes in Type I diabetic identical twins

	HLA B phenotypes		
	B8, X	B15, X	"High risk" combinations
Concordant (n = 40)	14 (35.0)[a]	6 (15.0)	9 (22.5)
Discordant (n = 49)	13 (26.5)	10 (20.4)	5 (10.2)

[a] (percent)

Table 5. Distribution of HLA phenotypes and persistent ICA in 115 Type I diabetics with > 5 years duration

HLA phenotype	ICA positive (per cent) (n = 34)	ICA negative (per cent) (n = 81)	Chi-squared (Yates)	p value (Fisher-Irwin)	Relative risk
B8	70.6	49.4	3.55	0.029	2.39
B15	14.7	17.3	NS	NS	0.87
B18	8.8	9.9	NS	NS	0.96
B40	32.4	12.3	5.15	0.014	3.33
B8, B15	14.7	6.2	NS	NS	2.59
B8, B40	17.6	2.5	6.34	0.008	7.25
B8, B18	8.8	1.2	NS	NS	4.13

Table 6. Prevalence of the "Type" of diabetes in families

		Siblings		Parents		2nd and 3rd degree relatives	
		Type 1	Type 2	Type 1	Type 2	Type 1	Type 2
Type 1	Onset < 30 yrs (n = 274)	46 (16.8)[a]	3 (1.1)	14 (5.1)	7 (2.6)	48 (17.5)	18 (6.6)
Probands (insulin-dependent)	Onset > 30 yrs (n = 54)	9 (16.7)	4 (7.4)	5 (9.3)	3 (5.6)	data unreliable	
Type 2	Onset 31–79 yrs (n = 111)						
Probands (insulin-independent)		2 (1.8)	21 (18.9)	0	14 (12.6)	data unreliable	

[a] percentage in parentheses

whom there was no evidence of an association between ICA and HLA phenotypes [60].

(b) In a study of newly diagnosed diabetics (mean time interval of 5.5. days from diagnosis to taking of blood samples), sera were tested for neutralising antibodies to Coxsackie B virus types 1–5 [60]. Analysis of mean log antibody titres in relation to HLA phenotypes demonstrated a significant increase in Coxsackie B1 antibody titres in subjects who were B8, B15 positive compared with those subjects who possessed B8 or B15 alone and in particular those who were B7 positive. There were also suggestive but non-significant increases in the Coxsackie B2, B3 and B4 titres in subjects who were B8, B15 positive although there was no evidence to suggest any differences in mean log antibody titres to mumps, adenovirus, mycoplasma pneumoniae or parainfluenzae in relation to HLA phenotypes. Five out of six B8, B15 positive subjects who developed diabetes in the 1976 winter peak had high neutralising antibody titres to Coxsackie B4.

Clinical Aspects

a) Duration of Symptoms: Analysis of duration of symptoms in new cases of 'juvenile onset' diabetes suggests that in many instances the onset is subacute or even associated with lengthy periods of ill health [60, 61]. It would seem from ongoing studies that the length of history is age related, a longer duration of symptoms often being elicited in adolescents and adults compared with that obtained from younger children or their parents, but there is no evidence of heterogeneity for age of onset and particular HLA phenotypes [33, 37]. Probably at least 80% of the beta cell mass has to be destroyed or rendered inactive before serious insulin deficiency develops, and it seems likely that in many cases the initial damage to the beta cells occurs some time before the onset of symptoms. The development of insulin dependence may be the end result of either cumulative islet cell destruction due to repeated exposure to particular pathogens, or a continuous destruction (? autoimmune) following the initial exposure. The detection of islet cell antibody before the development of clinical diabetes or glucose intolerance has been demonstrated in a number of cases and therefore ICA may be a useful marker for subclinical beta cell damage [62]. It is still not certain whether ICA occurs in all cases of Type I diabetes at some stage of the pathogenic process. Irvine (1977) [63] favours the concept that ICA occurs in a proportion of cases whilst in others viral mediated damage may destroy the beta cells without ICA production. Further studies are required to clarify this issue particularly in view of the recent finding of ICA in six out of 18 spouses of newly diagnosed cases [64].

b) Genetic Counselling: The prevalence of a positive family history of Type 1 and Type 2 diabetes among the relatives of 439 probands is shown in Table 6. These results give general support to the idea that the same "Type" of diabetes tends to occur within kindreds [22, 25, 56, 65]. Accurate identification of HLA A-B-C-D(-DR) genotypes within families will indicate which siblings are likely to carry the major susceptibility gene(s). The studies of identical twins and families suggest that penetrance is of the order of 25–50%.

c) HLA Antigens and Diabetic Retinopathy: A possible hypothesis is that if different HLA linked alleles operate in different ways to produce disease, certain complications might result from particular pathogenetic processes. In a study of 52 patients with diabetic retinopathy there was no evidence of an extra increase in the frequency of particular HLA phenotypes in the group as a whole or according to whether the retinopathy was of the background or proliferative type [66].

Environmental Factors

It seems likely that environmental factors (? viruses) are operating to trigger the disease. Although there is evidence in animals that certain viruses may produce cytopathic damage to the beta cells [67, 68, 69, 70], there is no direct evidence that viruses may cause diabetes in man. Attempts to isolate viruses from throat swabs and faeces from newly diagnosed cases have been largely unrewarding [60].

The age of onset distribution (0–33 years) for 373 classical Type 1 diabetics resident in the Liverpool region is shown in Figure 5. The major peak occurs at 11 years and it would seem that there are other peaks between 5–7 years and in the third decade. A striking feature of the epidemiological studies relating to 'juvenile onset' diabetes in the U. K. [71] is the close similarity of the peaks in age of onset and of seasonal variation from year to year, which although generally consistent with an infective cause, is unlikely to reflect a single or specific virus as being the responsible pathogen because most viruses show some epidemicity. The observed seasonal peaks may be precipitated by a variety of non-specific phenomena (including seasonal virus infections), which have little relevance to the initial onset of beta cell destruction. Of considerable interest are the reports of an increased incidence of diabetes in patients with evidence of congenital rubella. Five out of 8 cases [72] under the age of 30 years were HLA B8 or B15 positive.

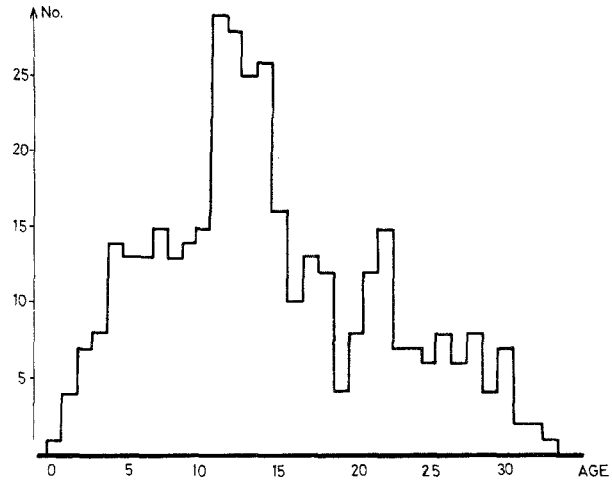

Fig. 5. Age of onset distribution for 373 classical Type I diabetics (0–33 years)

Conclusions

The studies of the HLA system in diabetes have provided new evidence for the existence of genetic heterogeneity in diabetes. Irrespective of age of onset, the major susceptibility to classical insulin dependent diabetes is conferred by genes in the HLA chromosomal region. The most convincing evidence for this emanates from the family studies indicating that where two affected siblings develop the disease, with rare exception they always inherit at least one identical HLA chromosomal region in common. Inheritance of HLA haplotypes which are identical with those of an affected sibling does not, of course, imply that diabetes is an inevitable consequence. Other genes outside the HLA chromosomal region, may also contribute to the overall susceptibility, and in addition there is the important question of environmental variability (e. g. ? exposure to possible pathogens; ? dose of virus; ? cumulative damage due to repeated exposure).

The mode of action of the HLA linked genes must remain speculative. A working hypothesis is that 'susceptibility' and 'protective' genes interact to determine the immune responsiveness to particular viruses which have a potential affinity for islet cells. The identification of environmental precipitating factors in genetically susceptible subjects theoretically could lead to the introduction of therapy designed to reduce the rate of beta cell destruction and/or to enhance regeneration.

Strong genetic factors which are not associated with the HLA system operate to produce susceptibility to 'maturity onset' insulin independent (Type 2) diabetes. One possible mechanism is the control of insulin receptor concentration and affinity which determines the level of insulin resistance and insulin response to glucose [73]. Evidence in support of this is provided by the heterogeneity of insulin response in normal subjects and patients with mild Type 2 diabetes [74].

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