L'héredité du diabète sucré:

Le cauchemar du genetician

Medical Grand Rounds

Parkland Memorial Hospital

July 20, 1978

Michael S. Brown, M.D.

INTRODUCTION

In 1965 the distinguished geneticist J.V. Neel described diabetes mellitus as "a geneticist's nightmare" (1). In so doing, he was summarizing the result of 30 years of intensive epidemiologic and genetic investigations whose net result was simply to show that some sorts of hereditary factors existed in diabetes mellitus. The data could not distinguish between three of the known modes of inheritance: autosomal dominant, autosomal recessive, and polygenic. As a result, geneticists in 1965 were no further ahead than they were in 1933 when the first genetic studies of diabetes were published (2).

In the twelve years following Neel's assessment, the first lights of dawn have appeared, and the geneticist has begun to be aroused from his troubled sleep. This progress has stemmed from two sources. First, geneticists have begun to carve up the "pie" of diabetes and to isolate from the mass of diabetics certain patients in whom the mode of inheritance can be clearly established. The phenomenon of genetic heterogeneity has been appreciated. Second, the availability of the HLA system, and the demonstration of its association with certain types of diabetes, has provided a powerful tool to dissect various forms of diabetes from each other. We can now begin to talk about certain types of diabetes as specific inherited entities. Although these entities account for only a small proportion of the total mass of diabetics, their recognition provides an essential first step in understanding the lesion in the large majority of the population.

Accordingly, in this Grand Rounds, I will first trace the history of the genetics of diabetes with respect to studies before 1965. These studies generally concluded that diabetes was an autosomal recessive disease. I will then turn to more recent studies that point to diabetes as a multifactorial as well as genetically heterogenous disease. I will review the evidence that has accumulated over the past five years demonstrating conclusively that adult-onset and juvenile-onset diabetes are two different genetic disease. Then I will discuss the classification of juvenile diabetes into several genetically and clinically distinct entities. And finally I will organize all of these data into a classification scheme for diabetes mellitus that should be of assistance in genetic counselling.

ADULT-ONSET DIABETES MELLITUS AS A RECESSIVE TRAIT: THE THIRTY-YEAR MYTH

The familial aggregation of diabetes has been known for centuries. Rondelet (3) in 1628 described 3 families in which diabetes occurred in father and daughter

The first systematic study of the inheritance of diabetes was published by Pincus and White in 1933 (2). Most of the patients were adult-onset diabetes. These workers found that 8% of the parents of diabetics were themselves diabetics, as compared with 2% of the parents of controls. Moreover, 6% of the siblings of the diabetics were affected, compared with only 0.6% of the siblings of controls. Pincus and White concluded that diabetes indeed was a familial disease, but the data didn't fit any known simple mode of transmission. Dominant inheritance was unlikely because of the preponderance of cases in which diabetic patients lacked a diabetic parent. Recognizing the inadequacy of word-of-mouth histories, these investigators conducted further studies in which they measured 2 hour postprandial blood sugar values or performed glucose tolerance tests on 169 "close" nondiabetic relatives of known diabetics and 125 controls. Relatives of diabetics were judged abnormal in 14.5% of the tests of postprandial levels and 25.3% of the tolerance tests in that they exceeded any of the control values (4,5).

Pincus and White concluded that these data were most consistent with the transmission of diabetes as an autosomal recessive trait in which the mutant gene had a very high gene frequency, but a reduced penetrance. This theory was to be accepted as fact for the next 30 years.

The sophisticated geneticists in the audience will immediately raise their eyebrows with regard to the conclusion of Pincus and White. Ordinarily, in recessive conditions, we do not expect the parents to be affected with the trait - only the siblings. However, Pincus and White observed an even higher percentage of affected parents than of affected siblings. Could this finding be consistent with an autosomal recessive trait? The data <u>are</u> compatible with autosomal recessive inheritance, and the reasons for this compatibility give some insight into two special conditions of diabetic inheritance that contribute to the geneticist's nightmare. The two special conditions are: 1) the possible presence of a recessive gene that is extremely common in the population, and 2) the problem of incomplete penetrance.

With regard to the high frequency of the diabetes gene, all of our conceptions of recessive inheritance are based on the fact that the known non-lethal Mendelian recessive traits, such as alkaptonuria or cystinuria, are due to rare recessive genes. Vertical transmission does not occur because the likelihood of an affected individual marrying a carrier is extremely small. However, if the recessive gene is common in the population, there is a finite likelihood that an affected individual will marry an asymptomatic carrier, and that offspring will be affected. Thus a recessive disease will appear to be transmitted from parent to offspring like a dominant. This situation is termed "pseudominant inheritance" (Fig. 1).

Fig. 1. "Pseudominant" Inheritance in a Recessive Trait

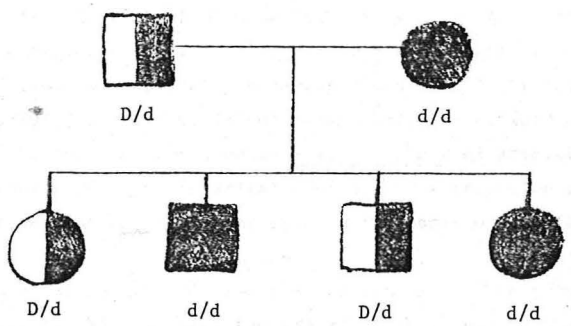


Fig. 2. Theoretical "pseudominant inheritance" in diabetes

d=frequency of diabetes gene=0.20

D=frequency of normal gene=0.80

Distribution of genotypes in population =

$$\underset{(0.64)}{\underline{\text{Normal}}\ D^2} + \underset{(0.32)}{\underline{\text{Carrier}}\ 2Dd} + \underset{(0.04)}{\underline{\text{Diabetic}}\ d^2} = 1$$

Likelihood of a diabetic marrying a carrier = 0.32

1/2 of all offspring would be dd

Therefore, 16% of all children of diabetics would be diabetic - even though it would be a recessive trait.

For example, consider the situation shown in Fig. 2 in which the recessive gene for diabetes (d) is postulated to account for 20% of the genes at that locus in the population (i.e., the d gene frequency is 0.20). By the Hardy-Weinberg law, the distribution of alleles in the population would be equal to $D^2 + Dd + d^2$, where D and d are the respective gene frequencies of the normal and mutant genes, respectively. If the mutant gene has a frequency of 0.2, then 64% of the population is homozygous normal, 4% of the population is homozygous diabetic, and 32% of the population are carriers. A homozygous diabetic patient would have a 32% chance of marrying a carrier, in which case half the children would be affected. Overall, 16% of the children produced by diabetic x normal marriages would be diabetic. In other words, the inheritance of a common recessive gene is difficult to distinguish from that of a dominant gene on the basis of population data alone.

In the case of diabetes mellitus, the problem is further compounded by the delayed age of onset. Fig. 3 shows the age of onset of symptomatic diabetes in the population. If one assumes that all of these people have a genetic disorder, it can be seen that the expression in most patients is delayed by many years. If one does a population survey of affected relatives at any instant in time, most of the affected relatives will not yet have manifested their diabetes, and hence it will be difficult to determine who is affected and who is not. Pincus and White got around the problem of incomplete penetrance in a clever way (Fig. 4). If we again express the normal gene at the diabetic locus as D and the mutant gene as d, then if the disease is recessive all of the marriages that produce diabetics in the population will be one of three types: Dd x Dd (normal carrier x normal carrier); Dd x dd (normal carrier x diabetic); and dd x dd (diabetic x diabetic). If one assumes complete penetrance of the diabetic gene then 25% of the offspring of Dd x Dd marriages should be affected, 50% of the offspring of Dd x dd, and 100% of dd x dd should be affected. If the penetrance were less than 100%, then the number of affected offspring in each group would be reduced, but the relative proportions should remain constant at 1:2:4. The actual ratios observed by Pincus and White were 1: 2.6: 3.7. These data were thus consistent with the inheritance of a common autosomal recessive gene with incomplete penetrance.

It should be pointed out that statistical population studies of this type can never unequivocally establish the mode of inheritance of any trait. They can rule out certain modes of inheritance that are incompatible with the data. However, if the data are compatible with a certain mode of inheritance, the conclusion can go no further. In most instances the data are not only compatible

Fig. 3. Age of Onset of Diabetes in the Population (31).

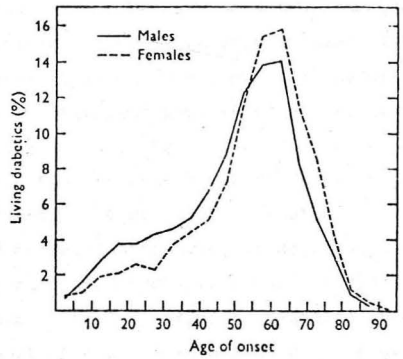


Fig. 4. Marriages that produce diabetic offspring (assuming a recessive trait).

			% of Offspring Affected	Ratio
Dd (Normal carrier)	x	Dd (Normal carrier)	25%	1
Dd (Normal carrier)	x	dd (Diabetic)	50%	2
dd (Diabetic)	x	dd (Diabetic)	100%	4

with one mode of inheritance, but they also are compatible with many other modes of inheritance. In the case of Pincus and White, the data are also compatible with inheritance by a multifactorial genetic system. They are also compatible with genetic heterogeneity, in which different forms of diabetes within the population are caused by different genetic or environmental agents.

Despite these reservations, the data of Pincus and White gained wide acceptance, and for many years diabetes was considered to be an autosomal recessive disease with incomplete penetrance. Is was assumed that offspring of diabetic x diabetic marriages were doomed to develop diabetes at some point in their life. A new name for these offspring was coined - that is, "prediabetic". Many studies were conducted in an attempt to find a marker of diabetes in these offspring that would pre-date the onset of glucose intolerance. One of these markers was said to be capillary basement membrane thickening. Underlying all of these studies was the assumption that diabetes mellitus was an autosomal recessive disease.

One of the predictions of the autosomal recessive hypothesis is that all offspring of diabetic x diabetic marriages should become diabetic if they live long enough. The major finding that called into question the autosomal recessive inheritance of diabetes was the uniform observation in several studies that the offspring of diabetic x diabetic marriages (also called conjugal diabetic marriages) rarely produced all diabetic offspring. Fig. 5, taken from Rimoin (31), summarizes the results of these studies. In general, when the presence of symptomatic diabetes is used as a criterion, only about 10% of the offspring of conjugal diabetic marriages express diabetes. This finding led investigators to use various types of provocative glucose tolerance tests in order to bring out the expression of latent diabetes in these offspring. However, even with the most generous criteria for diabetes, and even when one takes the highest value on a cortisone glucose tolerance test repeated 3 times, the percentage with "latent diabetes" is less than 50% (6). Even more striking was the finding that only 62% of the obese offspring of conjugal diabetic marriages had abnormal cortisone oral glucose tolerance tests (6). Similar results were reported by Tattersall and Fajans (7) who studied the offspring of 37 conjugal diabetic marriages. In 6 families all offspring were diabetic; in 21 families there was a mixture of diabetic and nondiabetic offspring; and in 10 of the families none of the offspring were diabetic. These data, even when interpreted in the most liberal light, would seem to refute autosomal recessive inheritance, at least among the majority of adult patients with diabetes mellitus.

Fig. 5 Diabetes and carbohydrate intolerance in the offspring of conjugal diabetics (for references see Rimoin [31]).

Author	Criteria	Percent abnormal
Simpson[20]	Clinical	3.0
Cooke et al.[86]	Clinical	5.0
Post[54]	Clinical	8.1
Harris[21]	Clinical	8.6
Kahn et al.[87]	Clinical	8.8
Steiner[41]	Clinical	30.0
Pieptea and Pavel[88]	Clinical	37.5
Jackson[80]	Oral GTT	15.0
Goto et al.[85]	Oral GTT	6-100*
Steinberg et al.[75]	Oral GTT	13-20.5†
Ricketts et al.[79]	Oral GTT	19.2
Lozano-Castaneda et al.[89]	Oral GTT	19.3
Pincus and White[90]	Oral GTT	25.0
Notelovitz[32]	Oral GTT	27.9
West[91]	Oral GTT	29.0
Taton et al.[92]	Oral GTT	35.0
Mimura and Miyao[40]	Oral GTT	51.6
Burkeholder et al.[27]	Oral GTT	56.0
Kahn et al. [87]	Oral GTT (single)	33.0
Kahn et al.[87]	Oral GTT (multiple)	55.0
Taton et al.[92]	IV GTT	16.0
Kahn et al.[87]	IV GTT	13.0
Kahn et al.[87]	IV TTT	20.0
Kahn et al.[87]	Cortisone GTT	13.0
Na arette and Torres[93]	Cortisone GTT	15.0
Navarette and Torres[93]	Triamcinalone GTT	67.2
Siperstein et al.[94]	Basement membrane thickness	53.0

*Depending on age of offspring.
†Depending on GTT criteria.

In conclusion therefore the pooled family data do not fit dominant or recessive inheritance, and geneticists will have to look elsewhere for the solution for their nightmare.

DIABETES MELLITUS: A MULTIFACTORIAL DISEASE

As the large scale studies have failed to assign diabetes to any of the single-gene modes of inheritance, geneticists have begun increasingly to consider adult-onset diabetes as a multifactorial disease (11). A multifactorial disease is one in which a combination of several abnormal genes at different loci are required to produce a genetic susceptibility to a disease in a given individual. This susceptibility is then turned into a disease when the individual comes into contact with one or more environmental factors. Such varying combinations of genes and environmental factors, when projected into a whole population, create a distribution of values that conforms to a bell-shaped curve. For example, height is a multifactorial trait, and so is intelligence. When one measures either of these parameters in members of a population and then plots the frequency distribution one comes up with a bell-shaped distribution. Certain combinations of genes place individuals in the upper, middle or lower ranges of this distribution, respectively.

This type of variation, which is also called continuous variation, is difficult to assess from a genetic viewpoint because the distinction between normal and abnormal members of a population is arbitrary and imprecise. For statistical purposes we generally state that persons who are beyond two standard deviations from the mean value of the population (i.e., beyond the 95% confidence limits) are abnormal. If one compares the distribution of values (for example, height) among members of individual families, one finds that within each family there is also a bell-shaped distribution, but the mean of these distributions varies from one family to another. Thus, some families tend to produce members who are on the average taller than other families.

In conditions in which a disease state exists, geneticists generally postulate that a certain minimal combination of genes is necessary in order for a person to be at genetic risk for developing a trait, after which environmental factors take over.

To illustrate genetic-environmental action, let us ask the question: How could the U.S. government create a genetic disease overnight? Most would say that the government would have to give everyone a dose of mutagenizing radiation

or a chemical mutagen. Even so, it would take one generation to create a genetic disease. However, the government could accomplish the same thing overnight by manipulating the environment. Suppose, for example, the federal government passed a rule that all doorways must be lowered to 6'2" in height. This would allow all of the people of "normal" height to pass through, and would save many millions of dollars annually in excess construction costs required for the additional steel framing for the excessively high doors that we now use. Unfortunately, a small fraction of the population that is over 6'2" in height would be at immediate risk of experiencing contused foreheads because of the large number of doors that one must walk through daily. Physicians would then describe a new disease state consisting of chronic contusions of the forehead, whose pathogenesis involved bumping into door jambs. The government would thus have created a genetic disease. Those people who had inherited genes that put them in the upper few percent tile for height would have a much higher incidence of contused foreheads than those who had inherited genes for the lower part of this distribution. The syndrome of "contused foreheads" would clearly show familial aggregation and in fact it would be classic multifactorial genetic disease.

All studies of the distribution of blood sugar in the general population have given evidence for a continuous distribution, just like the distribution of height. Whether one uses the fasting blood sugar, the 2-hour postprandial blood sugar, the glucose tolerance test, or the cortisone-primed glucose tolerance test, one finds that blood glucose levels show a continuous distribution with some degree of skewing to the right. There is no evidence for a true second mode. That is, there is no evidence for an absolute cutoff value between normal and abnormal. We generally classify as diabetic anyone who is more than 2 standard deviations above the normal mean. Such a finding is consistent with multifactorial inheritance for the regulation of blood sugar values.

The continuous distribution of blood sugar values in the population is analogous to the continuous distribution of height in the contused-forehead model. The environmental factor that corresponds to the lowered door-jamb is the excessive calorie ingestion. If one inherits a glucose homeostatic mechanism with blood sugar levels at the upper limits of normal, and one then stresses this genetic predisposition with the challenge of excessive calorie ingestion, diabetes mellitus will develop just as surely as a contused forehead will develop when a 6'5" man walks through a 6'2" door.

When faced with a continuously variable trait in the population geneticists try to quantify the genetic contribution to the variability by the use of the

term "heritability". The heritability of a trait is that proportion of the total variability that is due to genetic factors as opposed to environmental factors. The concept of heritability has been extremely useful to plant breeders and animal breeders, because it allows them to design breeding experiments and environmental manipulations that tend to maximize a desired trait. For example, if the animal breeder finds that 60% of the variation within a breed is due to genetic factors, he can hope to design breeding protocols to improve the yield of the desired trait. On the other hand, if the heritability is low he knows that he has to work on improving the environment in order to maximize the required property.

The concept of heritability, however, has not been helpful in assessing the human condition. This is largely because, in contrast to the animal and plant breeding experiments, in which the environment can be kept relatively constant, the environment of man is itself a variable. An excellent illustration of the problem is the one recently used by Lewontin. If a geneticist wanted to determine the heritability of skin color in man, and he went to New York City in the winter time and compared people of Irish origin with those of Italian descent, he would conclude that skin color is largely genetically determined, and that the only individuals with dark skin came from families with dark skin. On the other hand, if he happened to study the aunts and uncles of the same people, who had grown rich and moved to Florida, he would find a different situation. All individuals who had spent time in the sun would have deep tan colors, whereas those who had stayed in the shade would all be relatively pale by comparison. Now skin color would be judged to be strictly an environmental trait. Thus, the contribution of genes and environment can vary greatly in the same population under conditions of varying environmental stress.

A strictly comparable condition exists for diabetes mellitus. If one were to study a population of lean, physically fit adults who consume a low-calorie diet, one would expect to find that the diabetics among that population would come from families with an extremely strong tendency toward diabetes. On the other hand, if one were to include obese subjects, who have stressed their calorie homeostatic mechanism to the limit, one would find that the genetic component would be much less prominent, and the environmental component would be extremely strong.

The existence of just such a genetic-environmental interaction was recently shown in elegant fashion by Kobberling (12), and is summarized in Fig. 6. In studying the siblings of diabetic patients, Kobberling classified the probands

into 3 groups based on their degree of overweight. Group 1 contained patients of normal weight, and Groups 2 and 3 were progressively more obese. Kobberling calculated the frequency of diabetes among the siblings, using an age correction method that permitted calculations of the expected frequency of the disease assuming that all of the siblings lived to age 85. When he looked at the siblings of probands with adult onset diabetes, Kobberling found that the proportion of affected siblings was strikingly higher when the proband was of normal weight than when the proband was overweight. These data strongly suggest that thin adult diabetics have a much stronger genetic component for their disease, whereas the obese patients have a relatively small genetic component, coupled with a severe environmental challenge.

These data constitute a strong argument in favor of the hypothesis that adult-onset, nonketotic, stable, insulin-independent diabetes is a multifactorial trait. Given a certain genetic predisposition, the disease is brought out by obesity. Those who have many abnormal genetic factors do not require obesity in order to express this disease, whereas those who have relatively fewer abnormal genes require a stronger environmental challenge in order to produce the effect. These population data are also consistent with the familiar clinical observation that obese diabetics who lose weight can rapidly develop normalization of their blood sugar levels. The withdrawal of the environmental challenge can "cure" this genetic disease much as the restoration of door heights to 7 feet would "cure" the genetic syndrome of contused foreheads discussed above.

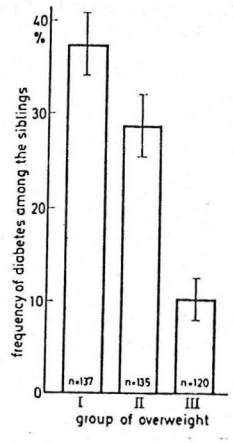


Fig. 6. Frequency of diabetes among siblings of diabetics with different degrees of obesity. Group I is non-obese. Groups II and III are progressively more obese. n = number of probands. From Kobberling (12).

MULTIFACTORIAL DISEASE VS. GENETIC HETEROGENEITY

Non-geneticists frequently confuse the concepts of multifactorial inheritance and genetic heterogeneity. Multifactorial inheritance is present when several different abnormal genes are required in any individual to produce susceptibility to a disease. Genetic heterogeity refers to a situation in which several different types of abnormal genes exist in the population, each of which can produce the disease when present in the heterozygous or homozygous state in a single individual. A classic example of genetic heterogeneity is sickle cell anemia. A similar syndrome can be produced by the combination of 2 genes for sickle cell hemoglobin (S-S disease), or by the occurrence of 1 gene for sickle cell hemoglobin (S) and 1 gene for thalassemia (sickle-thal disease). The disease is genetically heterogenous in that 2 different mutations can produce a similar clinical syndrome. However, the disease is not multifactorial because in each case disease expression requires only 2 mutant alleles.

As discussed above, the pooled population data strongly suggests that adult onset diabetes is a multifactorial trait, requiring a combination of several abnormal genes, coupled with an environmental insult, such as excessive calorie ingestion.

On the other hand, it has recently been realized that the disease is also genetically heterogenous. That is, several different syndromes that are superficially similar have been lumped together under the general term diabetes mellitus.

The first big separation within the large group of diabetics came with the realization that the genetic bases of juvenile diabetes and adult diabetes were different.

JUVENILE-ONSET DIABETES AND ADULT-ONSET DIABETES: TWO DIFFERENT DISEASES

All of the early family studies of diabetes lumped together the juvenile and adult onset cases. Because the number of adult onset cases in the population is many fold greater than the number of juvenile cases, the data were heavily weighted toward adult-onset diabetes. Professor Harry Harris, in 1950, was the first to note a genetic distinction between these two diseases. Harris found that siblings of juvenile onset diabetics tended to have juvenile onset diabetes, whereas siblings of adult onset diabetics tended to have adult-onset diabetes. This was an important observation, whose significance was not immediately appreciated. Part of the problem was due to Harris's conclusion from his studies - namely, that the juvenile state of diabetes represented homozygosity at the diabetic locus, whereas adult onset diabetes represented a heterozygous state. The reason for Harris's conclusion was probably that he believed that there was an increased incidence of adult-onset diabetes among the parents of juvenile diabetics, who would be obligate heterozygotes for the presume diabetic gene. This observation has not been borne out by subsequent studies.

The next important finding came from the work of Nancy Simpson in Toronto (13). Simpson made the striking observation that of the 466 parents of juvenile diabetics in Toronto, only 18 were diabetic. When the ages of these parents was taken into consideration, and the incidence of diabetes was compared with the known incidence of diabetes in the general population of Ontario, Simpson calculated that there was no increased frequency of diabetes among the parents of juvenile diabetics. On the other hand, the incidence of juvenile diabetes among the siblings of the juvenile diabetics was increased by 10-fold when compared with a

Fig. 7. Types of diabetes in siblings and offspring of juvenile-onset and adult-onset diabetes (14)

Diabetic Proband	Diabetes in Siblings		Diabetes in Offspring	
	Juvenile-Onset	Adult-Onset	Juvenile-Onset	Adult-Onset
Juvenile-Onset	11%	--	--	--
Adult-Onset	0.4%	26%	0.3%	33%

control population. Simpson concluded that there was no genetic relation between juvenile onset diabetes and adult onset diabetes - a revolutionary conclusion at the time.

The findings of Simpson have been confirmed in several other large studies. MacDonald studied the grandparents of 118 juvenile diabetics (14). By selecting the grandparents, he was stressing the maximal incidence of diabetes among older related individuals. Among 423 grandparents of the diabetic children only 7.8% were diabetic. This figure was not significantly different from the 7.1% incidence of diabetes in the grandparents of children who were not diabetic.

Kobberling has recently confirmed the separation between juvenile and adult onset diabetics in another way (15). Fig. 7 shows the frequency of juvenile and adult-onset diabetes among the relatives of diabetics of different types. These figures are age corrected and are predictive of the total number of diabetics who would have these conditions if they all lived to 85. In one first examines the siblings, one finds that when the proband was a juvenile-onset diabetic, 11% of these siblings had juvenile-onset diabetes. On the other hand, when the praband had adult-onset diabetes only 0.4% of the siblings had juvenile-onset diabetes whereas 26% had the adult-onset type. The data for offspring of adult-onset diabetics were similar. Only 0.3% of the offspring had juvenile-onset diabetes, whereas 33% would develop adult-onset diabetes by age 85.

The studies of Harris, Simpson, MacDonald and Kobberling and others like them, clearly indicate that juvenile diabetes mellitus is inherited, but that the mutant genes are different from those that produce adult-onset diabetes. They behave as 2 totally different genetic traits.

The difference between adult onset and juvenile diabetes that was suggested by the population genetic studies has been confirmed recently by two other types of studies - namely, studies of identical twins, and studies of the HLA system.

DIABETES MELLITUS IN IDENTICAL TWINS: EVIDENCE FOR A DIFFERENT GENETIC BASIS FOR ADULT ONSET AND JUVENILE DIABETES

In 1972 Tattersall and Pyke published the results of a striking study that clearly demonstrated a difference in inheritance of adult onset and juvenile onset diabetes mellitus (16). These two investigators studied 96 pairs of identical twins, one of whom was diabetic. Among these pairs, 65 were concordant (both twins were diabetic), and 31 were discordant (only 1 twin was diabetic). These

data are summarized in Fig. 8. Of the 59 pairs in which the index twin became diabetic before the age of 40, 31 were concordant and 28 discordant. But of the 31 pairs in which the index twin was diagnosed after the age of 40, all but 3 were concordant. In 47 out of the 65 concordant pairs, the second twin became diabetic within 3 years of the first. In 16 pairs the interval was between 3 and 10 years, and in only 2 did it exceed 10 years. The average interval for all concordant twins was 3.3 years, but it tended to be longer in pairs where the index twin was diagnosed before the age of 40 (4.1 years) than in those diagnosed after this age (2.6 years).

The first critical question that arises when viewing these data is whether the twins are discordant simply because there had been insufficient time for diabetes to develop in the second twin. However, this was not the case (Fig. 9). Among the discordant twins, over half had been discordant for more than 10 years, and in 6 cases the second twin was still not diabetic clinically or chemically 20 years after his twin developed diabetes. In 30 of the 31 discordant pairs, a glucose tolerance test was conducted on the affected twin and the results were normal. 27 of these twins were retested after 6 years, and glucose tolerance remained normal (Fig. 10). In fact, it even improved during the interval. Thus, there was no hint that the discordant twin would eventually develop diabetes.

Supporting this contention is the recent publication in 1976 of follow-up data on the twin pairs (17). When studied four years later, none of the previously discordant pairs of juvenile diabetics had become concordant. Moreover, on repeat glucose tolerance testing, there was no sign of deterioration in the discordant twins. The data in Fig. 11 show the length of discordance in these various twin pairs. In those pairs that became concordant, about three-fourths developed their diabetes within 3 years and nearly all of the rest by 10 years. On the other hand, 19 of the 35 discordant pairs have been followed for over 10 years and have remained discordant.

Fig. 12 shows the most recent data on the fo
addition to the striking lack of concordance in the pairs with age of onset less than 40, it is important to note that <u>all</u> of the pairs with age at onset greater than 50 are concordant.

Pyke and Nelson also summarized in retrospect the degree of discordance in previously reported studies of monozygotic twins (17). In the one other study for which data could be evaluated, the discordance rate was 75% among the juvenile onset diabetics.

Fig. 8. Age at diagnosis of diabetes in the index twin from pairs of concordant and discordant identical twins (16).

Age at onset	Concordant				Discordant			
	Male	Female	Total		Male	Female	Total	
0–10	4	7	11	31	3	4	7	28
11–20	6	5	11		2	6	8	
21–30	2	2	4		4	4	8	
31–40	3	2	5		3	2	5	
41–50	5	6	11	34	0	3	3	3
51–60	6	7	13		0	0	0	
61–70	1	4	5		0	0	0	
70+	3	2	5		0	0	0	
Total	30	35	65		12	19	31	

Fig. 9. Duration of Discordance in Pairs of Identical Twins Discordant for Diabetes (16)

Time	Number
Under 3 years	5
3–10 years	10
Over 10 years	16

Fig. 10. Mean blood-glucose and serum-insulin values of non-diabetic twins of diabetics (16).

—	No.	Blood-glucose (±S.E.M.) (mg./100 ml.)				Serum-insulin (±S.E.M.) (μU./ml.)			
		Fasting	30 min.	60 min.	120 min.	Fasting	30 min.	60 min.	120 min.
Discordant twins (tested in 1972)	27	76±2	103±3	86±4	69±2	15±2	44±4	39±3	20±3
Controls (tested in 1972)	18	75±3	108±6	97±5	67±3	12±2	49±8	45±7	15±2
P		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

N.S. = Not significant.

Fig. 11. Length of discordance in twin pairs (17).

	Number of twin pairs	
	Concordant	Discordant
3 years or less	50	2
4-10 years	16	14
Over 10 years	3	19

Fig. 12. Concordance and discordance for diabetes among 106 pairs of identical twins in relation to age at diagnosis in index twin (17).

Age at onset	Number of Pairs	
	Concordant	Discordant
< 40	32	32
40-49	13	3
50 +	26	0
All	71	35

The findings in these twin studies lead to several conclusions:

1) They support the notion derived earlier from family studies, noted above, that the genetic basis for juvenile onset diabetes and adult onset diabetes are different.

2) The 100% concordance rate for adult-onset diabetic twins suggests a stronger genetic component for adult-onset diabetes than had previously been recognized. Among the adult-onset twins who were concordant for diabetes after the age of 50, most had been living apart for at least 30 years prior to the onset of diabetes. Moreover, when diabetes appeared in one twin (for example, at age 55), there was an 80% chance that the second twin would become diabetic within three years even if the two twins had lived on opposite sides of England for 30 years. If adult-onset diabetes is multifactorial, as discussed above, then nearly all of the "multifactors" must be genetic. The environmental factors, if any, must be those which are common to the vast majority the population.

The power of the latter conclusion is limited somewhat because of the bias common to all twin studies. This bias arises from the fact that concordant pairs are more likely to be ascertained than discordant pairs. By definition, when one screens the population of diabetics, one has twice the chance of picking up a concordant pair, since it contains 2 diabetics, than one has of picking up a discordant pair. Hence, the high concordance rate in adult-onset diabetics cannot yet be considered as an absolute rate, and environmental factors may be more important than indicated above.

3) The finding of only 50% concordance in juvenile-onset diabetes indicates that this disease has strong genetic and environmental components. Since the monozygotic twins share all of their genes, the fact that half of them fail to develop diabetes indicates that an environmental challenge is absolutely necessary for the development of this disease. Moverover, the environmental challenge must be quite specific since on average it often only affects 1 of a pair of identical twin children, even though they both are living in the same household, eating the same food, etc. The fact that one of a pair of twins can be spared any environmental challenge half of the time is in itself quite striking.

An additional implication of these studies is that if a discordant monozygotic twin of a diabetic child survives childhood without developing diabetes, he will never develop diabetes. This finding suggests strongly that the environmental factor that triggers juvenile diabetes is a specific event of childhood. Two types of such events immediately come to mind. First, in childhood the balance of various hormones is distinctly different from that present in adult life.

Second, a host of infections takes place in childhood, and then cannot recur in adulthood, either because the individual has become immune to the infection or because he is no longer exposed to the common childhood pathogens. The implication that childhood viral infections can play some role in juvenile diabetes is supported by evidence that the immune system may be involved in this disease, at least as manifested by the HLA genes.

GENETIC DISSECTION OF JUVENILE DIABETES: THE HLA SYSTEM

Major support for the thesis that juvenile-onset diabetes and adult-onset diabetes are different genetic entities, and that juvenile diabetes itself may be heterogeneous, has come from an exciting series of recent studies of HLA antigens in diabetic subjects.

Figure 13 shows a diagram of the cluster of HLA genes on chromosome number 6 in man. You will recall that presently 4 genetic loci are recognized within the HLA or histocompatibility system. These loci are designated A, B, C and D. Each genetic locus codes for the production of a protein that is found on the surface of body cells, and that plays a major role in the rejection of transplants by delayed hypersensitivity. The genetic importance of the HLA system lies in the fact that each of these loci is genetically polymorphic. That is, many different structural forms of each HLA gene exist in the population. These different structural forms of the gene are called alleles. Since each person has two copies of the sixth chromosome, he has 2 alleles at each of the HLA loci - one on chromosome 6 derived from his mother and one on chrosome 6 derived from his father.

Each chromosome number 6 contains a specific combination of alleles at the A, B, C and D loci. The specific combination of alleles that occur on one chromosomes are called haplotypes. Each individual possesses 2 haplotypes. For example, on one chromosome No. 6 he may have allele number 2 at the A locus, allele number 8 at the B locus, allele number 12 at the C locus, and allele number DW3 at the D locus.

The HLA system has been shown to be related to a number of diseases, each of which involves a demonstrable type of organ-specific autoimmunity. In order to understand the significance of these relations, we must first understand the genetic term linkage . Linkage means that 2 genetic loci occur in close proximity on one chromosome. For example, since all of the HLA loci are on chromosome 6, they are all linked with one another. All of the genes on any chromosome are

Fig. 13. Location of the HLA genes on chromosome 6 of man

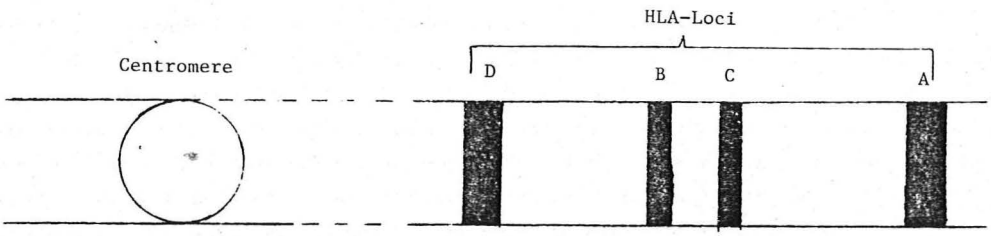


Fig. 14. Alleles at the HLA loci for which diabetics have been screened (22).

A-series	B-Series	D-series
HLA-A1	HLA-B5	HLA-Dw2
HLA-A2	HLA-B7	HLA-Dw3
HLA-A3	HLA-B8	HLA-Dw4
HLA-A9	HLA-B12	
HLA-A10	HLA-B13	
HLA-A11	HLA-B14	
HLA-A28	HLA-B18	
HLA-Aw19	HLA-B27	
	HLA-Bw15	
	HLA-Bw16	
	HLA-Bw17	
	HLA-Bw21	
	HLA-Bw22	
	HLA-Bw35	

linked to each other, but this linkage may be more or less tight depending on how close the genes are to each other on the chromosome. If they are very far apart on the chromosome, when they are transmitted to the offspring there is an excellent likelihood that a genetic recombination event will take place between them, and they will be transmitted in an independent manner. Such genes are considered to be loosely linked. On the other hand, when genes are very close together on the same chromosome, they will almost always be transmitted to the offspring in the same combination in which they were inherited, and thus they are said to be closely linked. Note that the term linkage refers only to the proximity of the genetic loci. It does not say anything about the specific alleles at those loci. The HLA-A and HLA-B loci are linked to each other in every individual, no matter which specific alleles are present at those loci.

Theoretically, considering the long duration of human evolution, the various alleles at the A, B, C and D loci should be independently distributed in the population. That is, if an individual has a certain allele at the A locus, this should not affect the allele at the B locus. This random assortment should be present since there has been ample time in evolution for crossing over to occur between all of the HLA loci so that the alleles are randomized. However, in the HLA system, such independent assortment is frequently not observed. For example, if a chromosome happens to have allele number 8 at the B locus, there is a high probability that it will also have a particular allele, namely DW 3, at the D locus. The existence of such a non-random association between two specific alleles is called linkage dysequilibrium.

The reason for the occurrence of linkage dysequilibrium is not known. At least two possibilities exist. First, the mutation that gave rise to the DW3 allele might have occurred on a chromosome that contained the B-8 allele, and sufficient time has not elapsed for crossing over events to have distributed these two alleles randomly in the population. Genetic considera tions make this unlikely, since the frequency of crossing-over within the HLA system is reasonably high, i.e., about 1%. The second hypothesis is that there is some selective advantage in having these two alleles in combination. It may be that if one has inherited the 8 allele at the B locus, one's survival is enhanced if one has also inherited the DW 3 allele at the D locus. This would produce a selective pressure to enhance the association between B-8 and DW 3 in the population.

The clinical importance of the HLA system was first deduced by analogy with a similar system that exists in the mouse. The mouse histocompatibility system is closely linked to genes on the same chromosome that control the immune response.

Moreover, certain of the histocompatibility antigens are in linkage dysequilibrium with certain alleles at the immune-response loci. Since the immune-response loci control the ability of an individual to respond to certain types of antigenic challenges, mice who have certain histocompatibility antigens, are frequently unable to respond to specific antigenic challenges.

The relevance of all of this to diabetes stems from the observation, now confirmed by several laboratories, that several HLA antigens show a striking increase in prevalence among juvenile-onset diabetics, but not among adult-onset diabetics.

In 1974 and 1975 the results of 2 studies of the association of HLA antigens with diabetes were reported - one conducted in Scandinavia (20) and one conducted in England (21). Both studies reached the same conclusion - that the incidence of 2 HLA antigens, namely HLA-A8 and HLA-BW15 was strikingly increased in patients with juvenile-onset diabetes, but was not increased in patients with maturity onset diabetes. The updated results of the Danish study have recently been presented (22). Fig. 14 shows the current HLA nomenclature used in this study, and lists the 8 antigens at the A locus, the 14 antigens at the B locus, and the 3 antigens at the D locus that were tested. Fig. 15 shows the two alleles that were increased in frequency. The HLA-B8 allele was increased from 23.7% in control subjects to 44.7% among 85 juvenile diabetics. Among 61 adult-onset diabetics the frequency of this allele was only 27.9%, a value that was no different than the control. Similarly, HLA-BW15 was increased from 17.9% in the control subjects to 32.9% in the juvenile diabetics. There was also an increase in the frequency of this allele in the maturity-onset diabetics (29.5%), but this was not statistically significant. In contrast, the HLA-B7 allele showed a statistically significant decrease in frequency among the juvenile diabetics, but not among the maturity-onset diabetics.

Fig. 16 shows the correlation of these antigens with obesity and with insulin dependency. HLA-B8 shows a striking increase only in those subjects who are nonobese or are insulin dependent, a finding in agreement with its increased frequency in juvenile diabetes. In contrast, BW15 shows some increase in all of the groups.

Another way of expressing HLA data is to calculate the relative risk that a subject incurs for developing a disease if he has a particular HLA allele as compared with his risk if he does not have that allele. The data in Fig. 17 show that patients with HLA-B8 and HLA-BW15 have 2.4-fold and 5-fold higher risks for developing insulin-dependent diabetes mellitus than do subjects without these

Fig. 15. Some HLA frequencies in patients with diabetes mellitus and in normal individuals (22).

	Control	Diabetics total	Juvenile diabetics	Maturity onset diabetics
	N = 1967	N = 146	N = 85	N = 61
HLA-B 8	23.7%	37.7%[a]	44.7%[b]	27.9%
HLA-Bw15	17.9%	31.5%[b]	32.9%[b]	29.5%
HLA-B 7	26.8%	15.8%	10.6%[c]	23.0%

Statistics: Fisher's exact test. P-values corrected for one-sidedness of the test (x2) and for the number of antigens investigated (x23).
[a] $p < 0.01$.
[b] $p < 0.001$.
[c] $p < 0.05$.

Fig. 16. HLA-B8 and BW15 in diabetes mellitus: Correlation with obesity and insulin dependency (22).

	Obesity		Insulin dependency		Controls
	No (N = 112)	Yes (N = 31)	Yes (N = 109)	No (N = 37)	(N = 1967)
HLA-B 8	46 (41.1%)	8 (25.5%)	46 (42.4%)	9 (24.3%)	(23.7%)
HLA-Bw15	36 (32.1%)	9 (29.0%)	38 (34.9%)	8 (21.6%)	(17.9%)
HLA-B 8 and/or Bw15	70 (62.5%)	14 (45.2%)	70 (64.2%)	16 (43.2%)	(39.2%)

Fig. 17. Relative risk of insulin-dependent and non insulin-dependent diabetes in HLA-B8- and BW-15-positive subjects (22).

	Insulin-dependent diabetes mellitus	Non insulin-dependent diabetes mellitus
	Relative risk	Relative risk
HLA-B 8	2.4 ($p = 1.9 \times 10^{-5}$)	1.0 (N.S.)
HLA-Bw15	2.5 ($p = 3.2 \times 10^{-5}$)	1.3 (N.S.)

Statistics: Fisher's exact test.

Fig. 18. HLA genotypes in a family including 7 cases of diabetes (black). The HLA-A_2, BW15, UPS (CW3) haplotype shared by all diabetic members of the family (and some nondiabetics) is underlined (22).

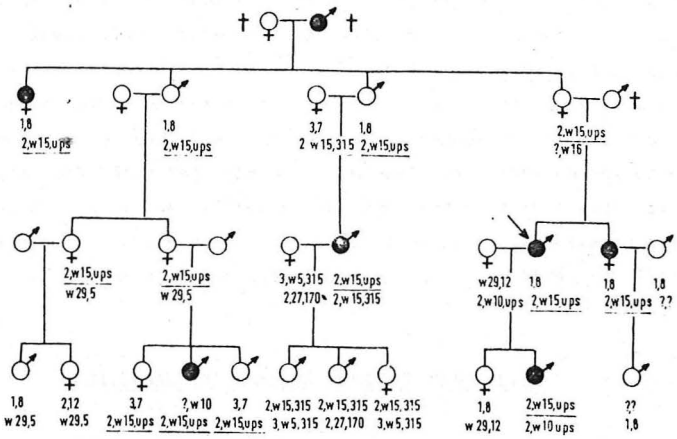


Fig. 19. Additive risk of HLA-B8 and HLA BW15 in juvenile diabetes (modified from Rimoin [23]).

Reference	Relative Risk		
	B8	BW15	B8 + BW15
Cudworth and Woodrow (24)	2.54	2.00	5.82
Nerup, et al. (22)	2.69	2.45	6.16
Borta and Simon (28)	2.03	1.17	18.25
Pooled relative risks	2.43	1.83	7.24
± Standard error	± 0.11	± 0.13	± 1.28

alleles. On the other hand, such subjects do not have a significantly increased risk for developing noninsulin-dependent diabetes mellitus. These findings have been confirmed independently by at least 2 other groups (22).

Figure 18 shows the pedigree of a family in which diabetes only occurred in those who inherited the same haplotype (i.e., only in those who inherited the same 6th chromosome). The astute observer will note that several persons in this family inherited the diabetogenic haplotype, but did not develop diabetes. However, we should not be surprised at this. The twin studies have shown that even when 2 individuals inherit all of their chromosomes in common, and one of them develops juvenile diabetes, the other one only has a 50% chance of developing diabetes. Stated another way, although the inheritance of this particular 6th chromosome appears to be necessary for the development of diabetes in this particular family, it is not sufficient. Additional environmental factors are clearly required.

ADDITIONAL INFORMATION FROM THE HLA SYSTEM

Further study of the HLA system in juvenile diabetes has disclosed findings of great interest. First, it has been demonstrated that an individual who possesses 2 copies of the B8 allele is at the same genetic risk as one who possesses one copy of the B8 allele (23). Similarly, individuals who are homozygous for the BW15 allele are at no greater risk than heterozygotes. On the other hand, individuals who inherit both the B8 and the BW15 allele have additive risks. The data is summarized in Fig. 19, adapted from a recent article by Rimoin (23). This striking finding suggests that the B8 and BW15 alleles cause susceptibility in a totally independent manner - as though one of them predisposed to an abnormal response to virus A and the other predisposed to an abnormal response to virus B.

Second, it has been found that patients with HLA-B8 associated juvenile diabetes can be distinguished on clinical grounds from patients with HLA-BW15. First, the HLA-8 form of the disease may have more severe microangiopathy. Barbosa and coworkers studied HLA antigens in a group of 110 juvenile diabetics who were undergoing kidney transplantation. They compared these data with the HLA antigens in living kidney donors, and with nondiabetic kidney recipients and healthy controls. The results showed that the HLA B8 antigen was more than twice as common among the diabetic patients as among the controls. However, the BW15 antigen showed no increased frequency among the diabetics (29). These data suggest that the HLA-B8 associated form of the disease produces more severe microangiopathy than do the other forms of the disease.

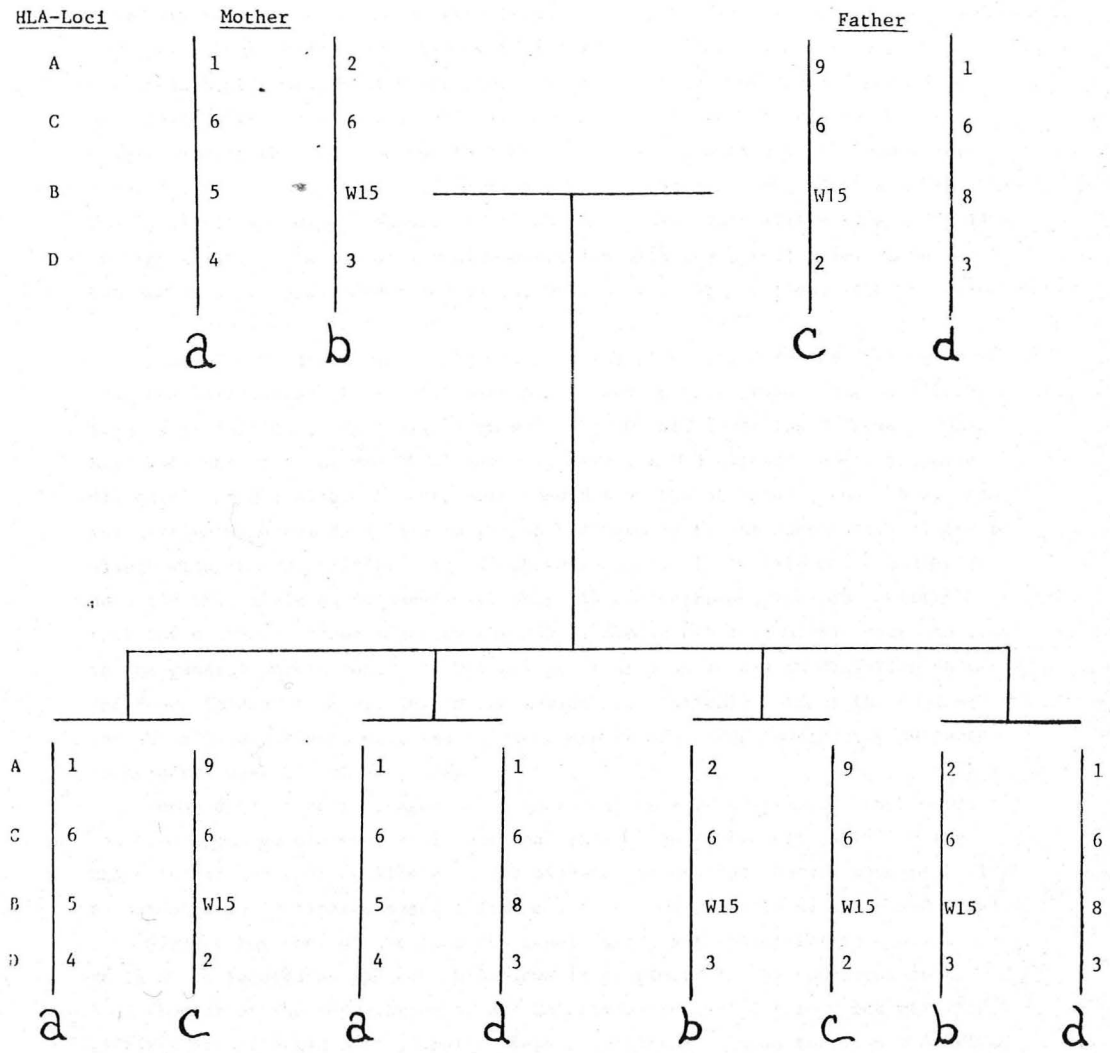
Fig. 20. Occurrence of islet-cell antibody in patients with juvenile diabetes (22)

	HLA-B8	Other HLA Types	Total
Islet-Cell	13/18	8/20	21/38
Antibody	72%	40%	55%

Fig. 21. Alleles at the HLA-D locus in juvenile diabetes mellitus (22)

	Diabetes	Controls N = 35	Relative Risk
DW3	29/50 (58%)	16%	6.4
DW4	33/75 (42%)	16%	3.7
Either DW3, DW4 or both	80%	24%	--

Fig. 22. Segregation of the sixth chromosome in a family



Certain cases of juvenile diabetes mellitus have long been known to be associated with other diseases in which organ-specific autoimmunity occurs. These include Addison's disease, pernicious anemia, Graves' disease, etc. All of these diseases are known to be associated with HLA-B8 (23), and it is not unreasonable to suppose that their association with diabetes is related to their common association with this histocompatibility antigen. In contrast, none of these diseases is associated with the BW15 allele (23). Of interest in this regard is the recent observation by the Danish group that the frequency of antibodies to pancreatic islet cells in juvenile diabetic patients is much higher among those who have the HLA B8 allele in comparison with those who don't have this allele (22). The data in Fig. 20 show that 72% of juvenile diabetics with the HLA-B8 allele have demonstrable antibodies to islet cells, whereas only 40% of those with the other HLA types, including BW 15, have such an antibody.

One of the interesting recent discoveries with regard to the HLA system is that the association of diabetes with HLA-B8 may be fortuitous. The B8 allele, itself, is in linkage dysequilibrium with the DW3 allele at the D locus. Thus, most patients with the HLA B8 allele also have the DW3 allele. Among juvenile diabetics the DW3 allele is even more common than the B8 allele, and the apparent association with the B8 allele is probably secondary to the association of the B8 allele with the DW3 allele. Fig. 21 shows that 58% of juvenile onset diabetics have the DW3 allele as compared with only 16% of controls (22). The relative risk for diabetes if one inherits the DW3 allele is 6.4 fold higher than the risk in the general population. The DW4 allele is also increased in diabetics (42% incidence in diabetics vs. 16% in the general population). Either the DW 3 or the DW4 allele, or both of these alleles, are found in 80% of diabetic patients as compared with 24% of controls.

These data strongly suggest that there exists a genetic locus whose product can predispose to diabetes mellitus; that this locus is closely linked to the HLA-D locus; and that an allele at the diabetes locus that confers susceptibility to diabetes is in linkage dysequilibrium with the DW 3 allele at the HLA-D locus.

Support for the concept that the gene causing susceptibility to diabetes mellitus is located on the 6th chromosome in proximity to the HLA locus comes from studies of the segregation of HLA haplotypes in families in which multiple siblings are affected with juvenile diabetes mellitus. These families are called diabetes multiplex families. Recall that each chromosome number 6 has a distinctive combination of alleles at the HLA locus, and thus both the maternal and paternal chromosome number 6 can be recognized in any individual (Fig. 22). Among each

Fig. 22. Segregation of the sixth chromosome in a family

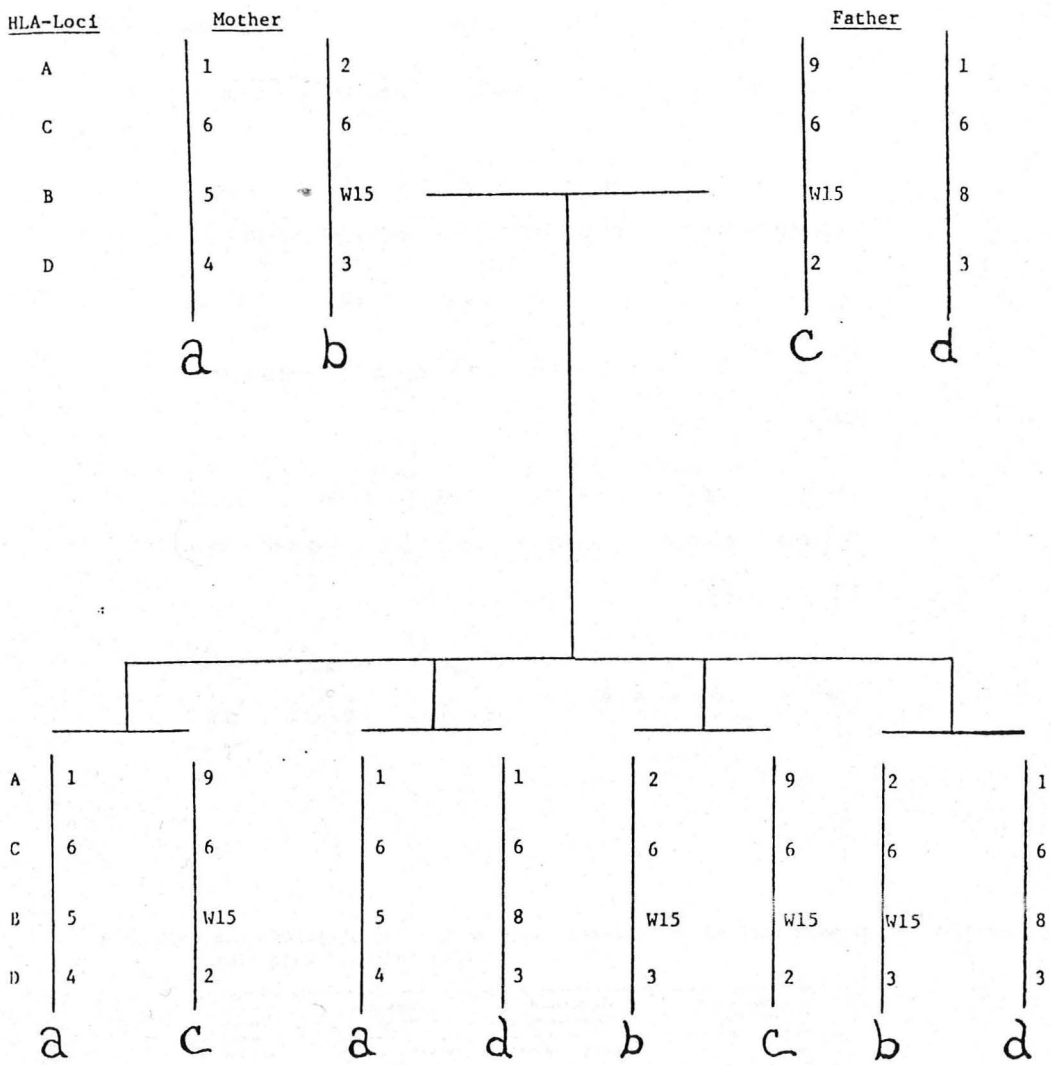


Fig. 23. Pedigrees of 24 diabetes multiplex families (25). The HLA haplotypes are abbreviated a,b,c and d.

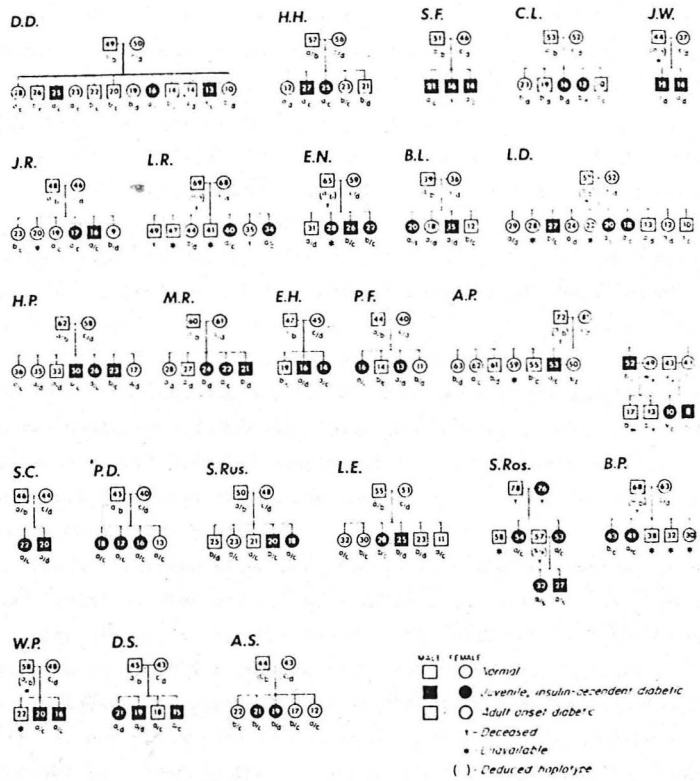


Fig. 24. HLA haplotype concordance for diabetic and healthy sibs in 24 diabetes multiplex kindreds (25).

Number of concordant haplotypes	Pairs of diabetic sibs (38)*		Pairs of diabetic-healthy sibs (112)*		Pairs of healthy sibs (86)*	
	Found	Expected	Found	Expected	Found	Expected
	%		%		%	
2	55 (21)*	25 (9.5)	22 (25)	25 (28)	28 (24)	25 (21.5)
1	40 (15)	50 (19)	51 (57)	50 (56)	48 (41)	50 (43)
0	5 (2)	25 (9.5)	27 (30)	25 (28)	24 (21)	25 (21.5)
	$P < 0.001$‡					

* Number of pairs in parentheses.
‡ Chi-square analysis. All possibilities for shared haplotypes were counted

pair of siblings, there is a 50% chance that they share the same maternal 6th chromosome, and a 50% chance that they share the same paternal 6th chromosome. There is a 25% chance that both of these chromosomes will be shared. Cudworth and Woodrow (24) originally noted that siblings with juvenile diabetes shared a common HLA haplotype more frequently than the 50% frequency that would be expected by chance. This finding was confirmed and extended by Barbosa and coworkers in a recent paper in the Journal of Clinical Investigation (25). These workers studied 24 families that contained 2 or more juvenile diabetic siblings. Fig. 23 shows these pedigrees. Fig. 24 shows that 55% of the affected siblings shared 2 HLA haplotypes in common, in contrast to the 25% expected. 40% of the siblings shared 1 haplotype in common (expected 50%) and only 5% of siblings shared no HLA haplotypes (25% expected). Stated another way, 95% of the affected pairs of siblings shared at least one HLA haplotype in common, instead of the expected 50%. In only one of the 24 families did a situation exist in which 2 diabetic siblings did not share 1 haplotype. As controls for these ratios, these workers compared the number of concordant haplotypes between diabetic siblings and normal siblings, and between pairs of healthy siblings within the population. In both of these latter instances the concordance ratio for haplotypes were precisely as predicted by Mendelian theory.

The tendency for the affected siblings to share HLA haplotypes was independent of the particular alleles at the HLA loci on these chromosomes. In other words, the particular alleles at the HLA locus on the diabetogenic 6th chromosome varied from family to family. Yet in each case one of the 6th chromosomes predisposed to diabetes. These data strongly suggest that in these families the HLA genes, themselves, do not predispose to diabetes. Rather, there must be a gene on the 6th chromosome located near the HLA genes, which predisposes to diabetes. When an individual inherits the abnormal 6th chromosome he develops diabetes. The HLA antigens only serve as markers that allow us to identify which chromosome carries the mutant gene. From the other population studies mentioned above we can speculate that the diabetogenic allele may be in linkage dysequilibrium with HLA-DW3.

Barbosa and co-workers were impressed that the number of siblings who share both 6th chromosomes was increased in the diabetic children, and they concluded that the inheritance of two abnormal 6th chromosomes gave a higher risk than the inheritance of one such chromosome. However, Rimoin recently pointed out that if two diabetic siblings are required to share one 6th chromosome, then they will have a 50% chance of sharing the second chromosome - a finding that fits the Barbosa data nicely. Thus, the Barbosa data are compatible with the conclusion

that only one copy of the diabetogenic gene is necessary to produce a susceptibility to the disease, and that the disease is then triggered by an environmental challenge. If only one copy of the gene is required one must still explain why the parent that contributed the diabetogenic 6th chromosome did not himself have diabetes. It would seem likely that some contribution from the genes of the other parent is required. Moreover, as suggested by Barbosa, two copies of the diabetogenic gene may be more dangeous than one.

Similar findings have been published recently by Rubinstein and coworkers (26). However, these investigators have interpreted their findings in such a way as to create controversy. Rubinstein and coworkers found that if one sibling had juvenile diabetes, any sibling who inherited an identical set of HLA haplotypes had a 50% chance of developing diabetes . Moreover, in several families there was a recombinational event such that the HLA D locus was separated from the A and B loci. In 3 cases siblings who were identical at the D locus, but differed at the A and B loci, developed diabetes. Therefore. Rubinstein concluded that the gene for diabetes was most strongly linked to the D locus, a finding that is compatible with data from other series noted above.

The part of Rubinstein's conclusion that is controversal relates to his description of the disease as autosomal recessive with 50% penetrance. The issue resolves around the question of whether one absolutely requires 2 genes for the expression of diabetes, or whether the inheritance of 1 abnormal 6th chromosome, and 1 normal 6th chromosome can produce the disease. As described above, Cudworth and coworkers, and Barbosa et al., observed numberous instances in which diabetes occurred in siblings who shared only 1 HLA haplotype. They therefore concluded that the heterozygous state was compatible with the disease. On the other hand, even though he observed a similar finding, Rubinstein suggests that finding could have been possible if one of the parents had been a homozygote for the recessive gene at the diabetes locus, and thus the transmission of either of his chromosomes would produce the disease. Since the penetrance of the disease is postulated to be only 50%, it is possible that one of the parents should have been homozygous for the diabetes gene but not have expressed diabetes.

The issue cannot be absolutely resolved at present. However, in reviewing the literature, I would summarize the juvenile diabetes story as follows:

1) There is a genetic locus that predisposes to juvenile onset diabetes mellitus. This locus is on chromosome 6 near the D locus of the HLA system. In the general population, several alleles are present at this locus. Some of these alleles are dominant, i.e., they can produce diabetes when present in a single

dose. Other alleles require the presence of an abnormal allele at the corresponding site on the other 6th chromosome in order to produce diabetes.

2) One of the alleles that strongly predisposes to diabetes is in linkage dysequilibrium with the DW3 allele at the D locus. Hence, individuals who inherit the DW3 allele have a higher risk of inheriting the diabetes gene. Similarly, this allele, or another allele, is in linkage dysequilibrium with the DW4 allele. Finally, an additional diabetic allele is in linkage dysequilibrium with HLA BW15. This allele may be at the same locus as the D-linked diabetic locus or at a different locus.

3) Individuals who inherit two chromosome 6's that each bare diabetogenic alleles are at extreme risk for developing juvenile diabetes mellitus. Nevertheless, even in the face of this strong genetic predisposition, an environmental insult is required.

The implications of these findings for genetic counseling in juvenile diabetes will be discussed below.

MATURITY ONSET DIABETES OF YOUNG PEOPLE (MODY)

Time does not permit an extensive discussion of this topic. However, no discussion of the genetics of diabetes would be complete without its mention. Tattersall and Fajans (27) studied the families of 26 subjects who developed so-called maturity onset diabetes of young people (MODY). A patient with MODY was defined as one in whom diabetes was diagnosed before the age of 25 years, and in whom fasting hyperglycemia, if present, could be normalized for more than 2 years without insulin. When these subjects were identified, Tattersall and Fajans found that diabetes could be traced through their families as a clear-cut autosomal dominant trait, with 50% of relatives affected. Although, these patients are detected as juveniles, they differ from classic juvenile onset diabetics in that they do not show a long-term requirement for insulin. On the other hand they differ from adult onset diabetics in 2 respects: First, they are of normal weight; and second, the age of onset tends to be below age 40.

The diabetes in this patients is extremely mild. Retinopathy and vascular disease are rare. It is generally a chemical diagnosis. For this reason some investigators prefer the term MOHY (maturity onset hyperglycemia of the young).

The studies of Fajan's families have been repeated with families from London (28), and it is generally accepted that this autosomal dominant biochemical abnormality does exist.

The major unresolved question is: How common is this entity? Is is possible that a significant proportion of adult-onset diabetics are really patients with MODY? Although these questions are not yet answered, the existence of MODY may explain many of the apparent autosomal dominant pedigrees for diabetes that have appeared in the literature.

Classification of Diabetes Mellitus - 1978

Type	Probable Mode of Inheritance	Factors Responsible For Penetrance
I. Adult-Onset (nonketotic)	Multifactorial (mostly genetic)	Obesity
II. Juvenile-Onset		
A. Ketotic		
1. HLA-B8 (DW-3)	Dominant	Auto-immunity
2. HLA-BW15	Dominant	? Viral infection
3. HLA-B8 (DW3) + HLA-BW15	Overdominant	Auto-immunity +/- virus
B. Non-ketotic (MODY)	Dominant	None
III. Associated with other genetic diseases	Dominant or Recessive	Variable

REFERENCES

1. Neel, J.W., Fajans, S.S., Conn, J.W., and Davidson, R.T.: Diabetes mellitus. In Neel, J.V., Shaw, M., and Schull, W.: Genetics and Epidemiology of Chronic Diseases. US Department of Health, Education and Welfare, Public Health Service, 1965.
2. Pincus, G., and White, P.: On the inheritance of diabetes mellitus. Am. J. Med Sci, 186:1, 1933.
3. Rondelet, G.: Opera omnia medica, Chouet, Geneva, cited in Rimoin, D.L. and Schimke, R.N., Genetic Disorders of the Endocrine Glands, St. Louis, C.V. Mosby Co., 1971, pg. 152.
4. Pincus, G., and White, P.: On the inheritance of diabetes mellitus. II. Further analysis of family histories. Am. J. Med. Sci. 188:159, 1934.
5. Pincus, G., and White, P.: On the inheritance of diabetes mellitus. III. The blood sugar values of the relatives of diabetics. Am. J. Med. Sci. 188:782, 1934.
6. Kahn, C.B., Soeldner M.D., Gleason, R.E., et al.: Clinical and chemical diabetes in offspring of diabetic couples. New Engl. J. Med. 281:343, 1969.
7. Tattersall, R.B., and Fajans, S.S.: Prevalence of diabetes and glucose intolerance in 199 offspring of 37 conjugal diabetic parents. Diabetes 24:452, 1975.
8. Burnstein, N., and Patterson, M.: Heredity in diabetes: Report of five generations of a diabetic family. Southern Med. J. 42:119, 1949.
9. Simpson, N.E.: Multifactorial inheritance: A possible hypothesis for diabetes. Diabetes 13:462, 1964.
10. Simpson, N.E.: The genetics of diabetes mellitus - A review of family data. In Creuzfeld, W., Kobberling, J., and Neel, J.V.: The Genetics of Diabetes Mellitus, New York, Springer Verlag, 1976, pp. 12-20.
11. Neel, J.V., Diabetes mellitus - A geneticist's nightmare. In Creuzfeld, W., Kobberling, J., and Neel, J.V.: The Genetics of Diabetes Mellitus, New York, Springer Verlag, 1976, pp. 1-11.
12. Kobberling, J.: Studies on the genetic heterogeneity of diabetes mellitus. Diabetologia 7:46, 1971.
13. Simpson, N.E.: The genetics of diabetes: A study of 233 families of juvenile diabetics. Ann Hum. Genet. London 26;1, 1962.

14. MacDonald, M.J.: Equal incidence of adult-onset diabetes among ancestors of juvenile diabetics and nondiabetics. Diabetologia 10:767, 1974.

15. Kobberling, J.: Genetic heterogeneities within idiopathic diabetes. In Creuzfeld, W., Kobberling, J., and Neel, J.V.: The Genetics of Diabetes Mellitus, New York, Springer Verlag, 1976, pp. 79-94.

16. Tattersall, R.B., and Pyke, D.A.: Diabetes in identical twins. Lancet ii:1120, 1972.

17. Pyke, D.A., and Nelson, P.G. Diabetes mellitus in identical twins. In Creuzfeld, W., Kobberling, J., and Neel, J.V.: The Genetics of Diabetes Mellitus, New York, Springer Verlag, 1976, pp. 194-202.

18. Johansen, K., Soeldner, J.S., Gleason, R.E., et al.: Serum insulin and growth hormone response patterns in monozygotic twin siblings of patients with juvenile-onset diabetes. New Engl. J. Med. 293:57, 1975.

19. Nelson, P.G., Pyke, D.A., and Gamble, D.R.: Viruses and the aetiology of diabetes: A study in identical twins. Br. Med. J. 4:249, 1975.

20. Nerup, J., Platz, P., Andersen, O.O., et al.: HL-A antigens in diabetes mellitus. Lancet ii:864, 1974.

21. Cudworth, A.G., and Woodrow, M.D.: HL-A system and diabetes mellitus. Diabetes 24:345, 1975.

22. Nerup, J., Platz, P., Andersen, O.O., et al.: HLA, autoimmunity and insulin-dependent diabetes mellitus. In Creuzfeld, W., Kobberling, J., and Neel, J.V.: The Genetics of Diabetes Mellitus, New York, Springer Verlag, 1976, pp. 106-114.

23. Rotter, J.I., and Rimoin, D.L.: Heterogeneity in diabetes mellitus - Update, 1976. Diabetes 27:599, 1978.

24. Cudworth, A.G., and Woodrow, A.G.: Evidence for HLA-linked genes in "juvenile" diabetes mellitus. Br. Med. J. 3:133, 1975.

25. Barbosa, J., King, R., Noreen, H., and Yunis, E.J.: The histocompatibility system in juvenile insulin-dependent diabetic multiplex kindreds. J. Clin. Invest. 60:989, 1977.

26. Rubinstein, P., Suciu-Foca, N., and Nicholson, J.F.: Genetics of diabetes mellitus: A recessive gene closely linked to HLA-D and with 50 per cent penetrance. New Engl. J. Med. 297;1036, 1977.

27. Tattersall, R.B., and Fajans, S.S.: A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. Diabetes 24;44, 1975.

28. Barta, L., and Simon, S.: Role of HLA-B8 and BW15 antigens in diabetic children. New Engl. J. Med. 296:397, 1977.

29. Barbosa, J., Noreen, H., Emme, L., et al.: Histocompatibility (HLA) antigens in diabetic microangiopathy. Tissue Antigens 7:233, 1976.

30. Falconer, D.S., Duncan, L.J.P., and Smith, C.: A statistical and genetical study of diabetes. Ann. Hum. Genet., London, 34:347, 1971.

31. Rimoin, D.L., and Schimke, R.N.: "Genetic Disorders of the Endocrine Glands", St. Louis, C.V. Mosby Co., 1971, pg. 159.