Heredity in Diabetes Mellitus

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Pincus and White[1] and William Allan[2] were the first to examine by quantitative methods the nature of the genetic factor in the causation of diabetes mellitus. They concluded that susceptibility to diabetes is due to a recessive gene. They found no evidence to cause them to distinguish between the severe, brittle diabetes with onset usually before the age of thirty, and the more benign diabetes which occurs in older patients. Other investigators were reluctant to accept these conclusions, presumably because diabetes is so variable in its clinical expression.

These fine pioneer investigations were followed by a series of studies, too numerous to be reviewed here, leading to several different conclusions.

Some examples of the larger studies will illustrate my point. Cammidge[3,4] scanned the pedigrees of 1,000 diabetic patients and concluded that severe diabetes with early onset (juvenile diabetes) is due to a recessive gene, while mild diabetes with late onset is due to a dominant gene, presumably at a different locus. Harris[5] and Lamy, Frézal, and de Grouchy[6] concluded that early onset diabetes is due to homozygosis for a gene which leads to late onset diabetes when heterozygous. Levit and Pessikova[7] and von Kries[8] believe, on the basis of their studies, that susceptibility to diabetes is due to a dominant gene with incomplete penetrance (i.e., some of those carrying the gene do not develop diabetes). Grunnet,[9] using life table methods, concluded from his study of the families of 261 probands that some of the mild cases of diabetes in elderly individuals are probably nongenetic and that a majority of the severe cases are probably due to a recessive gene. Grunnet fails to state what causes the remainder of the cases. As I have stated elsewhere,[10] the reasons for Grunnet's conclusions are not apparent from his analysis. There have been many other studies of early and late onset diabetes but the conclusions of all of them fall into some one of the above categories. I have reviewed the data from many of these studies in previous reports[10-12] and have there given reasons for concluding that all available data which have been presented in a manner to permit appropriate re-analysis may be explained on the assumption that a recessive gene causes susceptibility to diabetes and cannot be explained by any other simple hypothesis.

I may remark, in passing, that I am unaware of any genetic studies having been done on the J-type of diabetes (onset in young, thin individuals, insensitivity to insulin, and absence of ketosis) reported by Hugh-Jones[13] and by Cosnett.[14] It is to be hoped that this deficit will soon be remedied.

The varied nature of diabetes, the great variation of the age at onset, the profound variation in its severity, its sensitivity to emotional stress and to nutritional status, all contribute to make it a most difficult character for the geneticist to analyze. Indeed, even its relatively great frequency contributes to the complexity of the analysis. If we had very large samples and excellent vital statistics data, we could probably correct for variable age at onset and compute the true expected frequency of diabetes among the sibs of patients from families in which neither, one, or both parents are diabetic. We might also correct for failure to detect diabetes in a prediabetic parent. These corrected figures could be compared with those called for by genetic theory. We do not have the necessary data for such calculations. Alternatively, and preferably, we could make an accurate analysis if we had a method for detecting the prediabetic. Conn and his colleague, Fajans,[15,16] report that the cortisone stressed glucose tolerance test is such a method. Unfortunately, although they apparently have much family data,[16] none of it has been reported in a form which can be analyzed from the genetic viewpoint. Furthermore, there is evidence in papers by Fajans and Conn,[16] by West,[17,18] and by Jackson[19] that prediabetics may have a normal cortisone stressed glucose tolerance test. Drs. I. Zeytin and Priscilla White have kindly permitted me to quote their unpublished data concerning four patients who had a diabetic response to the standard glucose tolerance test and a normal response to a cortisone stressed glucose tolerance test given some time later.

In a paper which appeared in 1959 I wrote, "It would be of interest to know how the frequency of abnormal glucose tolerance tests varies with the age of those

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tested."[10] Such data will permit us to evaluate the effectiveness of the test. If prediabetics are detected with equal facility regardless of how close they are to becoming frank diabetics, the frequency of positive tests should be independent of age. If only those relatively close to becoming diabetic can be detected, the frequency of positive tests should increase with age. West[17,18] and Jackson[19] report that young individuals are less responsive to the glucose tolerance test and to the cortisone stressed glucose tolerance test than are older individuals. Jackson[19] summarizes his conclusions concerning his experience with the cortisone stressed glucose tolerance test as follows:

"1. The mean rise in the tolerance curve after administration of cortisone in apparently normal people over forty-five years of age is higher than in those under forty-five (confirming West's finding[17]).

"2. The mean rise in normal pregnant women is higher than in nonpregnant controls.

"3. A proportion of mild diabetics show no rise at all after cortisone.

"4. A high proportion of patients who are almost certainly prediabetic (on obstetric grounds and/or on account of both parents or an identical twin being diabetic) give negative responses.

"It would therefore appear that although this test may be of some value in indicating the potential diabetic, it frequently fails to do so, whereas in older people or during pregnancy it may appear falsely positive unless the criteria of abnormality are raised."

The available evidence seems to indicate that the cortisone stressed glucose tolerance test may give false positive as well as false negative results.

At present we have no adequate method to correct the family samples for the variable age at onset, nor do we have a method for detecting prediabetics for genetic analysis. Fortunately, we may analyze the data, albeit without the sensitivity we would like, without these desirable aids. It can be shown[11,20] that the relative frequencies of matings with neither, one, and both partners affected among the parents of individuals homozygous for a recessive gene is as p^2: $2pq$: q^2, respectively, where q equals the frequency of affected parents. These frequencies are independent of age at onset and of present age. The data from seven samples have been tested in this way. The results are shown in table 1.

We must agree with Pincus and White[1] and with Allan[2] that susceptibility to diabetes mellitus is due to a recessive gene. As I have stated earlier, there is reluctance on the part of many to accept this simple hypothesis, because of the great variability in the expression of the disease. This variation may simply be the variable expression of the effect of the gene causing the disease. I have discussed and illustrated this elsewhere.[22] This implies that diabetes is basically a unitary disease and is in accord with the view held by many physicians. Jackson[19] has stated it this way: "Although the mild obese diabetic and the severe ketosis-prone diabetic are very different clinically, both have the same obstetrical complications and their fetuses are subject to the same embryopathy both in their prediabetic and their overtly diabetic years. The basic similarity between these two types of diabetic is further shown by their similar modes of inheritance, their appearance together in the same family, and the proneness of both types to the same degenerative vascular disease."

While it seems reasonable to conclude that all major studies indicate that susceptibility to diabetes is due to homozygosis for a recessive gene, we have no evidence that susceptibility in every case is due to homozygosis for the same recessive gene. It is possible that in some, susceptibility to diabetes is due to genotype d_1d_1, in others to d_2d_2, etc., where d_1 and d_2 indicate different genes.

TABLE 1

Comparison for seven sets of data of expected numbers of each of three kinds of matings yielding diabetic offspring with the observed numbers. The expected numbers are computed on the assumption of recessive heredity.

No. of diabetic parents	Steinberg and Wilder[11]		Pincus and White[1]		Allan[2]		Harris[5]		Thompson and Watson[21]		von Kries[8]		Lamy et al.[9]	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
0	1,589	1,588.6	440	440.6	124	122.8	1,124	1,119.1	1,404	1,408.2	1,137	1,135.0	439	437.1
1	370	370.8	80	78.8	17	19.4	109	118.8	223	214.6	160	164.1	58	61.7
2	22	21.6	3	3.6	2	0.8	8	3.1	4	8.2	8	5.9	4	2.2
Total	1,981	1,981.0	523	523.0	143	143.0	1,241	1,241.0	1,631	1,631.0	1,305	1,305.0	501	501.0
ψ^2_1	0.009		0.119		2.109		8.573		2.492		0.885		1.703	
P.	>0.90		>0.70		>0.10		<0.01		>0.10		>0.30		>0.20	

Such a situation is not unprecedented in man. Elliptocytosis,[23] for example, has been shown to be due to at least two different genes.

Unfortunately, no evidence concerning the number of loci leading to susceptibility to diabetes may be derived from the published data, because in collecting the data each family is found via a diabetic child. This means that each parent must carry at least one recessive allele of the same gene present in the homozygous condition in the child, i.e., both carry d_1 or d_2, etc., so that the child may be d_1d_1, d_2d_2, etc.

I have on previous occasions stated that the method most likely to distinguish between the alternatives of a single locus versus two or more loci is to follow the offspring of families in which both parents are diabetic, the families having been selected via the parents without prior knowledge of the condition of the children. If only one locus is concerned, all children should be liable to diabetes and, if followed to a sufficiently advanced age, at least one child in each family should become diabetic. Furthermore, if the number of offspring is large (say 200) it should be possible to estimate the number who are expected to be diabetic. The required data are the distribution of the ages of the offspring and the distribution of the age at onset of diabetes in a large, randomly selected group of diabetics. If two or more loci are involved there should be many families with no diabetic children and the observed frequency of diabetic children should be significantly lower than the computed number.

West[18] has recently published data for ten families which appear to have been ascertained via the parents, although he does not state this explicitly in his paper. His table 1 shows fasting hyperglycemia in one or more children in five of the ten families. One or more children showing an abnormal glucose tolerance test, or an abnormal cortisone stressed glucose tolerance test, or both, were found in four additional families. Thus, nine out of the ten families had at least one child with diabetes or an abnormal glucose tolerance test. In the one family in which this was not so, only one offspring, aged thirty, was examined. He was tested by a prednisone stressed glucose tolerance test, but not by a standard or a cortisone stressed glucose tolerance test. West's data support the view Dr. Russell Wilder and I expressed in 1952,[11] that the vast majority of cases are due to a simple recessive mutation at one locus. However, more data are required and my colleagues and I are collecting them. It would help if others in a position to do so would collect records of families in which both parents are diabetic; *the families being found via the parents, with no previous knowledge of the health of the children.*

I have recently developed equations which may be used with appropriate data to determine if more than one locus is concerned in determining a recessively inherited character, and, if so, to estimate how many loci are involved. The equations are complex and need not be presented here. They will be published in detail elsewhere.[24] The data required to permit their application to diabetes are: (a) the frequency with which diabetes occurs among the first cousins of diabetic patients, both of whose parents are nondiabetic (other families could be used, but they would require a modification of the equations and the collection of additional data); (b) the age distribution of all the first cousins, diabetic and nondiabetic; (c) the distribution of the age at onset of diabetes among a large random sample of diabetics in the general population; (d) an accurate estimate of the number of diabetics in the population; and (e) the age distribution of the population. Such data may be collected in countries with socialized medicine and plans are under way to collect them in Scotland.

If we accept the hypothesis that most, if not all cases of diabetes are due to homozygosis for the same recessive gene, we can estimate the frequency of the gene in the population and, using this estimate, the probability that various relatives of a diabetic patient would be liable to diabetes (Steinberg[12,25]). It is estimated that the gene frequency is about 22 per cent, and that about 5 per cent of our population is genetically liable to diabetes.[11] Since only about 2 per cent of the population is diabetic (detected and undetected, Joslin et al.[26]), it follows that the frequency of the disease may be expected to increase as our population ages. Table 2, from Steinberg,[12] presents a summary of the probability of being genetically liable to diabetes (*dd*) as a function of the relationship to a diabetic patient. The risk runs from less than 20 per cent to 80 per cent. The table does not include the risks incurred when a sib is diabetic because these are clearly 25, 50, and 100 per cent if neither, one, or both parents are diabetic.

While it is of some use to be able to offer probabilities of being liable to diabetes, it would be much more satisfactory to be able to detect the prediabetic; failing that, it would be gratifying to be able to predict ages at onset, and to be able to say that after a given age the risk is essentially nil. The possibility of doing this was raised by Woodyatt and Spetz[27] who concluded from their study of 100 pairs of parent and child diabetics that the average age at onset decreases twenty years per generation, and that a child would rarely, if ever, become diabetic at a greater age than had his parent. This is known as anticipation. Steinberg and Wilder[28] showed that,

TABLE 2

Probability that an individual will be genetically liable to diabetes if he has one or more diabetic relatives*

Probability that person is genetically liable to diabetes†	Diabetic relatives
Up to and including 20 per cent	1. First cousin 2. Uncle or aunt 3. One grandparent 4. Two grandparents (spouses) or one affected parent
30 to 40 per cent	1. Two grandparents (not spouses) 2. One parent and first cousin on nondiabetic parent's side
50 to 80 per cent	1. One parent and a sib of the nondiabetic parent 2. One parent and a parent of the nondiabetic parent 3. One parent, a sib, and a grandparent via the nondiabetic parent

*Relatives refer to parents, grandparents, aunts, uncles, and first cousins.

† Within each group the relatives are listed so as to yield an increasing probability that the person is "dd." Thus, an individual with only a first cousin diabetic (1 of the first group) has the lowest probability of being "dd" while a person with one parent, a sib, and a grandparent via the nondiabetic parent (3 of the last group) has the highest probability of being "dd."

among children of diabetics, the younger age at onset of diabetes is a statistical and not a biological phenomenon. These conclusions were based on an analysis of 200 parent-child pairs for which the ages at onset were known for both parent and child.

More recently I analyzed[10] the data published by Steinberg and Wilder[11] in their paper on the genetics of diabetes. They presented data for 301 parent-child pairs; these included the 200 pairs previously reported.[28] Table 3 presents a summary of these 301 pairs. Onset was in a prior decade of age in 63.4 per cent of the offspring. Hence, as Woodyatt and Spetz[27] reported, prior onset occurs in the majority of the diabetic children of diabetic parents. It may be demonstrated, however, that this frequency of prior onset is precisely what would be expected if we assume that there is no biological relation between the age at onset in parent and child.[28]

The calculations are illustrated in table 4. The expected frequency of children with prior onset for each decade of onset in the parent is obtained by multiplying the value for the proportion of parents with onset in a given decade by the percentage of all diabetics with onset before that decade. Thus, for parents with onset during the fifth decade (forty to forty-nine years), the expected percentage of children with prior onset is $.169 \times .316 \times 100 = 5.3$ per cent. If this operation is repeated for

TABLE 3

Number of patients whose age at onset was in a decade prior to that at onset of the diabetic parent (Data from Steinberg and Wilder[11])

Age of parent at onset	Total no. of parent-child pairs	No. of patients with onset in a prior decade of life
20-29	3	1
30-39	15	5
40-49	51	18
50-59	93	43
60-69	85	71
70-79	41	40
80-89	13	13
Total	301	191

$$\text{Per cent prior onset} = \frac{191}{301} \times 100 = 63.4$$

TABLE 4

Derivation of the expected frequency of prior onset among 301 patients (values are in per cent)

Age, years	Cumulative distribution of age at onset*	Distribution of age at onset among 301 parents	Expected frequency of prior onset in the children
0-9	4.9	—	—
10-19	11.8	—	—
20-29	19.4	1.0	0.1
30-39	31.6	5.0	1.0
40-49	54.1	16.9	5.3
50-59	81.1	30.9	16.7
60-69	96.4	28.2	22.9
70-79	98.8	13.6	13.1
80-89	100.0	4.3	4.2
Total		99.9	63.3

* Based on data of 12,740 patients published by Joslin et al.[26]

the sets of parents with onset in each of the decades, the total expected frequency may be derived. This frequency, 63.3 (table 4), is almost identical with the observed frequency, 63.4 (table 3).

It has been shown that neither the diabetic nor the prediabetic state in the mother influences the age at onset or the probability of occurrence of diabetes in the child (Steinberg and Wilder,[28] Steinberg[10]). Table 5 presents a summary of the data evaluating the possibility of a maternal effect on the age at onset in the child. Table 6 presents the data showing the frequency of diabetes among the sibs of the probands as a function of the sex of the diabetic parent.

In the sample of diabetic parent-child pairs the mean difference between the ages at onset of the parents and the probands is nineteen years. It may be shown by calculations similar to, but more detailed than those illustrated

TABLE 5

Age at onset and frequency of prior onset vs. diabetic parent

Diabetic patients		Diabetic parent Mother (186)	Father (115)
Per cent with prior onset		63.4	63.5
Mean age at onset in years	(a)*	49	48
	(b)*	42	39

*(a) All patients with a diabetic parent.
(b) Patients whose diabetic parents became ill before age fifty: forty-four mothers, twenty-three fathers.

TABLE 6

Frequency of diabetes among the sibs of diabetic patients as a function of the sex of the diabetic parent*

Diabetic parent	Number of patients	Sibs Total	Diabetic No.	Diabetic Per cent
Mother	220	1,000	113	11.3
Father	150	620	72	11.6
Total	370	1,620	185	11.4

* Data from Steinberg and Wilder.[11]

in table 4 that the expected advance in age (assuming independence of age at onset of parent and child) is also nineteen years.[28]

We may conclude that anticipation has no biological significance, that the prediabetic state in the mother does not influence the condition of her child with reference to diabetes, and that we cannot use the parent's age at onset to predict the child's age at onset or the end of the period of risk for the child.

Various investigators[5,6,11] have reported a correlation between the age at onset of diabetes in the proband and in his affected sibs. Harris[5] showed, for his sample, that, assuming no correlation of the age at onset between the proband and the sibs, an apparent spurious correlation of 0.401 would be obtained, because of the curtailing of the distribution due to the lower average age of the sibs of the probands with early onset. The observed correlation (0.695) was, however, significantly greater than the expected (0.401). This led Harris to conclude ". . . that sibs of the early-onset diabetics are very much more likely to develop diabetes in childhood or early adult life than are the sibs of the late-onset diabetics." Steinberg and Wilder[11] also found a significant correlation between the age at onset of the probands and that of their affected sibs, albeit a significantly lower one than that reported by Harris (0.549 vs. 0.695). These authors agreed with Harris that a large portion of the observed correlation was probably spurious because of the similarity in age between the probands and their sibs. They pointed out, however, that much, if not all, of the correlation not accounted for by the distribution of the age of the probands and their sibs may arise ". . . from the peculiarities of establishing the presence of diabetes. For example, if diabetes is diagnosed in a child or young adult living at home, it is probable that others in the home will be examined for diabetes. Therefore, even mild diabetes, which might otherwise continue for a long time before diagnosis, would be detected soon after its onset. Among older persons who had already left home this would be less likely to occur. Other factors are the probable greater accuracy of knowledge of sibs when the patient is young than when the patient is old and the greater similarity of environment between the patients and sibs when the patient is young. The problem requires an intensive investigation of the method of ascertaining the age at onset in the different families. It has characteristics in common with those encountered in 'anticipation' and may very well have no greater biological significance than was shown to be the case for 'anticipation.'" We must conclude that we have no satisfactory way of predicting age at onset. It is worth noting also that a significant correlation of 0.30 (the difference between the spurious and the observed correlations reported by Harris) reduces the total variance by only 9 per cent and hence would hardly be expected to cause sibs of the early-onset diabetics to be "very much" more likely to develop diabetes in childhood or early adult life than are the sibs of the late-onset diabetics.

In summary, it appears that we may be reasonably certain that susceptibility to diabetes mellitus is, with rare exceptions,[10,29] due to homozygosis for a recessive gene; that we have some evidence[18] that only one recessive gene is involved; and that age at onset is not influenced by diabetes in the parent, nor in all probability is it correlated with the age at onset in a diabetic sib.

ADDENDUM

Since this paper was delivered, Dr. Gordon Allen of the National Institute of Mental Health has correctly called my attention to the fact that the method of analysis used by Steinberg and Wilder (1952) is fundamentally a test for random mating (mating without regard to the presence of diabetes) among the parents of the diabetic probands, and not purely a test for the frequency of affected offspring among the different matings as Dahlberg and Hultkranz (1929), who originally derived the method, and as the author, who rederived it independently, believed.

We must conclude, therefore, that simple recessive inheritance, while probable, is not yet proved. The analyses excluding dominant and sex-linked inheritance remain valid.

SUMMARIO IN INTERLINGUA

Hereditate in Diabete Mellite

Il pare satis certe (1) que le susceptibilitate de disveloppar diabete mellite es — con rar exceptiones — le effecto de homozygose pro un gen recessive, (2) que nos es justificate a interpretar le datos a significar que solmente un gen recessive es interessate, a (3) que le etate del patiente al tempore del declaration del morbo non es influentiate per le presentia de diabete in le parente o correlationate con le etate al qual diabete mellite se declara in un fraterno.

ADDENDUM

Depost le presentation de iste discurso, Dr. Gordon Allen del Instituto National de Sanitate Mental ha correctemente portate a mi attention le facto que le methodo de analyse usate per Steinberg e Wilder (1952) es fundamentalmente un test pro le conjugation aleatori (i.e. conjugation sin reguardo al presentia o absentia de diabete) del parte del parentes de probandos diabetic e non purmente un test pro le frequentia de prole afficite de diabete in diverse conjugationes, como Dahlberg e Hultkranz (qui primo—in 1929—derivava le methodo) e como le autor (qui derivava le methodo independentemente) lo credeva.

Per consequente, nos debe concluder que un simple hereditage recessive—ben que probabile—es non ancora provate. Le analyses que exclude le possibilitate de hereditage dominante e de hereditage ligate al sexo remane valide.

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