Tentative Explanation of the High Incidence of Diabetes

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INTRODUCTION

From the point of view of population genetics and evolution, the high incidence of diabetes mellitus presents a problem. In almost all modern populations it is considered a "common" disease, and it has been well known since ancient times in areas as widely separated as China, India, Palestine and Europe.[1] Nevertheless it has been killing sufficient numbers—prior to the development of modern therapy—at early enough ages (i.e., before the end of the reproductive period) to have been making a constant drain on the frequency of the gene or genes which are assumed to produce it.

Present consideration of this problem rests on conclusions presented in an editorial of DIABETES (*1*:307, 1952), principally that (1) predisposition to diabetes in a great majority of pedigrees is inherited as a simple Mendelian recessive; and that (2) the frequency of the diabetes-producing genotype (which may be termed *dd*) in the United States today is estimated at about 5 per cent, and the disease incidence at about 1 per cent. Thus about one *dd* person in five develops the disease—i.e., penetrance of the genotype is about 20 per cent.

Most genetically determined diseases are rare. Unless favored by selection the incidences of the provocative genes are low multiples of their mutation rates, reflecting the low reproductive rates of the affected persons. Maximum estimates of the mutation rates of human genes are only 6 to 8 per 100,000 per generation.[2] These figures fall far short of the frequency of the gene *d* estimated above at 22,400 per 100,000 (the square root of 5 per cent, which is the estimated frequency of the genotype *dd*).

No explanation of evolutionary change in gene frequency of such magnitude is adequate except that of a very strong force or forces of positive selection.

The presence of such a force is suggested by various published series of data aggregating several thousands on the sizes of families having *Dd* and *dd* parents. In three types of matings—(A) both parents diabetic, (B) one parent, and (C) neither parent diabetic—these data indicate a positive association between *dd* parents and family size, as noted by Steinberg.[3] Unfortunately for the present purpose the data are biased in that all families were selected for having at least one diabetic child, but a correction of this bias (which cannot be made properly from all of the series as published) would tend to increase the apparent association rather than to diminish it. In the following summary (table 1) it is noted that the average number of living offspring from mating types (A), (B) and (C) are respectively 5.3, 5.0 and 4.5.

The association between the number of parents who are diabetic and the number of children they produce has been cited as evidence that higher parity may precipitate diabetes in women who are potentially diabetic.[4] Such induction has also been termed, in effect, 'not yet proven,'[5] and it is clear that the mere fact of association between two variables does not prove that one is cause and the other is effect.

Admittedly the data of table 1 are unsatisfactory for several reasons. They include no matings of *DD* parents. They make no distinction in the parents' sex, so that the relative procreative success of *dd* mothers and fathers cannot be compared. They were collected in part before, in part after the development of insulin therapy. The average sizes of families proceeding from all three types of matings are large. (This may be explained in part, however, by the facts that most families were larger one or two generations ago than today, that many of these families were rural, and that each had at least one child, i.e., there were no childless families.) The shortcomings may be explained largely by the fact that the data were collected to demonstrate genetic phenomena and not differential fertility.

Another large body of data showing association between diabetes and family size which is not included in the table is that of Pyke.[4] He reported that 394 mothers with diabetes onset at forty-five or over, having at least one child surviving its first year, averaged over 3.2 live births per woman, contrasted with an average of slightly

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TABLE 1

Average number of children in families having at least one diabetic child for three types of matings

Author	(A) Both Parents Diabetic			(B) One Parent Diabetic			(C) Neither Parent Diabetic		
	Number of families	Total children	Average size	Number of families	Total children	Average size	Number of families	Total children	Average size
Steinberg & Wilder 1952	22	122	5.6	370	1,990	5.4	1,589	8,253	5.2
von Kries 1953	8	35	4.4	160	663	4.1	1,137	4,877	4.3
Harris 1950	8	43	5.4	109	484	4.4	1,124	4,541	4.0
Thompson & Watson 1952	4	28	7.0	166	937	5.6	828	4,664	5.6
Pincus & White 1934	(2 or 3)			81	380	4.7	440	1,935	4.4
White 1932	2	4	2.0	33	101	3.1	491	1,453	3.0
Totals	44	232		919	4,555		5,609	25,723	
Pooled Averages			5.3			5.0			4.6

under two live births for English and Welsh women having at least one child surviving its first year according to the 1951 census. Smaller bodies of data have also sustained the association[6, 7, 8] and none is known which refutes it. Until the relationship between diabetes and pregnancy is better understood, however, the conclusion that the *dd* genotype increases fertility must be considered suggestive rather than definitive.

If it be true that diabetics of either sex or both are apt to have more children than nondiabetics (considering only those onsets which follow the childbearing years) a selective superiority would be attributable to the homozygous genotype *dd* over the other two genotypes, *Dd* and *DD*. This would be surprising, since it is the heterozygote which has the highest selective value in the few cases which have been described of differential selection among the three genotypes produced by a single gene mutation. Nevertheless, there is no a priori reason to deny the possibility of the recessive homozygote *dd* having selective advantage over both *Dd* and *DD*, with little or no selective difference between them, under normal conditions.

HYPOTHESIS

A possible explanation of the adaptive superiority of persons with the *dd* genotype may be found in the early adolescent growth spurt and sexual maturity of diabetics which has been reported by White,[9] Wagner *et al*[10] and others. Small groups with childhood and adolescent onsets have been shown to be approximately one year younger than expectancy as to height, weight, carpal and metacarpal development, and several manifestations of sexual maturity.

While one is inclined to attribute this rapidity of growth to the effects of the disease, the suggestion has been made that it might be a pleiotropic effect of the *dd* genotype not directly associated with diabetes.

If it could be demonstrated that persons who later in life become diabetic (and thus have the *dd* genotype but no diabetes during adolescence) become sexually mature at significantly younger ages than normal, it would not be unreasonable to suggest that this genotype might produce larger families—at least under primitive social and economic conditions.

Partial substantiation of this argument is found in a report by Solth[11] of an appreciable association between the ages of mothers at first delivery and their ages of inception of the menarche. Tabulation of his data follows:

Menarchial ages	Number of cases	Interval between menarche and first delivery	Average age at first delivery
9-12	188	12.1	23.0
13-14	613	10.5	24.4
15-16	316	9.1	25.1
17-22	97	8.4	27.9

Since mothers whose menarchial ages are younger than the average apparently tend to have their first pregnancies earlier, it is not unreasonable to suggest that they may also have larger families, or that they used to in primitive cultures.

COLLECTION OF DATA

An exploratory test of this hypothesis was made by investigating the age of inception of the menarche of two groups of diabetic girls, one group with diabetes onset before age eleven, the other with onset at least two years following the menarche and in no case before eighteen. Both groups are composed of recent patients of the Jos-

TABLE 2

Mean menarchial ages of students from four state Universities by separate year of birth (From Mills, 1941)[11]

In each University series the lowest mean is underlined.

Birth Year	University of North Carolina Number	Mean		P.E.	Kansas University Number	Mean		P.E.
1915	563	13.54	±	.032	318	13.44	±	.048
1916	536	13.52	±	.033	269	13.38	±	.049
1917	641	13.42	±	.032	274	13.32	±	.048
1918	669	13.31	±	.030	291	13.20	±	.051
1919	621	13.34	±	.029	295	13.15	±	.049
1920	600	13.35	±	.030	233	13.23	±	.060
1921	476	13.40	±	.034				
1922	59	13.42	±	.086				
	University of Cincinnati				University of Wisconsin			
1915	301	13.38	±	.044	901	13.47	±	.028
1916	281	13.33	±	.044	991	13.36	±	.028
1917	303	13.31	±	.046	986	13.34	±	.028
1918	339	13.20	±	.045	1,098	13.29	±	.025
1919	246	13.09	±	.049	967	13.28	±	.026
1920	277	13.20	±	.054	896	13.26	±	.028
1921	258	13.13	±	.047	775	13.22	±	.030
1922					280	13.23	±	.050

TABLE 3

Variation of menarchial age with year of birth in two groups of diabetics

Birth year	Diabetes onset at eighteen or over Mean	Median	Number	Diabetes onset before eleven Mean	Median	Number
1915	12.8	12.2	6			
1916	12.9	13.0	8			
1917	12.3	12.1	9			
1918	12.9	12.6	14			
1919	13.1	13.2	9			
1920	13.1	13.1	20	15.4	15.1	9
1921	12.9	13.1	18	13.3	12.9	7
1922	13.1	13.1	9	15.7	15.5	12
1923	13.1	12.8	18	15.0	15.0	13
1924	12.7	12.6	12	14.3	14.3	11
1925	12.5	12.8	14	14.9	15.2	10
1926	13.2	13.1	11	13.6	13.4	11
1927	12.8	12.5	15	14.9	15.0	9
1928	12.8	12.9	5	14.3	14.8	8
1929	13.0	13.2	13	14.0	13.7	6
1930	12.4	12.5	7	14.0	13.6	11
1931	12.1	12.0	8	13.4	13.3	14
1932	13.0	13.8	9	13.3	13.4	6
1933	13.5		2	13.1	13.3	14
1934	11.2	11.5	3	13.3	13.2	12
1935	12.5	12.3	3	12.9	13.1	12
1936	13.6		1	14.1	14.2	21
1937	13.3		1	13.7	13.3	14
1938	13.5		2	13.4	13.1	18
1939	12.7		1	12.8	12.0	7

lin Clinic in Boston. Patients born or residing over 300 miles from Boston, nonwhite patients and patients having other serious illness prior to age twenty were excluded to attain greater homogeneity. Birth dates ranged from 1915 to 1939. All diagnoses were confirmed by Dr. Elliott P. Joslin personally.

Data were derived from returns of a mailed questionnaire inquiring (1) "What was the date of your first menstrual period? ——— (Year) ——— (Month)." (2) "How old were you then? ——— (Years) ——— (Months)." (3) "Is your answer to the above correct to within one month, or two months, or three months? ——— Or, more than three months? ———."

About one quarter of the addressees failed to respond to the questionnaire, even upon second request. Replies were eliminated if not consistent with the date of birth

on file at the Clinic, or if not stated to be correct to within three months. These constituted a second quarter. The remaining half are believed to be satisfactorily reliable, since almost all of the Clinic's patients have proved themselves to be conscientious, and almost all of those who answered the questionnaire had been corresponding with the Clinic in answer to periodic letters concerning the course of the diabetes, response to changes in therapy, complications, pregnancy and other matters. Many replies mentioned incidents or occasions which had fixed the date of menarche in mind. Some were based on the memories of the mother or older relatives or friends, some on diaries.

Controls were obtained from records of medical examinations of Wellesley College students born and residing within 300 miles of Boston, excluding those of non-European descent. Results were subdivided by year of birth, since this factor has been shown to be closely associated with menarchial age.[12]

Several weaknesses of the data should be indicated. (1) While the failure of about one quarter to answer the questionnaire may be attributed to indifference, indisposition, ignorance etc., there is no evidence that those who did reply were an unbiased sample of the total. With a second quarter eliminated for inaccuracy the possibility of bias in the remaining half cannot be overlooked. (2) The ages at which patients made their replies varied from eighteen to forty, while the ages of the Wellesley College students at the time of examination varied from eighteen to twenty. This differential in age may introduce a bias. (3) The students were asked about their menarchial age by personal contact, and were not permitted to avoid making reply.

RESULTS AND COMPARISONS

The two groups of diabetics are clearly differentiated in average menarchial age, the group with onset of diabetes after adolescence coming into the menarche 1.1 years earlier than those with childhood onset, a difference which is about seven times its standard error and may be considered significant, viz:

	Number	Mean	S.E. of Mean
Diabetes before eleven	222	13.96	±0.127
Diabetes at eighteen or over	219	12.84	±0.086
Difference		1.12	±0.053

The diabetics with childhood onset have an average menarchial age which is higher than that of any of the most comparable groups found in the literature. The highest mean of any such group is 13.54 years ± 0.032 (P.E. of mean) reported by Mills[12] for 563 students at the University of North Carolina born in 1915. The difference of 0.42 years is over three times its standard error and may be considered significant (t=3.8, P under .001).

The diabetics with postadolescent onset have an average menarchial age which is lower than the Wellesley student controls' average by 0.33 year, a difference which is over three times its standard error and may also be considered significant:

	Number	Mean	S.E. of Mean
Wellesley College students	1,185	13.17	±0.033
Diabetes at 18 or over	219	12.84	±0.086
t=3.8 P under .001		0.33	±0.092

Only eighty-three diabetics with postadolescent onset were born during the seven birth years of the Wellesley students, 1916-1922. These eighty-three have an average menarchial age of 12.89 ± 0.15 years which is not different from that of the remainder of the sample.

The most comparable groups found in the literature are students of four state universities subdivided by year of birth reported by Mills.[12] Their average menarchial ages for the years of birth 1915-1922 are presented in table 2. Not one birth year group has an average menarchial age as low as that of the diabetics with postadolescent onsets, nor as high as that of the childhood onset diabetics.

These differences are presented graphically in figures 1 and 2.

The variation of menarchial age with year of birth of both groups of diabetics is shown in table 3. Since the number of patients in each birth year is small, the medians are given as well as the means.

Two conclusions may be drawn from the above: (1) that childhood diabetes tends to retard the inception of the menarche, and (2) that girls having the *dd* genotype come into the menarche at somewhat earlier ages than the students, provided they have no diabetes until at least two years following the menarche inception. This situation suggests that possibly the *dd* genotype produces a pleiotropic effect. (Incidentally, since approximately 5 per cent of students would be expected to have the *dd* genotype, insofar as the entire population is estimated to have this frequency, and students might be expected not to include very many juvenile and adolescent cases, therefore the difference of 0.33 years shown above may be regarded theoretically as a maximum.) The statistical significance of the second conclusion is uncertain, however, because of the possibilities of bias described above.

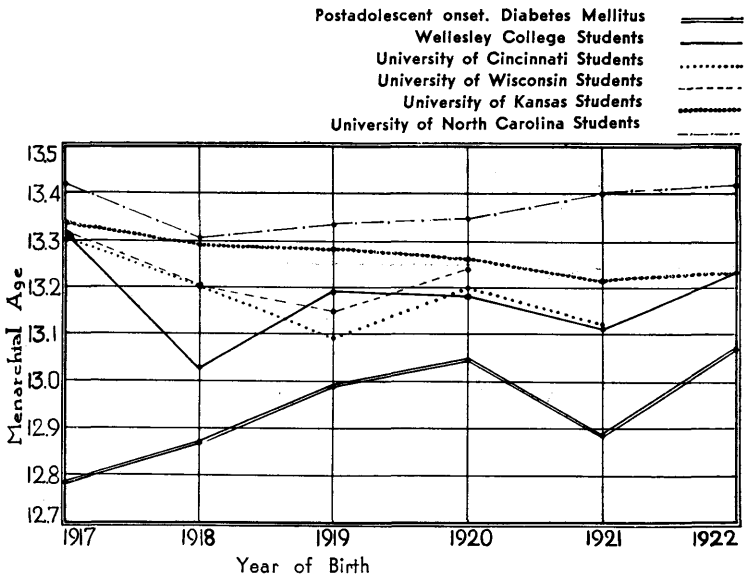

FIG. 1. Menarchial ages of girls diabetic at eighteen or over, compared with five Student Groups, subdivided by Year of Birth.

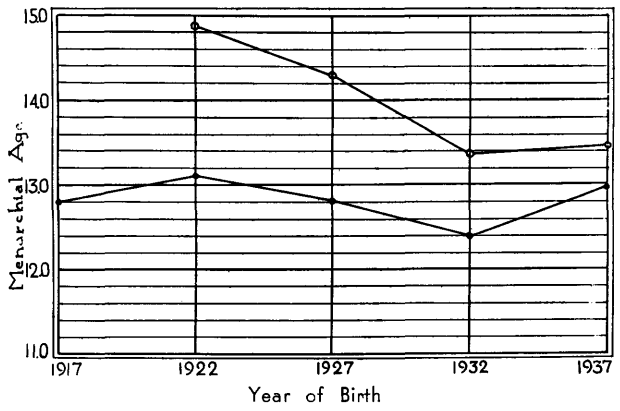

FIG. 2. Menarchial ages of diabetics with onsets at age eighteen or over (●) and before age eleven (o).

SUMMARY

Average menarchial age of 222 girls who developed diabetes before age eleven is 13.96 years with standard deviation 1.89 years. This is later than the average of any comparable group known. It suggests that childhood diabetes may retard the inception of the menarche.

Average menarchial age of 219 girls who developed diabetes at eighteen or over is 12.84 years, with standard deviation 1.27 years. This group, with diabetes onset following adolescence, has an average menarchial age earlier than that of a control of Wellesley College students, and earlier than that of any comparable group of nondiabetics found in the literature. This early maturity may be attributable to a pleiotropic effect of the diabetes-producing genotype which is apparently unconnected with the overt disease. However, comparison with student groups is not fully justifiable because of possibilities of bias in the collection of data.

SUMMARIO IN INTERLINGUA

Explication Tentative del Alte Incidentia de Diabete Mellite

Le etate medie al tempore del menarche in 222 pueras qui disveloppava diabete ante le etate de dece-un annos esseva 13,96 annos, con un deviation standard de 1,89 annos. Isto excede le correspondente etate medie in omne comparabile gruppo unquam reportate. Se impone le notion que diabete juvenil retarda le inception del menarche.

Le etate medie al tempore del menarche in 219 pueras qui disveloppava diabete a o post le etate de dece-octo annos esseva 12,84 annos, con un deviation standard de 1,27 annos. Iste gruppo, in que diabete se declarava post le adolescentia, habeva un etate medie al tempore del menarche infra le correspondente etate medie de un gruppo de controlo consistente de studentes del Collegio Wellesley e infra illo de omne altere gruppo de non-diabeticas trovate in le litteratura. Iste precoce maturitate es possibilemente attribuibile al effecto pleiotropic del genotypo diabetogene, un effecto que apparentemente es sin connexion con le morbo in su manifestationes patente. Tamen, le comparation de gruppos de studentes non es integremente justificabile a causa del possibilitate de preconditionamento distortive per le selection del datos.

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Race, Sex and Fatal Acute Myocardial Infarction

The over-all incidence of acute myocardial infarction was five times as high among the whites as among Negroes. The difference was much greater in the period 1940 to 1954 than in the period 1910 to 1939 because the incidence among white individuals had risen tremendously but that among Negroes had risen only slightly. The difference in incidence increased with increasing age because the incidence rose sharply among whites with increasing age but showed little change among Negroes. The increasing difference in the incidence of acute myocardial infarction with increasing age is not simply a matter of difference in longevity, because the data on incidence refer to the percentage incidence among those who survive to a given age. For example, more than 25 per cent of a group of white women who reached the age of seventy died of myocardial infarction and the corresponding figure for a group of Negro women over seventy years old was only 2 per cent. The incidence of acute myocardial infarction among Negroes was similar in the two sexes in both periods that were studied. . . .

No evidence was found to indicate that the changing sex ratio of acute myocardial infarction could be accounted for by a changing incidence of diabetes mellitus, hypertension, or obesity. However, it should be pointed out that in both periods (1910 to 1939 and 1940 to 1954) the relative incidence of acute myocardial infarction in the two sexes was different among diabetic patients than among nondiabetic patients (among diabetic patients before 1940 the sex ratio for acute myocardial infarction was 1:1, but after 1940 there was a preponderance of women; among nondiabetic patients before 1940 the sex ratio was 2.3 women to 1 man and after 1940 it was 1.4:1). Although a change has occurred in the relative sex incidence among diabetic patients and nondiabetic patients, acute myocardial infarction is still slightly more common among male nondiabetic patients than among female nondiabetic patients and it is slightly more common among female diabetic patients than among male diabetic patients.

From "Fatal Acute Myocardial Infarction: Sex, Race, Diabetes and Other Factors," by Wilbur A. Thomas, M.D., in *Nutrition Reviews*: *15*:4, April 1957, pp. 97-101.