Inheritance and Anticipation in Diabetes Mellitus in Relation to Carbohydrate Metabolism During Pregnancy

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In a recent splendid review and synthesis of the literature on carbohydrate metabolism during pregnancy, Hoet[1] underscored the effects of pregnancy on prediabetic and diabetic women and their offspring. He partially summarized his evaluation of his own data as well as those published by others as follows:

"1. In patients with a diabetic trait or with latent weakness of insulin production, pregnancies provoke a disturbance in the regulation of carbohydrate metabolism, as evidenced by the hyperglycemic tolerance curve.

"2. It appears that the transitory diabetes which occurs at each pregnancy is transformed by such repetition into permanent diabetes.

"3. The fetal loss rate progresses from 20 to 50 per cent in proportion to the increasing severity of the disordered glucose metabolism. A large number of the infants who are born alive have an excessive weight . . . .

"4. The tendency to obesity, hyperglycemia, and finally diabetes which characterizes the ultimate development of a great number of these infants are the consequence, on the one hand, of heredity and, on the other hand, of the maternal environment of *milieu intérieur* at the time of embryonal development."

Hoet offers methods to prevent the undesirable consequences of the stress of pregnancy on carbohydrate metabolism.

Physicians will want to examine the clinical aspects of Hoet's conclusions. Geneticists will be concerned with the implications of his conclusions concerning the genetics of diabetes and the so-called phenomenon of "anticipation."

As a geneticist, I am interested in the latter problems. I should like to discuss Hoet's theses as they pertain to the expression of diabetes, first in the mother and then in the offspring of prediabetic and diabetic women.

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PREGNANCY AND THE EXPRESSION OF DIABETES IN THE MOTHER

Hoet's view that pregnancy may precipitate diabetes in a woman genetically predisposed to the disease is, in principle, in accord with many well-known instances in the literature in which the expression of a gene-determined character is conditioned by variations in the environment.

Geneticists have long recognized that the expression of a genetically determined character is never independent of its environment, internal as well as external. In general, we may say that all genes require a suitable environment to function and that the effect resulting from the action of a gene or genes (the phenotype) may be modified by proper manipulation of the environment. The method of doing this is not always obvious, and indeed, in some instances, we know of no way of doing this short of killing the organism. The blood types of man and other animals are an excellent example of genetically determined characters whose expression has thus far defied all efforts to change them.

At the other extreme are characters so sensitive to variations in the environment that it has been impossible to stabilize them even after many generations of inbreeding. An example is the phenotype of mice homozygous for the recessive mutation "myelencephalic blebs."[2] Despite many generations of inbreeding, mice homozygous for this mutation may show no abnormalities at all, or they may have abnormalities of the eyes, feet, or coat or combinations of these. The abnormalities shown by these structures vary widely. According to Bonnevie[3] and others, these defects result from the pressure exerted by blebs in the regions in which they come to rest.

Most gene-determined characters lie between these extreme types. It is the intermediate types that are of most interest, because the expression of diabetes with regard to age at onset and severity seems to be sensitive to environmental changes, and because the tendency to diabetes appears to be gene-determined.[4]

Many different types of variation of the environment

have been shown to affect the expression of genes. The mutant gene called Danforth shorttail (symbol Sd) leads, in heterozygous mice (Sd sd), to a reduction of the tail to one-eighth or less of the normal tail length.[5] Mice homozygous for this gene (Sd Sd) are born tailless, with an imperforate anus and no genital papilla. They die within twenty four hours after birth. In the stock in which the mutation was first described all homozygotes regularly lacked both kidneys. The majority of the heterozygotes had kidneys which were smaller than normal. Crosses of the original strain to various other strains modified the expression of the gene in both homozygotes and heterozygotes. In some crosses none of the heterozygotes had detectable kidney changes, while the homozygotes had various grades of reduction ranging from a slight reduction of the kidneys to complete absence of the kidneys and the ureters.[6] No effect on the imperforate anus has been observed.

In man the erythrocytes of individuals with the sickle cell trait (heterozygous for the sickle-cell gene [Si si]) can be caused to sickle in reduced oxygen atmospheres. These individuals have no clinical complaints. Similarly, individuals with Cooley's trait (heterozygous for the gene which when homozygous leads to Cooley's anemia) have no clinical complaints. They may be recognized by the presence of oval erythrocytes, target cells, decreased red blood cell size, decreased fragility of the erythrocytes in hypotonic saline, and so on.[7]

Individuals heterozygous for both these genes (Si si, Co co) suffer a chronic hemolytic anemia clinically indistinguishable from sickle-cell disease. Electrophoretic studies of the hemoglobin show, however, that individuals with "true" sickle cell disease do not have fetal hemoglobin, while those whose disease is due to the interaction of the sickling and Cooley's trait genes do.[8-10]

The foregoing are illustrations of the modifications of the effects of genes by other genes. Let us now consider some examples of the interaction of a gene or genes with the nongenetic environment.

Rabbits homozygous for a certain recessive gene lack the enzyme which converts ingested xanthophyll into a colorless substance.[11] Accordingly, such animals have yellow fat rather than the white fat of normal rabbits. When, however, such rabbits are fed a xanthophyll-free diet, their fat is white and is indistinguishable from normal fat.

A not very dissimilar illustration may be taken from man. There is considerable evidence that susceptibility to hay fever is genetically determined. If an individual susceptible to ragweed pollen is never exposed to it, he suffers no hay fever and cannot readily be distinguished from individuals who do not form antibodies to ragweed pollen proteins.

It is well-known that several inbred strains of mice develop cancer spontaneously. Work with some of these strains is of particular interest for our present purposes. In one strain almost 100 per cent of the mice develop lung tumors at an average age of about twenty months. When young animals from this strain are treated with a tumorigenic agent they develop tumors at an earlier age than when they are not so treated. In addition, the tumors show many more foci than when no treatment is used. Animals from the strains which do not develop lung tumors spontaneously will also develop lung tumors when treated with a tumorigenic agent, but the tumors develop a longer time after treatment and show fewer foci.[12] Both types of mouse strain respond to the tumorigenic agent, but the strain that is genetically predisposed to tumor formation does so more readily and more vigorously.

A more striking parallel to what Hoet describes for the role of pregnancy in the prediabetic woman may be derived from a consideration of some strains of mice in which a large proportion of the females develop mammary carcinoma spontaneously. It has been demonstrated for some of these strains that litter bearing increases the probability of the animal's developing breast cancer.[13]

These few illustrations, chosen from a great many that are known, should suffice to demonstrate that geneticists have for a long time been aware that the environment, internal as well as external, may enhance or suppress the expression of a genetically determined character. The direction and magnitude of the effect depend on the character and the environmental variation under consideration. Hoet's suggestion that pregnancy may precipitate diabetes in a woman who is genetically predisposed to the disease is, therefore, in complete agreement with known genetic experience and, consequently, is readily acceptable to the geneticist. From the geneticist's point of view, the problem is not "Is this a possible or probable event?" but rather "What will be the observed effect on genetic ratios if the phenomenon occurs?" and "What data do we need to detect the effect?"

It is, of course, well-known that factors other than pregnancy, such as overeating, infections, or emotional stress, are believed to precipitate diabetes in susceptible individuals. If these factors are of more frequent occurrence than pregnancy as causes of frank diabetes, or if these factors do not occur with equal frequency among

women with children, childless women, and men, the effects of pregnancy as a cause of frank diabetes may be obscured when studied from a statistical viewpoint. On the other hand, if pregnancy is a relatively frequent precipitant of diabetes in prediabetic women, we might expect certain events to follow:

1. Diabetes should be more frequent among women with children than among childless women or men.

2. The age-specific incidence for diabetes after age thirty should be greater among women with children than it is among childless women or men.

Munro, Eaton, and Glen[14] attempted to determine by statistical means the effects of pregnancy on the prevalence and characteristics of diabetes. They found no correlation between the age at onset or severity of diabetes and childbearing among women forty-five years or older at the time of onset of diabetes. A much higher proportion of the diabetic women who developed diabetes after age forty-four had large families than did hospital visitors of similar age. This observation may, however, be an artifact because hospital visitors may well have fewer children than women in the general population. It is easier for women with few children to visit a hospital than it is for women with many children. It is unfortunate that the authors did not compare their values with those for the general population and with those for other hospital patients.

In the hospital sample examined by Munro and his colleagues, the age-specific prevalence of diabetes among individuals more than thirty-four years of age was much greater among married women than among single women or men. This difference was particularly striking among those forty-five years or older at the time of the study. This observation also may not be taken at face value because a hospital population is not necessarily (indeed is not likely to be) representative of the population at large. One must consider such factors as the comparative probabilities of diabetes being diagnosed in an affected man, an unmarried woman, and a married woman and the comparative probabilities of a diabetic man, an unmarried woman, or a married woman attending a clinic. We must conclude that the data of Munro, Eaton, and Glen are not satisfactory for obtaining an answer to the problem.

Age- and sex-specific death rates for diabetes have been quoted to indicate that there is a greater incidence of diabetes among older women than among older men. The death rates for white males and females are essentially the same to age fifty. Thereafter the death rate for females is greater than that for males, reaching a maximum ratio of about 1.8:1 for the age group of sixty to sixty-nine years.[15] However, unpublished data collected by Lombard[16] show that in Massachusetts among 1,000 adults who died during the period 1949 to 1952 and were known to have had diabetes, only 41.4 per cent of the women and 30.7 per cent of the men had diabetes listed as the primary cause of death. Twenty-five per cent of the death certificates for men and 17 per cent of those for women failed to list diabetes at all. The total number of deaths of men and women with diabetes has been made equal by equating each to 100 per cent. In other words, in this sample the ratio of the number of females who died with diabetes, but not necessarily because of it, to the number of males who died with diabetes, but not necessarily because of it, is 1.0. According to the death certificates which list diabetes as the primary cause of death this ratio is 1.3.

Dahlberg and his co-workers[17] found essentially the same phenomenon in their data. Table 1 (based on their tables 15 and 16) indicates that the proportion of males (based on rates per 1,000) is greater among the living diabetics than among those who died. Their data show also that the proportion of males among those dying of diabetes has been decreasing over the course of time. Joslin and his associates[18] have reported the same thing for the United States, and Harris[19] has reported a similar phenomenon for England. We are left in some doubt, therefore, as to what is the true sex ratio. Here again there is evidence that oft-quoted data may not be pertinent to our problem.

The data required to provide a decisive answer to the question of whether pregnancy plays a statistically significant role in provoking the onset of diabetes are the age- and sex-specific incidence rates of diabetes, with the rates for childless women and women with children given separately. Such data are not available. They could

TABLE 1

Proportion of men among diabetics*

Age	Among living	Among deaths
yrs.	per cent	per cent
30-34	56	50
35-39	70	62
40-44	63	59
45-49	58	55
50-54	61	49
55-59	57	52
60-64	48	44
65-69	48	

*Based on tables 15 and 16, Dahlberg and associates.[17]

be obtained during a survey of diabetes in an entire community such as that done by Wilkerson and Krall.[20]

The closest approach to data of this type of which I am aware are those of Dahlberg, and his co-workers.[17] These investigators made a strenuous effort to detect all *diagnosed diabetics* in the city of Stockholm. They used the State Foods Commission Register of diabetics and the records of all hospitals in Stockholm. On the basis of these data, they were able to compute age- and sex-specific prevalence rates (see table 2). It is interesting to note that the total prevalence rate is slightly greater among men than among women and that the prevalence rate among women exceeds that among men only in the age interval sixty through sixty-nine years. These data suggest, but do not prove, that pregnancy is not of statistical importance as a precipitant of diabetes.

About 60 per cent of the Stockholm diabetics uncovered by Dahlberg and his associates reported their ages at the onset of diabetes. The authors used these data to estimate the age- and sex-specific incidence of diabetes. Unfortunately, the authors do not tell us what population base they employed for these calculations. More importantly, they do not state what proportion of those at each age group supplied data concerning their ages at the onset of diabetes. With statements from only 60 per cent of the sample, it is readily seen that important biases could result. The data are presented in table 3. The incidence is greater among women only in the age intervals 50 to 54, 55 to 59, 60 to 64, 65 to 69, and 75 to 79.

TABLE 2

Age- and sex-specific prevalence rates of diabetes in Stockholm*

Age	Number of diabetics		Diabetics per thousand population	
	Male	Female	Male	Female
0- 4	4	3	0.2	0.2
5- 9	9	13	0.7	1.1
10-14	29	14	2.5	1.2
15-19	46	33	2.6	1.7
20-24	48	45	2.1	1.5
25-29	53	47	1.9	1.4
30-34	66	66	2.4	1.9
35-39	68	38	2.8	1.2
40-44	86	62	4.0	2.3
45-49	84	75	4.2	3.0
50-54	148	115	8.3	5.2
55-59	212	195	13.9	10.5
60-64	197	283	17.2	18.8
65-69	141	226	19.1	20.6
70-74	80	145	18.1	18.2
75-79	49	92	18.2	16.1
80-84	16	32	13.4	11.1
85-	2	2	5.1	1.9
Totals	1,338	1,486	5.1	4.6

*Based on table 3, Dahlberg and associates.[17]

TABLE 3

Age- and sex-specific incidence rates of diabetes in Stockholm*

Age at onset	Male	Female
0- 4	1.11	0.55
5- 9	1.80	1.71
10-14	2.49	2.18
15-19	1.78	1.14
20-24	1.34	0.66
25-29	1.50	1.31
30-34	2.44	1.17
35-39	2.33	1.41
40-44	3.28	1.84
45-49	5.16	4.13
50-54	6.69	8.08
55-59	7.29	10.46
60-64	6.81	7.79
65-69	3.39	4.93
70-74	4.28	1.96
75-79	1.50	2.98
80-84	1.32	0.51
85-	—	—
Totals	2.98	2.71

*Based on table 6, Dahlberg and associates.[17]

In conclusion, it appears that the data are not available for a decisive examination of the statistical importance of pregnancy in precipitating diabetes, and that the available data suggest that pregnancy is not of major statistical importance in the initiation of frank diabetes. This conclusion is in no way intended to imply that pregnancy may not in many cases lead to frank diabetes in prediabetic women. It means only that there is no evidence that statistical genetic analyses will be significantly biased if they fail to consider childless women as a group to be separated from women who have had children.

DIABETES IN THE OFFSPRING OF PREDIABETIC AND DIABETIC MOTHERS

Hoet's suggestion that the uterine environment supplied the fetus by prediabetic and diabetic women is instrumental in precipitating diabetes in children genetically predisposed to the disease is, in principle, in accord with many investigations concerning the expression of gene-determined characters. A few examples will help to make this clear.

Mice carrying the dominant mutation Fused may be entirely normal or show one or more of the following changes: asymmetrical fusions of vertebrae, fusions of ribs at the proximal ends, absence of ribs, bifurcation of the tail tip, and absence of part or all of the tail. Reed[21] has shown that about 50 per cent of the mice carrying the gene are normal in appearance if the mother carries the gene and the father does not, while only about 20 per cent are normal if the mother does not have the gene and the father does.

Wright[22] reports that in some inbred strains of guinea pigs a certain proportion of the animals have extra toes on the hind feet. In the strain with the highest frequency 42 per cent of the animals had extra toes. Since these were highly inbred strains, the animals within a strain were all essentially genetically identical; therefore, the variation among them could not have been genetically determined. Wright was able to show that a very important factor contributing to this variation was the age of the mother. Young females produced more polydactyls than did mature ones.

MacDowell, Furth, Law, and others have demonstrated that the frequency of spontaneous leukemia is lower in crosses between a mouse strain with a high rate and one with a low rate when the female comes from the low-rate strain than when she comes from the high-rate strain. Law states that in the former case the rate is lower still when the females are older than when they are younger. These experiments revealed also that the life expectancy for the mice that died of leukemia as well as those that escaped leukemia is greater for animals born of older mothers than for those born of younger mothers. The above material is reviewed by Law.[23]

The foregoing illustrations will recall the case of mongolism in human beings in which the age of the mother is also an important factor in the causation of the disease, albeit in an exactly opposite manner to that for the above cases, older mothers being more likely than younger mothers to give birth to a mongol.[24]

The etiology of erythroblastosis fetalis is an excellent example in human beings of the interaction of the fetus' genotype (genetic composition) with the environment provided by the mother. Erythroblastosis fetalis will not develop if the mother does not have a circulating antibody to an antigen present in the fetus' red cells. The red cell antigens are genetically determined. It has been demonstrated repeatedly that it is not the child's genotype as such that leads to the disease, but the combination of the child's genotype plus an appropriate antibody produced by the mother.

The illustrations described thus far were not concerned with known changes in the external environment impinging on the embryo through their effect on the mother. Such effects, however, are well-known. Some illustrations will demonstrate their relation to genetic phenomena. It has been amply demonstrated that various vitamin deficiencies and poisons can affect the development of mammalian young, presumably through their effect on the mother.[25] Recent work has demonstrated that in mammals, as in other vertebrates and invertebrates, the response of the embryo is conditioned by its genotype. As an example, one such experiment in mice involving the effect of cortisone on the occurrence of cleft palate will be described.[26]

Pregnant mice of three different inbred strains were treated with 2.5 mg. of cortisone daily for four successive days. The course of treatment was begun on different days of gestation in different experiments. Table 4 presents a summary of the data obtained when treatment was begun on the tenth day of gestation. In two of the strains (A and N) a very high proportion of the mice derived from treated females had cleft palates; in the third strain (C57) a much lower proportion had cleft palates. These strains were highly inbred and were reared under controlled conditions. The difference in response must be assumed to be due to genetic differences between the "sensitive" strains (A and N) and the "resistant" strain (C57). Crosses between the A strain (sensitive) and the C57 strain (resistant) support this conclusion. Fewer offspring of treated A females had cleft palates when such females were mated to C57 males than when they were mated to A males. It is clear from these experiments that the genetic constitutions of the mother and of the fetus determine the frequency with which cleft palate will occur in the offspring in response to a given

TABLE 4

Incidence of cleft palate among offspring of pregnant mice treated from the 10th through the 13th day of pregnancy with 2.5 mg. of cortisone per day*

Cross	Number of offspring	Cleft palate No.	Cleft palate Per cent
A ♀ x A ♂ or N ♀ x N ♂	30	30	100
C57 ♀ x C57 ♂	78	14	18
A ♀ x C57 ♂	31	16	52
C57 ♀ x A ♂	65	3	5

*Based on table 1, Fraser and associates.[26]

course of cortisone.

These experiments, as well as those reviewed by Warkany,[25] recall the correlation between rubella in the first trimester of pregnancy in human beings and various abnormalities shown by the resulting offspring.[27]

The examples discussed thus far concern changes which are present congenitally. While it is true that most examples reported are of this type, others exist in which the "maternal" effect does not become evident until considerably later in the offspring's life. Most of these examples concern studies of the development of spontaneous cancer, primarily, because only in cancer experiments are animals retained to determine the presence or absence of a maternal effect in older animals. Other experiments are designed to detect congenital deviations only. The data have recently been reviewed by Wooley.[12] (See also the earlier discussion of leukemia.)

Hoet's suggestion that the prediabetic or diabetic condition of a pregnant woman might affect the expression of the disease in her child is, as we have seen, in complete agreement with genetic thinking on such problems. Here, as in the case of the effect of pregnancy on the mother, the question is not "Is this possibility in contradiction to genetic theory?" but rather "Is this phenomenon — if it occurs — sufficiently frequent to affect statistical genetic studies?"

Steinberg and Wilder[28] have already investigated one aspect of this problem with exactly the point of view expressed by Hoet in mind. They were statistically evaluating the phenomenon of "anticipation." After establishing, on the basis of three independent sets of data, that the statistical evidence indicated that prior onset of diabetes occurred in the child of an affected parent only about as frequently as one might expect by chance, these authors stated:

"Among the reasons for the reluctance of some workers to consider the phenomenon of anticipation as being of physiologic significance are the facts that no instance of anticipation has been discovered in animals other than man and that no satisfactory biologic explanation for it has been offered. In the case of diabetes, however, there is a possible biologic rationale for anticipation when the patient's mother is diabetic. This may be based on the recognition that many infants born of prediabetic and diabetic women evidence characteristic abnormalities. It may be assumed that this unfavorable uterine environment causes earlier onset of diabetes among the offspring in whom the disease will subsequently develop. This does not apply when the patient's father is the affected parent because children of diabetic fathers do not suffer from these disabilities."

Steinberg and Wilder then examined the data derived from 124 patients with diabetic mothers and 76 patients with diabetic fathers. They concluded that "the unfavorable uterine environment provided the fetus by diabetic or prediabetic mothers is not a *major* factor in determining the age of onset of diabetes in their diabetic offspring."

Examination of the data from a larger sample (which included the above cases) of 186 patients with affected mothers and 115 patients with affected fathers revealed that the frequency of prior onset was 63.4 per cent for the former group and 63.5 per cent for the latter (based on data used by Steinberg and Wilder in their study of the genetics of diabetes). Analyses of these data similar to those reported by Steinberg and Wilder[28] entirely confirm their earlier conclusions.

Finally, if the prediabetic or the diabetic state in the mother tended to precipitate diabetes in their susceptible offspring in an appreciable number of cases, the frequency of affected offspring should be greater in families with a diabetic mother than in families with a diabetic father. Table 5 (based on data from Steinberg and Wilder[4] indicates that the frequency of diabetic offspring is the same regardless of which parent is affected.

TABLE 5

Frequency of diabetes among the sibs of diabetic patients with one diabetic parent*

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

*Based on data from Steinberg and Wilder.[4]

We may conclude that the available evidence does not indicate a major effect of maternal diabetes on the frequency of diabetes in the child.

SUMMARY

1. The data necessary for a decisive evaluation of the statistical importance of pregnancy as a precipitant of diabetes are not available.

2. The data that are available suggest that pregnancy is not of statistical importance in the initiation of frank diabetes.

3. The prediabetic state in the mother is not of statistical importance in determining the age at onset of diabetes in her diabetic children.

4. The prediabetic state, as such, in the mother is not a statistically significant influence in determining whether or not her child will become diabetic.

5. This analysis has no bearing on the specific clinical problems discussed by Hoet so far as they refer to individual patients.

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SUMMARIO IN INTERLINGUA

Hereditate e Anticipation in Diabete Mellite in Relation al Metabolismo de Hydratos de Carbon Durante le Pregnantia

1. Le datos que esserea necessari pro un evalutation decisive del importantia statistic del pregnantia como precipitante de diabete non es disponibile.

2. Le datos que de facto es disponibile suggere que pregnantia non es de importantia statistic in le initiation de franc diabete.

3. Le stato prediabetic del matre non es de importantia statistic in determinar a qual etate diabete se declara in su prole diabetic.

4. Le stato prediabetic del matre non es, in se mesme, de influentia statisticamente significative in determinar si o non le prole va devenir diabetic.

5. Iste analyse non affice le specific problemas clinic discutite per Hoet in tanto que illos concerne patientes individual.