The Genetics of Diabetes Mellitus

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On reading the literature dealing with diabetes, everyone must be struck by the lack of precise knowledge which exists concerning the method of inheritance of the disorder, and in such a situation it is almost certain that what *is* known will provide the ingredients for heated controversy.

"Oh never, never let us doubt,
The things we are not sure about."

However, if we think about the matter it is perhaps not surprising that confusion exists because diabetes is such a heterogeneous condition that different investigators may well be dealing with predominantly different types of the disease. For example, some will be investigating it in Scots, others in Englishmen, and others still in Jamaicans and Kampalians. There will, therefore, be both racial and dietetic differences to take into account. Then there are fat diabetics and thin diabetics, late-onset diabetics and early-onset diabetics, those fertile and those barren, and those with other conditions such as acromegaly, thyrotoxicosis, hemachromatosis and "stress" syndromes such as burns, and patients with coronary thrombosis. In this list some are insulin-sensitive and some resistant, some give a clear-cut family history, while in some it seems doubtful whether there is an inherited component at all—gluttony or steroids may be the only factors.

What is generally agreed by all authorities is that sibs of those affected are themselves more often diabetic than are the sibs of nondiabetic controls. This situation is not peculiar to diabetes for it is found in many other common diseases—duodenal ulcer, hypertension, rheumatoid arthritis, disseminated sclerosis and pernicious anemia, to mention but some of them—and it seems that once a disease becomes common its method of inheritance ceases to obey the simple Mendelian laws. Thus there are never nearly as many affected sibs as there ought to be, that is to say, as there would be if we were measuring the height of garden peas. To get over this difficulty the geneticist usually falls back either on the idea of incomplete penetrance or on that of multifactorial inheritance. By incomplete penetrance is simply meant that some individuals genetically liable to a disease do not, in fact, develop it. Now while it is easy to pour scorn on this "way out," yet there is nothing inherently improbable in the idea, and it can be shown in fact to be true in animal work where sometimes other genes or an environmental factor are necessary before the effects of a major gene can become manifest. In diabetes it would be reasonable to suggest that age, weight, parity and, to a slight extent, the ABO blood groups, might all influence the degree of penetrance of a gene or genes responsible for diabetes mellitus. By multifactorial inheritance we mean that a character is controlled by many genes, and when applied to diabetes it would mean that there is a continuous range from normal right through to the severest type of diabetes, the last having the complete "set" of genes influencing the character.

Now while every known type of inheritance has been invoked in diabetes, two principal views have been advanced to explain the majority of cases. Most favored is the recessive-gene-with-incomplete-penetrance hypothesis, but close behind it is the theory that the disorder is multifactorially controlled.

THE RECESSIVE HYPOTHESIS

An affected individual is designated "dd" and if both his parents are unaffected they must both be of genotype "Dd." That is to say the mating will have been between two heterozygotes and if the penetrance were complete 25 per cent of the offspring would be affected. If one parent of an affected individual were a diabetic the mating must have been between dd $\times$ Dd, and in these circumstances half the offspring would be diabetic. Lastly, if both parents were affected all the offspring would eventually be expected to develop the disease. The ratios of affected offspring in these three types of mating are therefore 1:2:4.

Pincus and White[1] collected the sibs of 106 propositi where none, one or both parents were diabetic. They found abnormal glucose tolerance tests in 6.8 per cent, 17.9 per cent and 25 per cent respectively. This is a close fit (1:2.6:3.7) to the ratios expected on a single

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gene hypothesis, always assuming the individuals with abnormal glucose tolerance tests are in fact prediabetic.

Steinberg and Wilder,[3] in a similar survey, analyzed 1,981 consecutive patients and found 4.7 per cent, 11.4 per cent and 16 per cent of their sibs were diabetic (a ratio of 1:2.4:3.4) according to whether none, one or both their parents respectively were affected. These results are again in keeping with the single recessive gene hypothesis, the penetrance being much reduced—to about 25 per cent in Pincus and White's series and to about 18 per cent in Steinberg and Wilder's if the propositi are excluded.

On the other hand, Walker[5] in a complete survey of the Leicestershire village of Ibstock (population 5,500), found that 167 individuals (excluding the known diabetics) had postprandial glycosuria when given 50 gm. of glucose. All but 25 of these submitted to a glucose tolerance test and the curves obtained showed a gradual change from seventy-five normal individuals (who presumably had renal glycosuria) through an intermediate group of forty-two cases to twenty-five undoubted new diabetics.

Again, Keen, quoted by Pyke,[2] found that 25 per cent of the first degree relatives of diabetics had glycosuria one hour after consuming 50 gm. of glucose, but only 15 per cent of control relatives did so. The distribution of blood sugar levels in the relatives in the two groups showed no natural division between values regarded as normal and abnormal.

Steinberg (personal communication) does not think that the above findings invalidate the single-gene hypothesis. He points out that in fibrocystic disease of the pancreas (known to be controlled by an autosomal recessive gene) there is a wide range in the concentration of electrolytes in the sweat of the homozygotes, heterozygotes and normals. In a personal survey carried out with Shwachman he did not find evidence of bimodality when comparing the heterozygotes with normals, though the former have on the average twice the concentration of electrolytes compared with presumed normals. He thinks that a similar situation may occur with respect to the blood sugar in diabetes mellitus.

The analogy is of interest, but as far as fibrocystic disease is concerned his findings must surely mean that this particular character is controlled by many genes, one of them being the major gene for the disease, here acting as a polygene; the environment is also almost certainly of importance when considering a character such as the composition of the sweat. Steinberg contests this interpretation; he points out (personal communication, 1960) that the variation in eye size of the "eyeless" flies in *inbred* lines of Drosophila varies from 0 to 400 or more facets, and yet the character is controlled by a single gene. It seems to the writer that "eyeless" in Drosophila corresponds to dd in the diabetics, and that in diabetes the expression of the homozygous state is (as in the flies) very variable, from complete impenetrance to an acute fulminating disease. If Steinberg were to take families of Drosophila which segregated for "eyed" and "eyeless," he would invariably find a bimodal distribution for this character.

What is not certain is how close a relationship exists between the primary action of the gene or genes and the blood sugar levels. However, blood sugar curves are essential to the diagnosis of the disease, and all genetic hypotheses, including Steinberg's, have been related to them.

A priori, it seems probable that the blood glucose level is nearer to the primary action of the gene in diabetes than is the composition of the sweat in fibrocystic disease. In support of this it would be easy to pick out nearly all overt diabetics from nondiabetics by looking at the results of glucose tolerance tests only, whereas it would not be nearly so easy to distinguish heterozygotes from patients with established fibrocystic disease simply by a knowledge of the electrolyte content of their sweat.

Since these two lines of research seem to indicate different types of inheritance, it would be worth while carrying out a further and more extensive investigation. Thus a large number of students who have no family history of diabetes should be tested for the range of blood sugar values after a glucose tolerance test. Thereafter a series of young diabetics should be found since these will have sibs of approximately the same age as the students. Glucose tolerance tests would be carried out on these sibs and if the blood sugar is directly related to a single gene controlling diabetes one would expect bimodality. Thus those who were not genetically liable (both homozygote normals and heterozygotes) might give figures approximating to the controls, whereas some of the sibs who were of the genetic constitution dd would be "uncovered" by the test and would show an abnormal curve. The main point of the investigation is that by using sibs genetic variability and differences in environment are minimized; if the latter could be entirely removed the glucose tolerance test would be bound to show bimodality if a single gene is responsible for the disease. In our investigation it would also be of interest to find the ABO blood group of the sibs to see if those who were group A were more readily "uncovered" than those who were group

O. There is strong but by no means overwhelming evidence that diabetes mellitus is commoner in those belonging to group A than in those who are not A. The association is less strong than with pernicious anemia (see Fraser Roberts[6]).

If bimodality of blood sugar values were found it would be support for the single gene hypothesis. If, on the other hand, the range from normal to abnormal showed a continuous distribution it would suggest either that the single-gene hypothesis was wrong in that the condition was multifactorially controlled or that the blood sugar level was not the best index of the disorder, and that it was worth looking elsewhere for other criteria.

Whichever type of inheritance is correct, genetics cannot at present give accurate information regarding the liability of any particular individual to develop the disease since there is no reliable test which will invariably "uncover" the prediabetic state. All that we are really in a position to say at present is that the disorder runs in families, and that the more relatives that are affected the greater the chance of an individual to develop the disease.

SUMMARY

The two most widely accepted views on the inheritance of diabetes mellitus are discussed. Both the recessive gene hypothesis and the theory of multifactorial control appear to have some supporting evidence, but in neither case is this conclusive. An outline of further work which is being started in Liverpool may be of help in deciding between the two standpoints.

SUMMARIO IN INTERLINGUA

Le Genetica de Diabete Mellite

Es discutite le duo conceptiones del hereditate de diabete mellite que es le plus extensement acceptate. Tanto le hypothese de un gen recessive como etiam le theoria de multiple factores determinatori pare haber un certe supporto objective, sed isto es conclusive ni in le un ni in le altere caso. Un delineation de studios additional currentemente initiate in Liverpool forsan va adjutar in decider in favor del un o del altere del duo punctos de vista.

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Lipid Mobilizing Hormone

The intricate mechanisms whereby the body regulates lipid metabolism continue to puzzle the imagination. The following is a unique concept.

In a summary of the past six years of studies, C. J. D. Zarafonetis, J. Seifter, D. H. Baeder and J. P. Kalas (*A.M.A. Arch. Int. Med.* *104*:974, 1960) describe a factor which releases fats into the circulating blood. They found that hyaluronidase and partially depolymerized hyaluronic acid induce clearing of lipemic serum of animals and that cortisone inhibits this effect. Studies of the nephrotic syndrome disclosed the presence of a substance which the authors called "lipid mobilizer hormone" (LMH), which was prepared from the serum of horses previously treated with cortisone. This substance, which was dialyzable, and seemed to be an octapeptide, was found to release triglycerides from omental and mesenteric fatty stores (Seifter and Bader, *Proc. Soc. Exp. Biol. Med.* *86*:709, 1954; *91*:42, 1956; *95*:318, 469, 1957).

Single injections of LMH into fasting patients induced increases in concentrations of cholesterol, fatty acids and lipid phosphorus of the peripheral blood. Patients fed a diet low in fat and given daily injections of LMH for two weeks developed marked degrees of hyperlipemia (Zarafonetis et al. *Am. J. Med. Sci.* *234*: 493, 1957). Prefeeding patients with glucose or fats prevented this hyperlipemic response, but prefeeding with amino acids did not. In animals, depletion of hepatic glycogen or exposure to substances injurious to the liver predisposed them to an exaggerated response to LMH. Evidence of endogenous secretion of LMH was obtained by studying patients during and after operation and animals subjected to various forms of stress. In these instances, a great increase in the concentration of venous fatty acids occurred, but the arterial concentrations did not increase. Cholesterol was affected to a lesser extent.

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