EDITORIAL

HEREDITY AND DIABETES

It is now almost twenty-five years since Pincus and White[1] presented quantitative evidence showing that susceptibility to diabetes is probably determined by a recessive gene. The great variability in the age at onset and in the clinical expression of the disease have, however, caused many investigators to be reluctant to accept a single gene hypothesis. It is argued that diabetes comprises a group of diseases, and that, therefore, several different genes must be involved in causing susceptibility to the disease, recognized clinically as diabetes. Nevertheless, it remains true that the data from all studies involving the families of large numbers of diabetics may be explained on the assumption of a recessive gene as the cause of susceptibility to diabetes.[2, 3] It is not established, however, that all cases due to a simple recessive gene are due to a change at the same genetic locus, i.e., the same gene. Neither clinical data nor genetic data have been of help in resolving this problem. Clinical data, because several types of diabetes (juvenile, adult, "brittle," stable, diabetes in thin individuals, and diabetes in obese individuals) may occur within a family; genetic data, because the method of collecting the data has been such as to preclude the obtaining of information to answer this question. We shall return to this at a later point.

We may accept as the best hypothesis to explain the available data, the hypothesis that those liable to diabetes are homozygous for a recessive gene, which we will symbolize as *d,* i.e., diabetics, and those liable to diabetes are *dd.* Estimates based on two different sets of data from this country indicate that about 5 per cent of the population of the United States are homozygous (*dd*) for the gene determining susceptibility to diabetes.[2] Because of the variability in the age at onset and in the severity of the disease, only about 1 per cent of the population is recognized to be diabetic.[4] It appears from various studies that an additional 1 per cent of the population is diabetic but not recognized to be so.[4] Hence some 60 to 90 per cent of those who are genetically liable to diabetes are not recognized by present routine methods of examination. The necessity for detection programs is obvious.

If we accept the estimate that approximately 5 per cent of the population are *dd* we may estimate the probability that given individuals are liable to diabetes as a function of their age, the age of their parents, and their relation to other affected individuals.[3] For example, if an individual has a diabetic sib and neither of his parents is diabetic, but his parents are aged, the probability that he is liable to diabetes is 25 per cent. Similarly, if one parent is diabetic the probability is 50 per cent. On the other hand, if the parents are relatively young, these probabilities become approximately 35 and 60 per cent, respectively. The probability that an individual is genetically liable to diabetes if both parents are diabetic is 100 per cent regardless of the age of the parents. Using the same assumptions, it has been computed that an individual with no diabetic sib but with an affected parent or two affected paternal or maternal grandparents has approximately 20 per cent chance of being *dd.* The risk for being liable to diabetes increases as more relatives are known to be diabetic. Knowledge of the risk of developing diabetes will influence the detail and the frequency of examinations for the disease; the greater the risk, the more vigorous the preventive measures the patient and physician are willing to undertake.

The cause or causes of the great variability in age at onset of diabetes remain obscure. It has been suggested that there is a relation between the age at onset in an affected parent and the age at onset in his affected child.[5] Analysis of several sets of data, however, has shown that this phenomenon is statistical and not biological.[6] It has also been suggested that the presence of diabetes or the prediabetic state in the mother could lead to an earlier onset of diabetes in the child.[7] There does not, however, appear to be statistical evidence to support this concept.[8] Pregnancy has been suggested as a precipitant of diabetes,[7, 9, 10, 11] but the data do not appear to be convincing.[8]

Evidence from twins[12] and from various theoretical considerations[9] strongly suggests that environmental factors as yet unidentified are of importance in determining the age at onset. As Guest and Warkany[12] have suggested, intensive longitudinal studies of identical twins, of whom at least one is diabetic, could provide important information toward a solution of this problem.

The most satisfactory data to resolve the question of how many loci are concerned in determining susceptibility to diabetes would be obtained with a reliable test for the prediabetic subject. Such a test may soon be

available,[13] but more time is needed before we can be convinced of its reliability. In the absence of such a test, an answer may be derived from (a) a series of families selected because both parents are diabetic (it is important that no attention be paid to the condition of the children at the time of selection of the families) and followed until all the children have passed age sixty or have died; (b) a series of families selected because one of the parents is diabetic (here again no attention must be paid to the condition of the children at the time of the selection of the families) and followed until all the children have passed sixty years of age or have died.

There is doubt concerning the sex ratio among those who became diabetic after the age of forty,[2, 9, 11] and concerning the relationship between parity and the frequency of onset of diabetes among women past the age of forty. While neither of these is directly a genetic question, both have bearing on the nature of the data collected for genetic studies, and both have bearing on the mode of expression of the gene(s) believed to cause susceptibility to the disease. A satisfactory answer to these questions could be obtained by following until death a group of men and a group of women of known parity, and known by examination not to have been diabetic at age forty.

The data needed to answer the several questions raised in the above paragraphs are not easily collected by any single center. A cooperative project, with several centers gathering the desired data, could supply information leading to an understanding of these problems. Such knowledge may shed light on some of the environmental factors which precipitate diabetes in those who are genetically liable to the disease. Physicians may then be in a position to prevent (or to reduce the likelihood of) the occurrence of diabetes in those genetically liable to the disease and thus be a major step closer in their conquest of diabetes mellitus.

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