EDITORIALS

TWINS AND DIABETES MELLITUS

There is increasing recognition of the fact that the expression of a tendency to a genetically determined disease, such as diabetes, may depend upon environmental factors.[1] It seems worth-while to emphasize that discordant monozygotic twins, a type often neglected in twin studies, furnish valuable evidence of the complex etiology of diabetes.

Long ago Galton suggested the study of twins as a method for the separation of hereditary and environmental influences in the development of human traits. Subsequently, twins have been studied extensively in research on the etiology of many diseases. The striking similarities (concordance) of monozygotic twins in physiological and pathological characteristics are usually compared with the similarities or dissimilarities of dizygotic twins in order to distinguish between genetic and nongenetic determination of the traits in question. Such comparisons have been made repeatedly among diabetic twins, both mono- and dizygotic. Joslin *et al.*[2] pointed out that, if diabetes is inherited, the incidence of the disease in both members of pairs of monozygotic twins should far exceed the incidence in dizygotic twins. Such an excess of monozygotic twins concordant with regard to diabetes has been demonstrated in several surveys[2, 3, 4, 5, 6, 7] thus giving support to the view that genetic factors play an important role in the etiology of diabetes.

Although in many instances both monozygotic twins develop diabetes, important exceptions have been reported. In a series observed by Joslin *et al.*[2] there were 33 sets of monozygotic twins. Of these both members were diabetic in only 16 pairs or 48.5 per cent, while 17 or 51.5 per cent were discordant when the study was made. Discordant monozygotic twins were also encountered by other observers.[4, 5, 7]

It is true that in the nondiabetic members of such monozygotic pairs a tendency to the disease is often demonstrable by glucose tolerance tests and that the member who is healthy at the time of the survey often develops diabetes in later life.[4, 5] In other words, one member of the pair may have the overt disease while the other has it in a latent form. Since it is a very different matter to the patient whether he has merely a genetic tendency to the disease or whether he suffers from diabetes and all its consequences, knowledge of the factors that convert an inherited latent tendency into frank diabetes would be of great practical importance. In case of discordance in the members of a pair of monozygotic twins, who by definition have the same genetic constitution, *nongenetic* factors must determine the development of a disease that appears in only one. It is important, therefore, to study not only concordant monozygotic twins but also discordant ones, who can, under favorable conditions, improve our knowledge of nonhereditary pathogenic factors.

A recent report of discordant monozygotic twin brothers[8] is of special interest, because one of the twins became diabetic in his eighth year, while the other twin remained free of the disease for at least seventeen years after the onset in his brother. Moreover, the nondiabetic brother showed a pronounced tendency to obesity, while the diabetic twin remained thin and wiry. The glucose tolerance tests of the nondiabetic twin yielded blood sugar curves within normal limits. The family history revealed that diabetes as well as obesity had occurred in relatives; therefore one can assume that the twins could have inherited a tendency to both diabetes and obesity. Inquiries made to ascertain what environmental influences might have made one of the twins diabetic and the other obese were not fruitful. The twins grew up in the same household and were exposed to the same environmental influences. The mother stated that the appetites of the twins were similar and never excessive during childhood. There was a history of a severe attack of pertussis with severe symptoms in the diabetic brother and of pertussis with milder symptoms in his twin; but the record left some uncertainty whether this episode preceded the onset of diabetes or immediately followed it. Thus no decisive event could be discovered in retrospect which might account for the discordance.

In some cases discordance with regard to diabetes can be explained, at least tentatively, by precipitating factors such as alcoholism,[6] infections,[5, 7] or repeated pregnancies[4, 7] in the affected twin. The last factor of course applies to adult females only. In the majority of cases, however, the decisive nongenetic factors cannot be ascertained.[5, 8] Such observations indicate that environmental factors, which convert an inherited tendency to diabetes to the manifest disease, may be much more subtle and evasive than is usually assumed.

Some of the cases of discordant monozygotic twins are of interest also because they throw some light on the relationship of obesity to diabetes. In 1938 Lemser[4] reported a pair of twins, one undernourished with diabetes, and one obese and free of diabetes, though showing decreased glucose tolerance. These twins were adult women when examined. The diabetic sister had been in poor economic circumstances and had undergone ten pregnancies. The nondiabetic sister could afford ample food and had only one pregnancy. In the twins recently reported,[8] who became discordant in childhood, the obese twin remained free of diabetes, while the lean one developed the disease. If the reverse had been true, overeating and obesity would have been considered by some as an accessory diabetogenic factor. There can be little doubt that some relationship exists between obesity and diabetes, especially in later years, but that does not mean necessarily that this relationship is a causal one. Some observations on twins,[4, 8] seem to indicate that obesity and diabetes sometimes may be parallel phenomena and not cause and effect.

Discordant monozygotic twins represent rare experiments of nature which can be of great value in etiologic research on diabetes and other diseases. Observations of concordant monozygotic twins with diabetes who differ in respect to various complications should also be highly informative. Sometimes such studies of a few exceptional cases may be more rewarding and less expensive than large-scale statistical research.

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FRIEDENWALD'S CONTRIBUTION TO *KNOWLEDGE OF DIABETIC RETINOPATHY*

The unsolved problem of diabetic retinopathy has received increasing attention in recent years. Interest has been stimulated by the rising incidence of this disabling complication and by recent progress in our understanding of the nature of the disease process. During the last ten years of his life, the efforts of Jonas Friedenwald provided the solid background and inspiration for much of the current work and many of the present concepts about the pathology and pathogenesis of diabetic retinopathy.

The ophthalmoscopic picture of diabetic retinopathy was clearly defined by Jaeger in 1855. In 1877 MacKenzie and Nettleship described the nature of the aneurysmal capillary disorder of the retina which accounted for the clinical picture. Unfortunately, this fine work was not generally accepted until its rediscovery by Ballantyne and Loewenstein in 1943.

In the course of the routine application of histochemical technics to ocular tissues, an intensive study of the mucopolysaccharides of the eye was undertaken by Friedenwald and co-workers in 1946. When Hotchkiss described the periodic-acid-fuchsin method for staining polysaccharides in fixed tissues, the procedure was modified in Friedenwald's laboratory for application to sections of human eyes. It became apparent upon examination of the very first sections that the basement membranes of the retinal vessels stained brilliantly. The application of this staining technic to flat preparations of the retina provided a most useful method for the microscopic study of its entire vascular tree. New light was thus shed upon the intimate nature of retinal vascular diseases. When retinas of diabetic patients were examined, a most impressive demonstration was afforded