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.

REFERENCES

[1] Steinberg, A. G.: Inheritance and anticipation in diabetes mellitus in relation to carbohydrate metabolism during pregnancy. Diabetes *4*:126-32, 1955.

[2] Joslin, E. P., Root, H. F., White, P., and Marble, A., Editors: Treatment of Diabetes Mellitus. Philadelphia, Lea & Febiger, 1952, 9th ed.

[3] Curtis, W. S.: Diabetes in twins. J.A.M.A. *92*:952-56, 1929.

[4] Lemser, H.: Untersuchungsergebnisse an diabetischen Zwillingen. München. med. Wchnschr. *85*:1811-15, 1938.

[5] Then Bergh, H.: Die erbbiologie des diabetes mellitus. Arch. Rassen. u. Gesellsch.—Biol. *32*:289-340, 1938.

[6] Umber, F.: Diabetes bei 3 eineiigen Zwillingspaaren. Deutsche med. Wchnschr. 60:544-46, 1934.

[7] Pannhorst, R.: Zwillingsuntersuchungen bei diabetes mellitus. Deutsche med. Wchnschr. 60:1950-52, 1934.

[8] Warkany, J., Guest, G. M., and Cochrane, W. A.: Discordant monozygotic twins. Diabetes mellitus and obesity. A.M.A. Am. J. Dis. Child. *89*:689-95, 1955.

GEORGE M. GUEST, M.D.
JOSEF WARKANY, M.D.
Children's Hospital
Research Foundation
Cincinnati 29, Ohio

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

of the innumerable capillary aneurysms that characterize diabetic retinopathy. Furthermore, the relationship of the aneurysms to the surrounding hemorrhages and exudates became apparent. Available for study in minute detail was the life history of the capillary aneurysm. In single specimens one could trace the development from a thin-walled dilatation to an onion-skin lamellated polysaccharide mass, which ultimately became hyalinized.

Friedenwald then undertook the study of the application of periodic-acid-fuchsin technic to other organs of diabetic patients. This resulted in the finding of similar staining and lamellation of the globular renal glomerular masses, previously described by Kimmelstiel and Wilson. In addition, serial sections of kidneys revealed true capillary aneurysms in the glomeruli of patients with retinopathy. A review of a large number of diabetics at autopsy revealed the occurrence of renal lesions only in those diabetics who had retinopathy. Thus were correlated for the first time the renal and retinal lesions of the diabetic, both as to appearance, staining characteristics, and occurrence in the same individuals.

Under the direction of Friedenwald, efforts were then concentrated on a comparison of the differences between diabetics with and without retinopathy. Thus was begun an intensive clinical and laboratory investigation in diverse directions and encompassing many related fields. Studies were undertaken of possible alterations in serum polysaccharides, plasma proteins, acetylating capacity, xanthurenic acid excretion following tryptophane administration, urinary vitamin B-12 output after parenteral administration, 17-hydroxysteroid excretion, eosinopenia following ACTH, etc. In addition, the studies of pathologic differences were continued and numerous attempts were made at experimental production in animals. From these extensive efforts the hypothesis which emerged that best accounted for the available clinical, histo-pathologic, and experimental data was that the adrenal cortex might play a role in the pathogenesis of diabetic retinopathy and nephropathy. Although this thesis remains unproved, subsequent studies and experiments have offered no outstanding evidence that negates the role of adrenocortical dysfunction in this disease process. This working hypothesis has provided a basis for various productive research projects. The perplexing problem of diabetic retinopathy remains unsolved, but there is every indication that its ultimate resolution will rest upon the solid foundation afforded by the brilliant work, the uncanny insight, and the stimulating suggestions of Jonas Friedenwald.

BERNARD BECKER, M.D.
Saint Louis, Missouri

MEDICAL RESEARCH: A MIDCENTURY SURVEY

The advent of two volumes under the above title invites editorial comment in appreciation and commendation of an invaluable critique of a half century of research in the medical sciences. A full awareness of the significance of these volumes requires a glance backward to the status of medical research in 1900.

At the turn of the century, scientific advance in the field of medicine proceeded at a snail's pace. What advances were being made were accomplished chiefly in the medical schools. The greatest experimental activities were in laboratories associated with departments of pathology. Here interest centered around morphology and the relations to basic sciences were either tenuous or nonexistent. Pharmacology was mainly materia medica and bacteriology was a new and essentially unexplored science which as yet had not penetrated appreciably into the medical schools. Clinical medicine was taught by busy practitioners and what experimental medicine they engaged in was largely confined to bedside observation, chiefly on the effects of therapeutic measures.

Now at the midcentury mark, the picture of the state of medical research is dramatic in its antithesis to that presented in 1900. Medical science is advancing at an ever accelerating rate. The basic sciences of chemistry, physics, and mathematics are assiduously mined for fundamental concepts which will lead to a better comprehension of the problems of disease. Not only in medical schools but also in independent foundations, large and small, and in the laboratories of innumerable pharmaceutical houses, research workers are pouring forth continually a torrent of literature on every aspect of medical science. The medical schools, both in the preclinical and clinical branches, are now staffed by men highly trained in many areas of the basic sciences. The lecture halls and clinics are flanked by numerous laboratories filled with elaborate and costly apparatus, manned by highly skilled technicians. These laboratories are constantly seeking to recruit to their staffs young men trained in basic sciences who are initiating careers in all areas of clinical medicine.

Financial support for medical research from government, private foundations, and from the public through the large national societies totals millions of dollars per year. Thousands of research projects directed by competent investigators are now supported by such foundations. Most individuals who have demonstrated reasonable competency in medical research can obtain adequate financial aid for investigative work in any direc-