The Type of Diabetes Mellitus Associated with Diabetic Retinitis

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A remarkable reduction in insulin requirement was observed in the case of an adult woman with diabetes; after requiring 80 units of insulin daily, she later managed without insulin and had normal blood sugar tests. The dominant clinical feature in later years was renal insufficiency. At autopsy, extensive renal changes of the Kimmelstiel-Wilson type were found.

Because of the apparent relation of the amelioration of the diabetes to the development of renal disease in this case, the incidence of renal changes and the severity of the diabetic state were studied in 190 cases of diabetes mellitus autopsied in recent years. These cases were divided into three groups: those with no renal disease, those with renal disease other than the Kimmelstiel-Wilson type and those with the Kimmelstiel-Wilson renal lesions.

The criterion used for the Kimmelstiel lesion was solely the lumpy loop or hyaline mass in the glomerulus. There were 57 patients with the lesion—an incidence of one-third of the diabetic study group. The duration of the diabetes did not differ from that in the two other groups. In general, the patients with the lesion were obese, became hypertensive, developed refractory edema, died in uremia. Their kidneys characteristically showed marked arteriolarsclerosis and arteriosclerosis.

In 60 per cent of the diabetics with the Kimmelstiel lesion, the amount of insulin required progressively decreased as time went on. In a few cases, the diminution of the insulin requirement was so marked that diabetics previously requiring large amounts of insulin became hypoglycemic during treatment with small doses. This illustrates the need for caution. The tendency to amelioration appeared late in the course of the diabetic disease.

Another unexpected finding in the cases with the Kimmelstiel-Wilson renal changes was a striking rarity of acidosis throughout the course of their diabetes, in contrast to its common and repeated occurrence among the controls. Both groups, however, had experienced equivalent stress ordinarily sufficient to cause acidosis, such as infection, gangrene and insulin withdrawal.

In 90 per cent of cases with the glomerular nodules, extensive retinal aneurysms were observed either ophthalmoscopically or by flat plate preparation of the retina at autopsy. These retinal changes were observed in only 10 per cent of the controls.

The statistical data suggest that retinal aneurysms are an intrinsic part of the same entity as the Kimmelstiel-Wilson lesion, an impression in accord with the contemporary studies of Friedenwald, Ashton and others. It was of additional interest in this regard, that 11 of the patients with the Kimmelstiel kidney lesions showed not only the characteristic glomerular nodular massing but neighboring associated aneurysmal dilatations of various other glomeruli, filled with red blood cells and beginning to hyalinize. Such may be the anatomical precursor of the glomerular nodule, and the finding implies a common pathogenesis for the changes in the retinal and renal capillaries.

CONCLUSION

It can be concluded that adult patients with diabetes mellitus who ultimately have Kimmelstiel-Wilson renal damage also develop typical diabetic retinitis, and that the diabetic state often tends to become milder and that it is characterized by a rarity of acidosis. The possibility is suggested that it is metabolically different from ordinary diabetes and that it is caused by factors other than failure of production of insulin by the pancreas.

DISCUSSION

JOSEPH H. BARACH, M.D., (*Pittsburgh*): Because of present-day limitations in our knowledge of the eti-

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ology of diabetes mellitus, I believe it will be better to project this discussion from the viewpoint of the diabetic patient with retinopathy rather than to attempt to describe special types of diabetes in which retinopathies are commonly found.

In the past, attempts have been made by various workers in this field to classify or group diabetics into types, but I have yet to see any classification or delineation of this disease that can stand up under critical analysis. However, in deference to Dr. Dana's approach to this problem, one must admit that if there is one group to which the term "type of diabetes" might be applied, it would be the Kimmelstiel-Wilson type of case. If and when it can be proved that the vascular lesions in the retina and the lesions in the renal glomeruli are of the same nature, and have a common origin, one would be justified in speaking of cases with these lesions as representing a "type" of diabetes mellitus. As things are, however, ultimate proof for this awaits final acceptance.

I have studied a group of 335 cases of diabetes, searching diligently for common denominators and leads toward a better understanding of the causes and mechanisms of this disease and its complications. These patients, having been seen within the past year, have been under more or less continuous care, some of them for more than thirty years, so that the natural course and evolution of their disease should reflect the pathologic processes inherent in diabetes mellitus.

One-third of the 335 cases showed retinal lesions when they first came for diabetic control. Two-thirds of the cases having retinopathy were between 50 and 70 years of age. Greater obesity was not associated with higher incidence or more serious retinal lesions. Hypertensive diabetics showed a higher incidence and greater severity of retinal lesions than diabetics without hypertension. Nevertheless, some of our hypertensive diabetics escaped retinal lesions for as long as 27 years. (In my experience it is not true that all diabetics will have retinal lesions after 20 to 25 years.) Of diabetics with retinopathy, 88 per cent required insulin, while in the general run of cases, only 60 per cent required insulin. Retinopathy may develop in cases of well-controlled diabetes, but these show fewer lesions and the lesions are less destructive than in poorly controlled cases. An increase in the blood cholesterol was found in 53 per cent of diabetics with retinopathy, and an increase in the S_f 12-20 lipoproteins in 40 per cent.

If the studies that are now being made prove that there is a positive relationship between lesions of the retinae and of the renal glomeruli, as seen in Kimmelstiel-Wilson disease, it will mark progress in our knowledge of diabetes and its complications.

JOSEPH T. BEARDWOOD, JR., M.D., (*Philadelphia*): I wish to say a few words concerning our clinical observation in cases of diabetic retinitis, particularly in association with Kimmelstiel-Wilson's disease. The clinical diagnosis of the latter is often impossible before autopsy findings, as frequently the same clinical picture is seen in patients with chronic urinary infections, particularly in the female. I think we are still at a loss to say what determines the development of this syndrome. The adrenal gland has been suggested as playing some part in this condition and it was of interest to us that in two recent cases in which Addison's disease developed, after six years and twenty years of diabetes respectively, no intimal lesions were noted at the time the Addison's disease was discovered. Why is it that this condition usually does not develop after ten years of diabetes? Why is it that many diabetics do not develop it even after twenty years of diabetes?

My experience has differed from that of Dr. Dana in that I have found patients developing retinitis who have been ofttimes severe diabetics and we have not seen any great improvement in their diabetes following the development of retinitis, which could not be attributed to more meticulous care of their disease because of the threat of oncoming blindness. My associates and I have recently checked 360 cases of diabetes with retinitis and there seems to be a definite difference in the incidence of retinitis in those cases adequately controlled as compared to those in which we feel the diabetes was not controlled according to our standards.

We have also been impressed with the number of juvenile diabetics who do well for five or ten years and then disappear from observation and apparently become careless about their disease for two or three years and report back with typical lesions in the eye and the clinical picture of early Kimmelstiel-Wilson's disease.

It has been our experience also that generalized systemic atherosclerosis is not necessarily part of this picture and that many patients have advanced peripheral and coronary atherosclerosis, but show no evidence of retinal change, and that many patients with well advanced retinitis will have little, if any, evidence of generalized atherosclerosis. There is obviously an unknown factor in these individuals, but from our standpoint we feel that proper control of the diabetes continuously, prompt treatment of urinary infections and in those patients who have increased capillary fragility, the use of antifragility drugs, are of definite value and are prophylactic measures of importance.

ARNOLD LAZAROW, M.D., (*Cleveland*): What per cent of your patients with Kimmelstiel-Wilson's syndrome showed a complete disappearance of the diabetes or showed a diminution in their insulin requirement? What is the order of magnitude of the decreased insulin requirement? I am particularly interested in these findings because of our observations reported last year concerning disappearance of alloxan diabetes in rats. In these animals the diabetes disappeared after it had been present for 12 to 20 months.

HENRY T. RICKETTS, M.D., (*Chicago*): We were all intrigued, I am sure, by Dr. Dana's statement that the patients who develop Kimmelstiel-Wilson syndrome are not those who have experienced acidosis. I should like to ask him in this connection how many of his patients with the Kimmelstiel-Wilson syndrome were originally juvenile diabetics. If there were an appreciable number in this category who were originally juveniles and who never went into acidosis or had a tendency thereto, it would be indeed surprising.

GEORGE W. DANA, M.D., (*Baltimore*): Dr. Barach and Dr. Beardwood have presented other aspects of this general problem, and I think it is important to have all sides of the problem explored.

In answer to Dr. Ricketts' question regarding onset of diabetes in the juvenile phase, our series was an adult series and there were only three or four patients who had onset of diabetes in youth. The problem of juvenile diabetes is different from that in adults.

As for Dr. Lazarow's comments, in 60 per cent of our cases with the Kimmelstiel-Wilson lesions demonstrated at autopsy, there was a real decrease in insulin requirement. One patient who had needed 80 units finally required no insulin at all; this patient almost went into spontaneous hypoglycemia. Approximately 10 patients required no insulin as the Kimmelstiel-Wilson syndrome progressed.

Patients who have been on the same dosage of insulin for a prolonged period should be watched carefully if this syndrome develops, to avoid danger from hypoglycemia.

The Use of Lipotropic Factors in the Treatment of Liver Disease

Studies in animals have demonstrated that a pathologic picture resembling that of portal cirrhosis may be produced experimentally by various methods. In certain instances, the use of lipotropic factors is of prophylactic and therapeutic value. This beneficial effect has been attributed largely to the stimulation of phospholipid formation.

In human beings with liver disease the therapeutic value of choline and methionine has not been definitely established. Since the phospholipid turnover in the liver is probably reflected by the amounts of newly formed phospholipids in the plasma, the use of radioactive phosphorus provides a method for determining the rate of phospholipid turnover and evaluating the effects of lipotropic agents.

In normal persons studied in this manner the rate of phospholipid turnover remains fairly constant for periods up to 6 months. A large dose of choline or methionine (10 gm.) does not increase the phospholipid turnover.

In cirrhotic patients with fatty infiltration of the liver proven by biopsy, a significant increase in the rate of phospholipid turnover is usually demonstrable after a single dose of choline or methionine. Failure of the phospholipid turnover to show such a response initially is believed to be a bad prognostic sign. This response to stimulation is no longer present after 8 weeks of treatment, when the liver fat has decreased or disappeared.

In patients having cirrhosis without fatty infiltration and in patients with uncomplicated infectious hepatitis, the rate of phospholipid turnover is not stimulated by choline or methionine.

Choline or methionine is indicated only at the beginning of treatment in patients with fatty infiltration of the liver who are acutely ill and cannot eat. The same lipotropic effect is achieved more slowly without choline or methionine in patients who will eat an adequate diet.

From an article by David Cayer, M.D., and W. E. Cornatzer, M.D., in *Gastroenterology,* March 1952.