The Natural History of Diabetes

H. ST. GEORGE TUCKER, JR.

Department of Medicine, Medical College of Virginia, Richmond

The familial tendency of diabetes has been recognized for centuries. The genetic studies of Pincus and White (1933), Steinberg and Wilder (1952), Post (1962), and others seem to indicate that diabetes is transmitted as a simple autosomal recessive trait. If this is so, it is obvious that the tendency to diabetes must be established at the moment of conception. What does this tendency to diabetes consist of, and what determines when the disease we have called "diabetes" will appear? What is the status of the predisposed individual prior to the onset of overt diabetes?

It has long been known that large babies are often born to mothers later destined to become diabetic. This and the observation that transient diabetes during pregnancy or other stress is often the forerunner of later overt diabetes led Jackson (1960), Conn and Fajans (1961), and others to regard this period before the development of obvious diabetes as an important one, a period of active dynamic changes which culminate in the appearance of clinical diabetes. Jackson, and Conn and Fajans have called this period "pre-diabetes." Others prefer the term, "diabetes premellitus."

We might define diabetes as a genetically determined metabolic disease, the predisposition to which is established at conception. It may ultimately progress to the stage of clinical diabetes with insulin insufficiency and the accompanying manifestations of hyperglycemia, glycosuria, and abnormal metabolism of protein and fat.

STAGES OF DIABETES

The life history of a diabetic patient may be regarded as consisting of three stages: (I) prediabetes, (II) asymptomatic or chemical diabetes, and (III) overt or symptomatic diabetes. Asymptomatic or chemical diabetes is sometimes further divided into diabetes present only with stress, and diabetes present without stress (Table 1).

In general, the diabetic patient appears to progress through one stage to the next, although in some patients, stage II is either very brief or unrecognized, and many diabetics may remain asymptomatic and never reach stage III. Diabetes appearing early in life is more likely to be severe, and diabetes developing late in life generally is mild and often asymptomatic. Some factors that can alter the natural course of diabetes are illustrated in Figures 1 and 2.

VASCULAR DISEASE AND BIOCHEMICAL CHANGES IN PREDIABETIC STATE

It would appear that the key to better understanding of the pathophysiology of diabetes might be found in the events occurring in the prediabetic period. The first problem lies in knowing how to recognize the prediabetic patient, since, by definition, all tests of carbohydrate metabolism are normal in this state. Camerini-Dávalos (1965a and b), Rees and their colleagues (1964) have attacked the problem by studying a group of children who were either the identical twins of diabetic patients or the children of two diabetic parents. Such children should all be genetically prediabetic, although all need not develop diabetes. These authors have marshalled impressive evidence both of beginning vascular disease of the diabetic type, and of certain biochemical abnormalities preceding the development of chemically detectable diabetes.

Vascular abnormalities found in prediabetes include: (a) abnormal finger pulse waves (Camerini-Dávalos, 1965a), (b) venular dilatation in the bulbar conjunctiva with increased venule : arteriole diameter ratio (Camerini-Dávalos et al., 1964), (c) thickened basement membrane of capillaries on gingival biopsy (Camerini-Dávalos, 1965b), (d) on ear lobe biopsy (Camerini-Dávalos et al., 1964), and (e) in the glomerular capillaries on renal biopsy (Camerini-Dávalos, 1965a). In addition it seems likely that some fetal abnormalities in babies of prediabetic mothers may result from vascular disturbances in the placenta.

Chemical changes reported in prediabetes include the following: (a) Although the glucose tolerance test of the prediabetic is within normal limits, the mean blood sugar of all prediabetics is significantly higher than that of non-prediabetic controls at 1, ½, 2 and 3 hours after glucose. (b) In prediabetes the fasting serum free fatty acids are increased, and their fall after glucose is delayed. (c) Serum sialic acid is increased in prediabetes. (d) Serum insulin-like-activity (ILA) is increased fasting and after glucose (Camerini-Dávalos, 1965a). (e) Synalbumin insulin antagonist
of Vallance-Owen is increased (Vallance-Owen and Ashton, 1963). (f)"Bound" insulin of Antoniades is increased (Camerini-Davalos, 1965a). (g) Prediabetics show an increased rise in blood growth hormone three hours after glucose, following the initial suppression of growth hormone levels by the glucose (Unger, 1965).

Many of these biochemical changes are slight and many need confirmation. The significance of increases in ILA or in "bound" insulin is in dispute. Nevertheless it does appear that there are biochemical abnormalities during prediabetes. Among these observations the most significant would seem to be the finding of increased amounts of insulin in the blood, even by immunoassay when measured 1 hour after glucose, not only in prediabetics, but early in the course of juvenile diabetes, and in most maturity-onset diabetics. The finding of a high insulin level at a time when blood sugar is high challenges our earlier concept of diabetes as a manifestation of simple insulin insufficiency. There must be a reason for the apparent ineffectiveness of insulin. This question is at the heart of much of the investigation in diabetes today. Some of the possible causes for insulin ineffectiveness that have been proposed are listed in Table 2.

THE PRIMARY METABOLIC DEFECT IN DIABETES

Whatever mechanism is ultimately found to be responsible for insulin antagonism, current thinking strongly favors the concept that the primary event in diabetes is not pancreatic failure, but extrapancreatic antagonism to insulin or inactivation of insulin of some sort. As available active insulin diminishes, some form of feedback mechanism, possibly a transitory rise in blood glucose, causes the pancreas to release more insulin until a new equilibrium is reached. During the stage of prediabetes, this compensatory process is able to maintain normal or nearly normal carbohydrate metabolism. If the antagonism to insulin continues, the pancreas may be driven to the point of failure. Such islet cell failure may be first manifest by inability to release insulin promptly in response to a rise in blood glucose. The process may be at first reversible to some extent, but later becomes irreversible with more or less complete failure of insulin secretion. This seems to be the case with many juvenile diabetics where early remission occurs after institution of treatment, only to be followed in a few months by total and permanent pancreatic failure. In the maturity-onset diabetic, the antagonism to insulin is less severe; pancreatic failure develops only late in life and seldom becomes complete. In many such patients the use of sulfonylurea drugs improves the release of insulin by the $\beta$-cells to a degree adequate to maintain carbohydrate homeostasis.

VASCULAR COMPLICATIONS OF DIABETES

The vascular disease of diabetes is chiefly a microangiopathy, i.e., a degenerative change in capillaries, venules, and arterioles throughout the body that eventually produces such pathologic lesions as retinopathy, glomerulosclerosis, and possibly neuropathy. These complications were formerly thought to result from years of deranged metabolism. The discovery of incipient microangiopathy in various sites in prediabetes and in the early stages of chemical diabetes casts doubt on the view that these changes result solely from the metabolic abnormality produced by insulin deficiency and supports the view that the metabolic disturbance and the vascular disease may be independent facets of the fundamental genetic disease. On the other hand, there is a sizeable body of clinical opinion that the progression of vascular disease is more severe in
Fig. 1—The course of diabetes with age is indicated as a line sloping upward as the disease becomes more severe. Prediabetes is indicated as a clear zone, and diabetes is indicated by stippling, which is heavier toward the top as the disease becomes more severe. The juvenile diabetic progresses rapidly through prediabetes and asymptomatic diabetes to the abrupt onset of overt diabetes, usually severe and with obvious symptoms. The maturity-onset diabetic follows a line with a smaller slope and reaches the stage of chemical diabetes in middle life. Other predisposed individuals may never develop diabetes at all. Along this course or life-curve, events producing stress such as pregnancy or infection can make diabetes worse and can bring out chemical or even symptomatic diabetes in a prediabetic individual. When stress is removed, diabetes may return to its previous undetectable state, or at least to a subclinical or asymptomatic state.

Fig. 2—Effect of obesity and weight reduction on the course of diabetes. Obesity often converts prediabetes or mild asymptomatic diabetes to overt diabetes. With weight reduction alone, the diabetes may disappear entirely or revert to a mild asymptomatic state.

TABLE 2
Possible Causes of Insulin Ineffectiveness

Considered, but ruled out:
1. Abnormal insulin
2. Increased insulin destruction

Currently suggested:
1. Binding or inactivation of insulin:
   a. "Free" and "bound" (Antoniades, 1964)
   b. "Typical" and "atypical" (Samoan, 1963)
2. Synalbumin insulin antagonist (Vallance-Owen, 1964)
3. FFA inhibition of insulin action (Randle, 1963)
4. Growth hormone
5. Auto-immune process
6. Tissue resistance to insulin

Those patients with the greatest metabolic abnormality, although Knowles (1964), reviewing all the literature, did not believe the question could be answered on the present evidence. The appearance of retinitis and glomerulosclerosis in patients with diabetes resulting from hemochromatosis (Becker and Miller, 1960) or pancreatitis, and the observation that similar lesions develop in dogs made diabetic by alloxan or growth hormone (Bloodworth, 1965), bring us back to the role of insulin deficiency and altered metabolism in the genesis of the vascular lesion. The fact that the glucose tolerance tests of prediabetes, while normal, show significantly higher blood sugar levels after glucose than in non-prediabetes suggests that there may already be some deficiency of effective insulin, which could be a factor in the appearance of vascular abnormalities at this stage. The final answers to these questions are unknown. In the meantime, our position should admit the possibility of both genetic and metabolic factors. It would seem reasonable to use the measures of treatment available to keep the chemistry of the diabetic as near normal as possible, while continuing the search for genetic or other factors that may be involved in the vascular degenerative process.
REFERENCES


H. ST. GEORGE TUCKER, JR.


