Problems in the Insulin Dependent Diabetic

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It is often useful for the physician to classify diabetes as stable or unstable. Maturity-onset diabetes is usually stable, and its management is not difficult, provided the patient is interested and coöperative. Tendency to obesity, relative insensitivity to insulin, and absence of ketosis are characteristic of such patients. Relative insensitivity to insulin does not imply unresponsiveness, but rather that the blood sugar is not overly labile and does not fall sharply in response to exercise or injected insulin. Many patients with such insensitivity to insulin are adequately managed on diet, alone or in combination with the oral hypoglycemic agents. When the latter fail, usually a single morning dose of long-acting insulin is satisfactory in controlling glycosuria and hyperglycemia during a 24-hour interval. Occasionally a small dose of crystalline insulin given in the same injection will be needed to control glycosuria between breakfast and lunch.

UNSTABLE DIABETES

Unstable or "brittle" diabetes usually is associated with the growth-onset type, although it may be present in many patients whose diabetes appeared after the age of 40. "Brittle" diabetics are insulin dependent and prone to ketosis. They are usually of average or below average weight and often are emotionally labile. Marked fluctuations in blood glucose following exercise or ingestion of food, as well as during infections, may lead to periods of marked hyperglycemia or hypoglycemia. These rapid and often unpredictable shifts in blood glucose are disturbing to the patient and his family and frustrating to the physician.

In considering the causes of unstable diabetes one must differentiate between primary instability and transient conditions which may influence diabetes unfavorably and cause temporary instability. Stable diabetes may be aggravated by a number of conditions such as infection, thyrotoxicosis, and physical or emotional stress. If treatment is poorly planned or carried out, erratic behavior of the blood glucose may result from giving excessively large doses of insulin, or from giving it at the wrong time of day. Rebound hyperglycemia and occasionally ketosis may result from excessive insulin administration and may, in some instances, be responsible for periods of instability in an otherwise stable diabetic (Somogyi, 1960).

Primary instability characterizes the "very brittle patient." The basic cause is complete or nearly complete lack of endogenous insulin production. This condition usually manifests itself during the growth years; after diabetes has been present five years or more, little or no insulin can be found in the blood. Examination of pancreatic tissue from a patient with this type of diabetes reveals little or no insulin. This fact accounts for unresponsiveness to the sulfonylurea compounds whose major action depends upon the ability of the pancreas to produce and release insulin.

The "brittle" diabetic is therefore totally dependent on exogenous insulin. Normal homeostatic mechanisms concerned with the release of pancreatic insulin in response to metabolic needs are no longer present. The physician then faces a difficult task in attempting to supply insulin by injection, in an effort to prevent glycosuria and to maintain the blood glucose at a normal level throughout each 24-hour period. As Dr. Alexander Marble paraphrased this problem, "One strives to mimic nature, and, of course, succeeds only imperfectly."

MANAGEMENT OF PRIMARY INSTABILITY

In the management of the unstable or "brittle" diabetic, those conditions which aggravate diabetes should be sought and treated. One should carefully avoid overdosage of insulin. This is extremely important since it is hypoglycemia, not diabetes itself, that most often incapacitates the diabetic in his job and in many other social situations. Management is based on an attempt to secure uniformity of the controllable factors which influence blood glucose. These include diet, insulin, and physical activity. The diet should be reasonably constant from day to day in conjunction with a relatively fixed, daily insulin dose. Physical activity lowers the requirement for injected insulin, and strenuous or unusual exercise may precipitate hypoglycemic episodes; in such circumstances additional food may be taken. If unusual physical activity is antici-

pated, an appropriate decrease may be made in the dose of insulin.

The "brittle" diabetic invariably requires daily injections of insulin. There are various insulin programs, most of which include giving the major portion of the day's insulin in the form of a long-acting insulin, either NPH or Lente insulin, as an "anchor" dose before breakfast. If one has been careful to keep uniform the patient's daily diet, exercise, and insulin dose, this single morning dose may be all that is needed to maintain blood glucose within the normal range during a 24-hour period. Unfortunately, this is most often not the case in the unstable diabetic. Lack of uniformity, either in diet or exercise, while receiving a relatively fixed dose of daily insulin accounts for many of the wide swings in blood glucose following insulin injection.

In either stable or unstable diabetes, despite satisfactory control in the afternoon and evening following a single morning dose of long-acting insulin, the fasting blood sugar may be high the following morning. One may effectively control this by a split dose of long-acting insulin, employing a smaller increment, usually 5 to 10 units, at bedtime. If the tests at supper are poor, then giving this smaller increment before supper along with a small dose of regular insulin may bring about satisfactory control. If either the single morning dose or split dose brings about satisfactory control before breakfast and supper, yet fails to control hyperglycemia and glycosuria before lunch, then a small dose of crystalline insulin may be given along with the pre-breakfast injection of longer-acting insulin.

Adjustments in insulin dosage are usually made in 3 to 5 unit increments, allowing two to three days between successive changes. Ordinarily, changes in insulin dose are not made frequently, and certainly not on the basis of a single test, but rather according to the general trend of tests at a given time of day. The patient should keep a record of urine tests so the degree of control at any given time of day can be easily ascertained.

Phenformin (DBI) has been recommended as an additional supplement to insulin in "brittle" patients in an attempt to lessen fluctuations in the blood sugar. This was tried without much success in approximately 20 juvenile patients over a two-year period at the MCV diabetic clinic. The insulin dose was significantly decreased, yet these patients remained just as "brittle" while on phenformin (DBI).

Causes of Primary Instability

Although the basic cause of primary instability seems to be nearly total lack of endogenous insulin production, the factors contributing to the "brittle" state are poorly understood. The rebound phenomenon following excessive insulin dosage (Somogyi, 1960) all too often is not corrected simply by reducing insulin dosage. In many instances this may result in an increasing frequency of periods of ketosis.

The capricious response of such patients to insulin therapy might arise from alterations in the handling and disposal of insulin in the body. Prout and Katims (1959) advanced the hypothesis that some type of plasma binding of insulin with erratic release of free insulin might result in a variable clinical response to the same dose of insulin. Lennon and others (1960) have demonstrated in vivo that such plasma binding is reflected in prolonged plasma disappearance of I^{131}-labeled insulin. Although altered degradation of insulin by impaired renal or hepatic function may play an important role, the influence of previous insulin therapy appears to be a major factor in this altered handling of exogenous insulin. This suggests that binding of insulin by insulin-neutralizing antibodies may be an important cause.

Differences in responsiveness of muscle and adipose tissue to free and complexed insulin may be important. Plasma-bound insulin may be free to act on adipose tissue, while only free insulin acts on muscle. Perhaps the insulin lability might result from the gradual saturation of plasma-binding sites with complexed insulin free to act only on adipose tissue. At a certain level of dosage, saturation of the binding sites occurs, and free insulin is then available to act on the mass of muscle tissue, thus precipitating hypoglycemia.

Bolinger (1964) demonstrated markedly delayed disappearance times of regular insulin in "brittle" diabetics. The characteristics of regular insulin in these subjects approached that of long-acting insulin. He postulated that regulatory difficulties should be exaggerated by the use of long-acting insulin, in that the slow release rate of insulin from injection sites approached the rate of degradation, thus permitting erratic filling of the plasma-binding sites. He found that in general the longer the disappearance time of insulin, the greater the proportion of regular insulin required for good regulation.

INSULIN RESISTANCE

Another problem in insulin-requiring diabetics is the patient whose insulin dose increases steadily. Insulin resistance has been arbitrarily defined as existing when the daily insulin requirement exceeds 200 units. However, some degree of resistance occurs in any individual requiring over 30 to 40 units daily, since this amount provides adequate replacement therapy in depancreatized human subjects. Many factors can increase the requirement for insulin in human diabetics and should be considered whenever insulin dosage has to be raised progressively. Insulin resistance resulting from any of these known factors is usually secondary to such factors as obesity, keto-acidosis, infection, stress, puberty, pregnancy, and a number of endocrine disturbances, notably thyrotoxicosis.

"Primary" or chronic insulin resistance is distinguished by the absence of any of the factors known to aggravate diabetes. In most cases it can be attributed to the development by the patient of γ-globulin antibodies to exogenous insulin and primarily against the bovine insulin component in most commercial preparations which are usually mixtures of 70% bovine and 30% pork insulin (Berson and Yalow, 1958; Berson et al., 1956; Field et al., 1961).

In some cases of apparently primary resistance, anti-insulin antibodies cannot be demonstrated, and high levels of active plasma insulin seem to be physiologically ineffective (Field, 1960). Tissue unresponsiveness to insulin has been postulated to explain such cases. It is also theoretically possible that primary insulin resistance could result from excessive amounts of binding substances found in association with serum albumin or the γ- or β-globulins.

Primary insulin resistance may occur in either sex, at any age, and in either stable or unstable diabetes (Smelo, 1948). Some authors think it occurs more commonly where insulin has been given intermittently (Calvin and Moloney, 1959). The onset is unpredictable and may terminate in a few weeks or persist for several years (Smelo, 1948). This fact makes evaluation of any therapeutic program difficult. Susceptibility to keto-acidosis is about the same as before the onset. Control of the diabetes is usually possible if enough insulin is given, and prognosis is good for ultimate subsidence of the resistance (Smelo, 1948).

TREATMENT OF INSULIN RESISTANCE

The first important measure is to give large enough doses of ordinary commercial insulin. In most cases there is a level which will ultimately overcome the resistance, with subsequent improvement in insulin sensitivity (Smelo, 1948). Success may depend on willingness to administer very large doses of insulin, and on the realization that subsequent increases in dosage must be made by geometric progression.

With our knowledge of insulin-neutralizing antibodies, a rational treatment can be based on measures which influence antibody synthesis. Adrenal cortical steroids have been used successfully (Field, 1962; Oakly et al., 1959), although the mechanism of their beneficial effect is uncertain. Their action may be mediated through an effect either on inhibition of antibody synthesis, or by influencing the rate of dissociation of the antigen-antibody complex.

Less antigenic types of insulin other than commercial beef-pork insulin have been used successfully. Since the major antigenic property of this mixture can be attributed to beef insulin, whose molecular structure differs considerably from human insulin (Harris et al., 1956; Berson and Yalow, 1959), pure pork insulin has been used successfully in a number of cases (Goldman and Kaye, 1962; Feldman et al., 1963). The molecular similarity of pork and human insulin probably accounts for its weaker antigenic properties (Harris et al., 1956; Berson and Yalow, 1959). The human insulin molecule consists of two long amino acid chains designated A and B chains joined by disulfide bridges (Harris et al., 1956). Pork insulin differs only by the terminal amino acid on the long B chain. Other more antigenic insulins such as beef insulin differ by additional changes in the sequence of the important amino acid triplet at the *8*, *9*, and *10* positions enclosed within the disulfide bridge on the shorter A chain.

Although not generally useful, the sulfonylurea drugs have helped in a few selected cases of mild insu-

lin resistance. These patients have usually been mild, maturity-onset diabetics whose insulin doses have had to be increased gradually over a period of one to two years. Varying the insulin dose has usually made little or no difference in the ultimate control of their diabetes. Since antibodies against commercial insulin of animal origin do not significantly neutralize endogenous insulin, stimulation of pancreatic insulin by these agents may bring about secretion of enough nonantigenic endogenous insulin to control the diabetes.

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