Enzyme Changes in Diabetes Mellitus

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ABSTRACT

Derangement of metabolic processes in disease is often associated with alteration in serum enzymatic activities, and the assay of serum enzymes has become an important diagnostic procedure. However, there has been some question concerning changes in serum enzyme patterns in diabetes mellitus. A large number of enzyme changes can be related to diabetes mellitus and these abnormal findings are complicated by concomitant coronary sclerosis, renal, retinal, neurologic disorders and other idiopathies. The complexity of the problem is illustrated by considering early versus late onset diabetes, acute versus chronic diabetes and the possible genetic basis of diabetes. Early-or juvenile and late-onset diabetes present very different patterns which suggest different enzyme pathology. The antagonistic actions of insulin and adrenergic hormones on the biosynthesis of glycolytic and gluconeogenic enzymes are described. The role of enzymes in metabolic pathways (TCA cycle, glycogen deposition, pentose pathway, fatty acid metabolism, energy transfer, gluconic acid formation) and the pathology of diabetes are discussed.

Introduction

The large number of enzyme changes which can be related to diabetes mellitus point to the basic problem inherent in study of the disease. Herman and Gorlin\textsuperscript{16} describe diabetes as a disease with protean manifestations, which may include coronary sclerosis, coronary artery disease, idiopathies, and renal, retinal and neurologic disorders. Many subjects with premature arterial disease show signs of preclinical or subclinical diabetes when tested for fasting blood sugar concentration or glucose tolerance and it seems necessary to consider how many of these protean manifestations are common to "basic" diabetes. Are there underlying enzyme changes responsible for these complications, which are found in all diabetics but are generally not well expressed because of the possibility of fairly good control? Or is it necessary to break
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The complexity of the problem can be illustrated by a consideration of early onset versus late-onset diabetes, the generally recognized clinical stages of diabetes, acute versus chronic diabetes and the possible genetic basis of diabetes. Early-onset or juvenile-onset and late-onset diabetes present very different patterns, which suggest different enzyme changes. Early-onset diabetes appears during the growth period, has an associated weight loss, presents the problem of severe ketoacidosis when insulin is withdrawn, has normal insulin sensitivity and shows decreased pancreatic and plasma insulin content. Late-onset diabetes appears during adult life, is associated with obesity, shows absence of severe ketoacidosis on withdrawal of insulin, has low insulin sensitivity and presents little evidence for decreased plasma or pancreatic insulin content.

Many clinicians divide late-onset diabetics into four successive and progressively more severe stages: (1) prediabetics who are essentially normal but have a high probability of later manifesting the disease because they are either the identical twin of a diabetic or the offspring of two diabetic parents; (2) subclinical diabetics who show abnormal glucose tolerance tests only in conjunction with cortisone usage; (3) latent diabetics with normal fasting blood sugar but abnormal glucose tolerance tests; (4) latent diabetics with elevated fasting blood sugar as well as abnormal glucose tolerance tests. A diabetic can move up or down the classification scale, and it is interesting to speculate on the probable enzyme differences between these stages. At just what point do the enzyme changes correlated with the numerous clinical manifestations appear? Do they appear only with increasing severity of the diabetes or are they related to the onset as Herman and Gorlin’s observations suggest?

Renold and Cahill discuss the difference between acute and chronic diabetes, and this is certainly an important classification to keep in mind when considering enzyme changes. This classification may not be enzymatically valid and needs further study. The acute diabetic syndrome is related to the hyperglycemia found in uncontrolled, overt diabetes. There is excess glucose in the urine (glycosuria) and excess urination (polyuria) which leads to excessive hunger and thirst. The glucose loss is related to excessive catabolic mobilization of proteins and fats, and this results in proteinuria and excess ketone bodies and accompanying ketonuria. Presence of excess ketone bodies and overloading of the Krebs cycle leads to production of excess H+ from the breakdown of oxybutyrate. This can lead to ketoacidosis cora and, in many cases, death. The chronic diabetic syndrome includes any, and possibly all, of the numerous clinical manifestations (such as the various angiopathic or retinal problems) as well as the acute manifestations.

Another problem associated with enzyme studies of diabetes is the nature of its genetic basis. There is evidence that it is frequently inherited as a simple Mendelian autosomal recessive, but this is certainly not the only basis of the disease. Renold and Cahill suggest the disease may represent a genetically conditioned susceptibility with variable penetrance dependent on non-genetic factors. Although these authors state that there is no really good evidence of etiologically distinct forms, this possibility should not be ruled out in view of the numerous clinical manifestations and the wide-ranging enzyme activity changes involved. The possible genetic basis of diabetes will be further considered with the changes in gluconeogenic and glycolytic enzymes and the suggestion that these two enzyme groups represent two distinct genomes.
The diversity of the classifications considered above suggest that further enzyme studies are necessary to determine the nature of the "basic" disease or the possibility of a number of genetically and/or symptomatically distinct forms which account for the wide variety of changes. It can be seen that any clear and inclusive definition of the disease is very difficult. However, hyperglycemia is still a good starting point in any attempt to understand this disease; it explains many of the symptoms. Also, it is valuable to consider the activity of the circulating insulin, its effects, its antagonists and its inhibitors.

Experimental Approaches

Studies on enzyme changes in diabetes have been carried out primarily with rats, although there has been some work with other vertebrates and some invertebrates as well. In most cases these studies involved drug-induced diabetes, although diabetic strains of mice and Chinese hamsters are sometimes used.

The most widely used drug is alloxan, and it induces a condition similar to diabetes. However, in addition to destroying the \( \beta \)-cells of the pancreas it also causes kidney and liver damage. Other common ways used to induce diabetes include use of a mixture of dehydroascorbic acid and alloxan or streptozotocin, which are both reported to have more gentle effects than alloxan alone. Anti-insulin-serums, pancreatectomies, prolonged administration of anterior pituitary extracts or pituitary growth hormones and prolonged administration of glucose are also used to produce diabetic-like conditions in experimental animals. The last two methods apparently exhaust the secretory capacities of the \( \beta \)-cells. A common feature of all these induced forms of diabetes is the decrease in circulatory insulin. It is important to remember that these conditions are only diabetic mimics and not thoroughly understood. They cannot be expected to illustrate all the complicating clinical manifestations, and thus severely limit the range of the studies and conclusions and the correlations possible with human diabetes. Inducers like alloxan present special problems because of the liver and kidney damage, and additional unrelated enzyme changes, particularly in serum determinations, can be expected.

Studies on enzyme changes in humans are rather scanty. In general, the authors are very careful to try and rule out patients with complicating factors such as liver or pancreatic disease, but the problem of "basic" diabetes again presents itself and one wonders if all the various clinical manifestations should be separated from the simple acute form. The degree of control of the disease also presents a problem; it seems important to determine how effective the treatment is at the time of measurement. Of course, there is the problem of lack of uncontrolled subjects for studies.

The Role of Insulin

Insulin activity occupies a central position in any study on diabetes. It is a regulator which promotes glucose metabolism, protein anabolism, fat disposition (increased lipogenesis) and, in general, it will reverse most of the basic changes of diabetes. It acts in opposition to many of the adrenal and pituitary hormones. How much of its effect is related to preferential glucose uptake in the various tissues, how much is due to a direct effect on enzyme synthesis and how much is just a "pulling" effect through the interrelated metabolic pathways is not well understood.

Bessman has suggested that one of the primary actions of insulin may be on the \( \text{Mg}^{++} \) dependent coupling of glucokinase to the electron transport chain at sites of ATP production. Here it would provide a means of dephosphorylating the ATP for the continuation of electron transport. Bessman has suggested that in the brain, insulin has no effect because all the hexokinase
is already attached to mitochondria. This would account for the insulin-insensitivity of the brain. Ilyin\textsuperscript{17} has suggested that insulin reverses the inhibition of hexokinases brought about by their binding to mitochondria.

There are numerous explanations for the changes in insulin activity observed in the various forms of diabetes; Renold and Cahill\textsuperscript{38} provide a good summary of them. Abnormal or inadequate numbers of cells are frequently found in early-onset diabetes; this accounts for the lack of insulin in this form. There may be an inability to store insulin. There is also speculation that there is a stored form and a circulatory form of insulin. The circulatory form has a half-life of about forty minutes and is rapidly inactivated.\textsuperscript{46} There may be an inability to release the stored insulin owing to membrane-passage problems or inadequate reaction in some peripheral tissue. There may be excessive binding to structural protein, insulin neutralization or destruction or excessive requirements for insulin brought about by high circulating blood glucose levels, resulting in eventual “exhaustion” of the $\beta$-cells. Any one of these or any combination of these proposed situations may be the actual mechanism.

It is probable that early-onset and late-onset diabetes involve different patterns; chronic manifestations may also be tied in. Weber et al\textsuperscript{45} have considered the antagonistic actions of insulin and the adrenocorticoid hormone on the biosynthesis of glycolytic and gluconeogenic enzymes. The interactions are summarized in figure 1. In general, insulin increases the synthesis of glycolytic enzymes and decreases the synthesis of gluconeogenic enzymes. It has been suggested that the gluconeogenic and glycolytic enzymes may be one genome which is repressed or derepressed as a whole. Additional studies have been carried out using subjects who have undergone pancreatectomy or who suffer from hemochromatosis which involves the deposition of iron pigments in the pancreas with resulting secondary fibrosis and loss of function. These studies have been used primarily to determine the nature of insulin action.

At present it is necessary to view most of the animal studies cautiously and to avoid excessive generalizations to human diabetes and to consider carefully the complications involved in human studies. Again, the safest conclusions appear to be
those involving the basic ramifications of hyperglycemia.

Enzyme Changes

Most of the enzyme changes to be discussed are summarized in figure 2. Although all the products and substrates are interconnected, several of the pathways or enzymes are found only in certain tissues. For instance, the glycogen transferase interconversion occurs primarily in white blood cells and the sorbitol dehydrogenase step is mentioned with reference to the eye.

Enzymes Affecting Insulin Directly

Insulinase is an insulin-specific, hydrolytic, enzyme found only in the liver and is responsible for the short circulating life of insulin. Its presence has been reported in rats, mice, rabbits, guinea pigs, cows, chickens, ducks, monkeys and men al-
though the concentration among species varies. Its activity increases after a high carbohydrate meal and also after a high protein meal, although more slowly. After fasting its activity is diminished. Mirsky also postulates that there is an insulinase-inhibitor produced in the liver. He suggests that diabetes may be the result of a metabolic derangement, which interferes with the synthesis of this insulinase inhibitor, which results in a higher level of insulinase and a lower level of insulin.

Glutathione-insulin transhydrogenase is found in the liver where it catalyzes the reduction of interchain disulfide bonds of insulin which results in its inactivation. One can speculate that it may also be involved in diabetic induced changes in insulin concentrations.

**GLUCONEOGENIC ENZYMES**

Changes in these enzymes have been discussed in the section on the role of insulin in diabetes. Glucose-6-phosphatase, fructose-1,6-diphosphatase, PEP carboxykinase and pyruvate carboxylase activities have all been shown to increase in the liver. Prasannan and Subrahmanyan found a decrease in glucose-6-phosphatase in the brains of alloxan-diabetic rats, which they felt accounted for the high glycogen levels found there.

**GLYCOLYTIC ENZYMES**

Glucokinase, phosphofructokinase and pyruvate kinase activities all decrease in diabetes. The effects of insulin and adrenocorticoid hormones on the synthesis of these enzymes has already been discussed. Pyruvate kinase and glucokinase have isoenzymatic natures which warrant further discussion. Two pyruvate isoenzymes have been reported. Type L is found exclusively in the liver; its activity has been shown to decrease in diabetes, and this action is restored by insulin. It has been electrophoretically divided into three sub-peaks of unknown significance. Type M, the muscle type, is found primarily in muscle although it is also present in the liver. It is, however, unaffected by insulin or diabetes. Tanaka et al speculate that the L isoenzymes are related to the metabolic control of gluconeogenesis and the M isoenzyme is a less differentiated form.

The hexokinase isoenzyme system is the one most widely studied in relation to diabetes. The majority of the work has been done with alloxan-diabetic rats, but the implications for the mechanism of control of metabolism are still very significant and worth considering. Katzen and others have reported a system of five isoenzymes: Types I, II, III and IV in order of increasing electrophoretic mobility toward the anode and the S.T. or sperm type which is found nearest to the cathode. Types I, II and III are hexokinases. They are not substrate specific and are found in all tissues although in different proportions. All three have a molecular weight of 96,000 and seem to be localized in the non-parenchymal cells of the liver. Type IV is found only in the liver, is known as glucokinase and is glucose-specific. It has a high Km for glucose in comparison to the other three hexokinases mentioned. Brown et al have suggested that this property would allow glucokinase to handle large glucose loads. Its activity drops sharply in diabetes. Sharma et al suggest that glucose and insulin are crucial in its induction and high levels and normal activity must be maintained. Borrebach and Spydevold suggest that they accomplish this by acting on the net balance between synthesis and degradation. The molecular weight of glucokinase is 48,000, approximately half the molecular weight of the hexokinase isoenzyme. Glucokinase is found in the parenchymal cells of the liver.

Katzen and Shimke have reported on the tissue distribution of these isoenzymes. Liver contains all four types with a large amount of Type III, brain and kidney contain mostly Type I, fat pad and muscle
contain primarily Type II and heart contains approximately equal amounts of Types I and II. It is usually difficult to get data on Type III because it is substrate inhibited.

Katzen et al\(^{\text{22}}\) have suggested that as the full complement of Types I, II and III increases (particularly Type I), the insulin sensitivity of the tissue decreases. This accounts nicely for the known insulin insensitivity of the brain and kidneys. Katzen\(^{\text{20}}\) has reported a further breakdown of Type II when it is electrophoresed without mercaptoethanol. A IIa fast band appears, which decreases preferentially in diabetes, and there is also a relatively stable IIb slow band. Katzen believes that mercaptoethanol catalyzes the conversion of IIb to II, and this accounts for the inability of most investigators to find a change in band II in diabetic specimens. Katzen feels that IIa is a monomer and IIb a dimer and interconversion occurring through thiol-disulfide interchanges. In addition he has suggested that these forms may be involved in an insulin-stimulated glucose carrier system across membranes. McLean et al\(^{\text{29}}\) however, have found a decrease in band II in alloxan-diabetic rats even in the presence of mercaptoethanol. It is possible that there may be significant differences between the streptozotocin-diabetic rats used by Katzen\(^{\text{30}}\) and the alloxan-diabetic rats used by McLean et al\(^{\text{29}}\). Pilkes and Hansen\(^{\text{35}}\) have found that Type IV hexokinase from alloxan-diabetic rat liver breaks up into two bands, IVf (fast), which preferentially disappears in diabetics, and IVs (slow), which is unchanged when it undergoes electrophoresis in the absence of EDTA. The molecular weight of each band is 48,000, which suggests that they are not subunits of band IV. Although Kaplan and Beutler's work\(^{\text{19}}\) does not relate directly to diabetes, it is interesting to note that they have found two bands of Type I in human red blood cells: Type If (fast) found only in fetal cells and Type Ia found only in adult cells. This finding suggests that these multiple sub-bands may be quite widespread in the hexokinase isoenzyme system.

Although most of the work on this system has been done on rats and Lauris and Cahill\(^{\text{27}}\) found no trace of glucokinase in the human as late as 1966, Grossbard et al\(^{\text{15}}\) have stressed the species similarities and the likelihood of finding similar systems in all the vertebrates. Brown et al\(^{\text{16}}\) have recently reported a five isoenzyme hexokinase system in men and dogs which is comparable to the rat isoenzyme system.

These are really only the beginnings in the study of hexokinase, but it is already clear that this isoenzyme system is important as a control mechanism in glucose metabolism and may have a very basic role in the changes occurring in the diabetic's metabolic processes. The possible linkages with membrane transport systems\(^{\text{30}}\) and the reversible binding to microsomal fractions, including increased binding of the hexokinases to the mitochondria with increasing glucose or insulin concentrations,\(^{\text{2,5}}\) could prove to be very important processes.

**Tricarboxylic Acid Cycle-Related Enzymes**

The TCA cycle is overloaded and suppressed in diabetes. McGilvery\(^{\text{28}}\) reports decreases in the activities of citrate cleavage enzyme and malic dehydrogenase. Malic enzyme also decreases.\(^{\text{26}}\) These changes are in line with the overall pattern of decrease in glucose-breakdown pathways and increase in glucose-forming pathways.

**Glycogen-Related Enzymes**

Pathologic glycogen deposits have been implicated in many of the clinical manifestations of chronic diabetes.\(^{\text{38}}\) Spiro,\(^{\text{41}}\) however, has reported a general decrease in glycogen levels in an alloxan-diabetic rat. It is generally recognized that the insulin deficiency of diabetes is accompanied by glycogen breakdown and hyperglycemia.\(^{\text{46}}\)
These findings are difficult to reconcile. Prasannan and Subrahmanyans work with cerebral cortex slices from normal and diabetic rats and guinea pigs suggests a possible answer. They have found there is a seven fold increase in brain glycogen in diabetic animals which is explained by a 640 percent increase in glycogen synthetase activity and a 133 percent increase in phosphoglucomutase activity. At the same time, however, phosphorylase activity is reported to decrease and McGilvery has reported a decrease in amylo-1,6-glucosidase activity in the diabetic. Although it is premature to form conclusions on the basis of work done on the brain alone, it is possible that these divergent findings can be accounted for by increases in both glycogen synthesis and glycogen breakdown with synthesis exceeding breakdown, as it appears to happen in the brain.

Serum amylase has been reported to increase in diabetic coma complicated by acute pancreatitis, and Tully and Lowenthal suggest that the concentration is normal in diabetes when the pancreas is not involved. Finn and Cope, however, report that its activity is decreased in simple diabetic coma.

A change in glycogen transferase from a glucose-6-phosphate dependent "D" form to a glucose-6-phosphate independent "I" form in white blood cells has been reported by Esmann et al. The conversion is mediated by insulin, which also increases the rate of the conversion. The combined I and D activity is low in uncontrolled diabetes. These two enzymatically interconvertible forms have also been found in muscle and liver, but their significance is not discussed.

**Pentose Pathway Enzymes**

Ilyin has reported a decrease in both glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase activity in alloxan-diabetic rats. This would result in the increased production of glucose-6-phosphate and glucose.

**Fatty Acid Metabolism-Related Enzymes**

In diabetes, there is a mobilization of free fatty acids to the liver and a decrease in lipogenesis. McGilvery has reported a decrease in acetyl CoA carboxylase activity which would result in a decrease in fatty acid synthesis; this provides an example of the general mechanism.

**Protein and Amino Acid Metabolism-Related Enzymes**

The glucose loss in diabetes results in a need for increased mobilization and catabolism of proteins. Mullan has reported an increase in serum leucine aminopeptidase in men with poorly controlled diabetes and a spillage of the enzyme into the urine when gangrene is present. Heavy proteinuria was found along with a marked increase in LAP excretion. McGilvery has reported an increase in serine dehydratase. Goldberg et al have reported an increase in serum gamma-glutamyl transpeptidase activity in 30 out of 85 diabetic patients, but found liver dysfunction in all cases of greatly increased activity. Kohot and Kuska have reported no distinct patterns of change in serum gamma glutamyl transpeptidase although all the diabetic fractions differed somewhat from normal.

**Energy-Transfer-Related Enzymes**

Adelman and Weinhouse have reported an increase in adenylate kinase activity in alloxan-diabetic rats, but the significance of this change and the resultant increase in ATP is not well understood. Kupiecki has reported a decrease in phosphodiesterase activity in spontaneously-diabetic mice which should lead to a buildup of cyclic 3',5'-AMP which is known to stimulate insulin release from the β-cells of the pancreas. This may account for the high level of plasma insulin found in these mice. This does not result in increased glucose utilization and could be due to the blockage of
the pentose phosphate shunt by the accumulation of cyclic AMP.

**Glucuronic Acid Pathway Enzymes**

Winegard and DePratti have found high fasting levels of serum L-xylulose in fasting diabetic patients and suggest that this may indicate greater usage of the glucuronic acid pathway. Miller et al have speculated that the increased usage of the pathway in diabetics may lead to an excessive deposition of mucopolysaccharides and glycoproteins, which are implicated in many vascular diseases. They have generally found increased serum β-glucuronidase in diabetics and a still higher average activity in diabetics with atherosclerosis. Miller et al suggest that the increase of this enzyme may be a way of preventing excessive buildup of polysaccharides in the basement membranes of the capillaries. Therefore, this increase may serve a protective function.

**Other Enzyme Changes**

In view of the high incidence of cataracts in diabetic patients, it is worthwhile to consider enzyme activity changes within the eye. Gabbay and O'Sullivan suggest that accumulations of sorbitol and fructose in lenses lead to diabetic cataracts. However, they found a 30 percent decrease in aldose reductase activity in the eyes of diabetic animals with cataracts. They suggest several explanations for this paradox: since Wallerian degeneration of the Schwann cells was used for enzyme localization, there may have been loss of aldose reductase activity owing to macrophage activity. This decrease in activity may occur only in certain Schwann cells while others continue to produce excessive amounts of sorbitol; or the reduction in activity may lead to localized accumulations of polyols, glucose and other sugars and the formation of sugar cataracts owing to hypertonicity of the lens followed by bursting. Pottinger has also found increased activity of glucose dehydrogenase and high levels of gluconic acid. Although Gabbay and O'Sullivan found no change in sorbitol dehydrogenase activity, the accumulations of fructose found in the eye of a diabetic animal with cataracts suggest that there may be an increase in this enzyme. Clearly, more work is needed on this subject. Nilson et al have reported some interesting changes in MAO (monoamine oxidase) in serum in diabetic patients. This enzyme catalyzes the oxidative deamination of several monoamines found in nerve endings to aldehydes and ammonia. Its level has been reported to be already increased at the first clinical appearance of the disease and its activity appears to be independent of complications, duration of the disease, therapy used, age of the patient, sex of the patient, type of meal or occurrence of pregnancy. Only 14 out of 340 diabetic patients showed activities within the normal range. Its characteristics make it a likely candidate for future use in diagnosis.

**Diagnostic Role of Enzyme Changes**

The diagnostic role of enzyme changes in diabetes is very limited at the present time. Most of the studies have dealt with changes in tissue homogenates rather than changes in serum levels. A major portion of the work to date has been done on the hexokinase isoenzymes, and these are found in the microsomal fragments. Some serum enzyme studies have been carried out, but the evidence is mostly inconclusive. Serum alkaline phosphatase has been found to increase in human diabetes and shows no correlation with sex, age, body weight, duration of diabetes, type of treatment, previous or present control, amount of insulin given, diet or blood cholesterol. In another study of 161 diabetic patients no changes in serum enzymes were found. Both papers are somewhat suspect because of the lack of screening for anything except recent coma and liver disease. Nakamura et al also report no changes in lactic de-
hydrogenase levels. Many changes have been reported in patients with ketoacidosis. Velez-Garcia and Coodley have reported increases in serum CPK during and after treatment for ketoacidosis. Normal diabetic patients showed little or no change in CPK levels and patients with ketoacidosis before treatment were normal. The levels increased as treatment progressed and showed no correlation with insulin dose or degree of ketoacidosis. These authors suggest that this could be the result of a direct effect of insulin on the membrane or due to the osmotic changes accompanying electrolytic and fluid shifts, resulting in membrane leakage. The latter possibility seems more probable in view of the severe pH and osmotic changes occurring in ketoacidosis. Janowitz and Dreiling have reported lower levels of serum α-amylase in diabetes and higher levels in pancreatic disease. Tully and Lowenthal reported elevated serum amylase in diabetic coma with associated pancreatitis, and suggest that it is not clearly distinguished from uncomplicated diabetic coma. Finn and Cope found a general decrease in serum amylase in diabetic coma unless there was pancreatic involvement. This was generally accompanied by an increase in circulating amylase. Serum GOT and GPT are alternately reported to be unchanged and slightly increased in newly diagnosed uncontrolled diabetes.

Mullan's studies on serum LAP have already been mentioned. There seem to be a variety of explanations for its increase. Its most valuable use could possibly be the indication of poor control in diabetic men, but the evidence seems very inconclusive. At the present time, serum MAO seems to offer the best possibility for diagnosis in view of its apparent increase before the onset of clinical diabetes and the lack of complicating factors.

In general, glucose tolerance tests with or without cortisone, fasting blood sugar levels and urinalysis still seem to be the most useful diagnostic tools for diabetes. Most of the enzyme change studies to date have been more valuable in elucidating the nature and range of the disease than the underlying metabolic changes.

Future Studies

It is interesting to speculate on what direction future research in this field will take. Most of the studies raise many more questions than they answer. A clearer definition of just what constitutes diabetes is necessary. The possible connection with the coronary angiopathies are certainly significant. More general clinical studies will help to clarify how closely interrelated these conditions are and which come first chronologically.

Winegard and De Pratti have found that L-xylulose is increased in the serum of the diabetic patient, and this would seem to point toward increased use of the glucuronic acid pathway, which would yield increased glycoprotein deposits. Excess glycoproteins are closely connected with many of the diabetic angiopathies and retinal problems. The presence or absence of coronary vascular complications may be closely related to the level of the β-glucuronidase enzyme. It may also be worthwhile to determine the frequency of changes in the pathways of the eye because of the connection with cataract formation. The evidence here is still rather contradictory.

In view of the probable appearance of serum MAO before clinical onset, it will undoubtedly receive much more attention and investigators are likely to search for other enzymes that show changes before clinical onset of the disease.

More studies of the hexokinase isoenzymes and other isoenzyme systems may provide information on the control mechanism involved in metabolism in normal and diabetic states. This work may give further insight into the genetic control about which Weber et al have speculated.
Although the differences between early-onset and late-onset diabetes certainly seem to suggest that there would be differences in accompanying enzyme changes, there seems to be little work in this area. This is probably due to the fact that these conditions cannot be studied in experimental animals. A better understanding of the differences in these two forms of diabetes may help clarify the genetic basis of the disease.

Much remains to be done. Much of the work done on rats must be verified in human studies before the conclusions can be considered valid. Before this can be successful, diabetes must be more clearly defined. Interplay between human and animal studies will probably provide the answers.

References


