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Diabetes

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Symposium on Diabetes Mellitus: The 37th Annual McGuire Lecture Series

COVER *by Raymond A. Geary.* OPPOSITE: *Electron photomicrograph of muscle capillary from a diabetic patient, showing thickening and reduplication of the basement membrane* (× *8500*). (*Dr. William J. S. Still*)

The Natural History of Diabetes

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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 "prediabetes." 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, 1½, 2 and 3 hours after glucose. (b) In prediabetics 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-Dávalos, 1965a). (g) Prediabetics show an increased rise in blood growth hormone three hours after glucose, following the initial supression 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.

TABLE 1
Stages in Life History of a Diabetic

I. Prediabetes	From conception to first evidence of impaired insulin reserve. No demonstrable abnormality in carbohydrate metabolism.
II. Asymptomatic or Chemical Diabetes	(a) With stress only: Blood sugar (BS) elevated only with stress, such as infection or pregnancy. Glucose tolerance test (GTT) normal. Cortisone GTT abnormal. (b) Present without stress: Postprandial BS elevated. Fasting BS normal or slightly elevated. Little or no glycosuria. GTT abnormal.
III. Symptomatic or Overt Diabetes	Persistent hyperglycemia and glycosuria. Polyuria, thirst, etc. GTT not necessary.

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 β-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

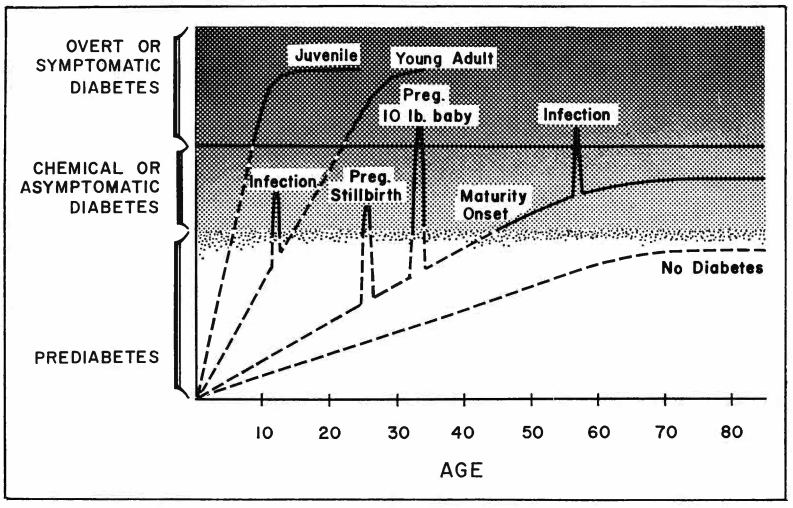

Fig. 1—The course of diabetes with age is indicated as a line sloping upward as the disease becomes more severe. Prediabetes is indicated as a clear zone, and diabetes is indicated by stippling, which is heavier toward the top as the disease becomes more severe. The juvenile diabetic progresses rapidly 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.

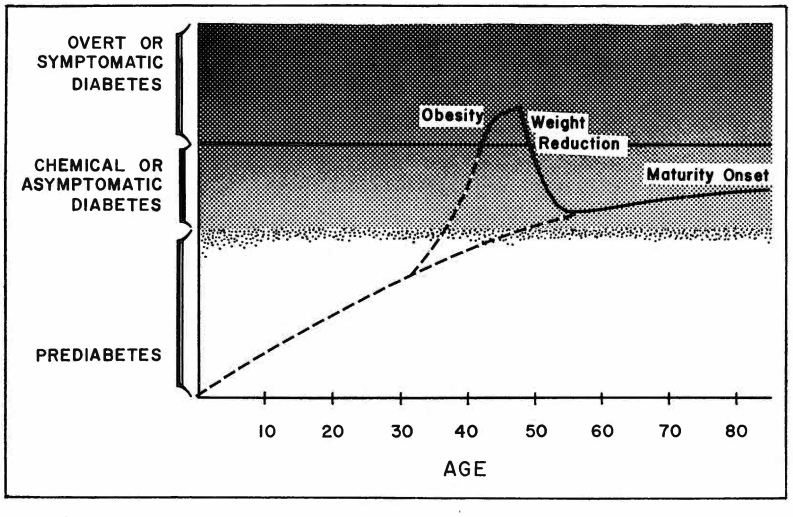

Fig. 2—Effect of obesity and weight reduction on the course of diabetes. Obesity often converts prediabetes or mild asymptomatic diabetes to overt diabetes. With weight reduction alone, the diabetes may disappear entirely or revert to a mild asymptomatic state.

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 prediabetics, while normal, show significantly higher blood sugar levels after glucose than in non-prediabetics 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.

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" (Samaan, 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

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The Treatment of Diabetic Acidosis

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The patient with diabetes mellitus who becomes unconscious presents a problem in differential diagnosis. We now recognize six possible causes of coma in the diabetic patient. These include the usual diabetic keto-acidosis, and five possible non-ketotic causes:

I. Keto-acidosis
II. Non-ketotic causes of coma
  A. Unconsciousness unrelated to diabetes, e.g. barbiturate intoxication, "stroke," uremia
  B. Hypoglycemia
  C. Lactic acidosis
  D. Hypernatremia
  E. Hyperglycemia

Of the non-ketotic types, the first may be considered to be a coincidence of unrelated events in a diabetic patient, i.e., diabetes plays no direct and immediate causal role in the coma.

Hypoglycemic coma most commonly follows excessive dosage of insulin, but may also be caused by the oral hypoglycemic agents, especially in patients with impaired renal function who do not excrete the sulfonylureas well. Hypoglycemia four to five hours after eating also may be a manifestation of early, untreated diabetes, with delayed secretion of insulin by the pancreas.

Lactic acidosis results from tissue hypoxia, with inability to convert lactate to pyruvate, the accumulation of lactic acid resulting in acidosis. This is most often seen in patients who have been in prolonged shock, as from slow bleeding or from myocardial infarction. Often they have an alcoholic history. The prolonged shock with tissue hypoxia causes excessive production of lactic acid, which is not adequately removed by the liver. The serum bicarbonate and pH are down, but no acetone is present in the urine or in the plasma.

Hypernatremic coma and hyperglycemic coma are both produced by cellular dehydration resulting from excessive hyperosmolarity of the extracellular fluid. Generally in hypernatremic coma serum sodium levels are as high as 156 to 188 mEq/liter. Hyperglycemic coma is characterized by blood sugar levels of 600 to 1000 mg% or higher. Hyperosmolar coma occurs chiefly in older individuals. Their diabetes is often of recent onset, with no treatment or inadequate treatment, and a slow development of stupor and unconsciousness. Treatment consists of the administration of hypotonic fluids and insulin as needed. These patients do not have the extreme resistance to insulin seen in keto-acidosis, and the amount of insulin required is usually much less than in keto-acidotic coma.

In the patient who develops keto-acidosis, a shortage of insulin is the key defect. This shortage can arise from a variety of circumstances, such as undiagnosed, untreated diabetes, omission of insulin in the known diabetic, or failure to meet the increasing requirement for insulin caused by infection, inactivity, or emotional disturbances. We recognize that the key ingredient in therapy is insulin. However, as the acidosis develops, there occur a number of changes in extracellular and intracellular fluid and electrolytes. I would like to spend a little time discussing these because they represent important facets of this disturbance.

FLUID AND ELECTROLYTE DISTURBANCES

Depletion of Cell Potassium

Patients who develop keto-acidosis usually have anorexia and vomiting. Obviously, anything that interferes with the intake of food and fluids will interfere with the intake of potassium, so that the ordinary supply of potassium is cut off. At the same time, the interruption of glycolysis, a source of energy for maintenance of the intracellular distribution of potassium, results in a leaking out of potassium from the cells. Also, because patients with keto-acidosis are not eating, they will have a negative nitrogen balance. Cell protein is ordinarily laid down in a proportion of 1g of nitrogen to 3 mEq of potassium. When a negative nitrogen balance occurs, potassium is lost from the cells. Also, the patient in diabetic keto-acidosis is not storing carbohydrate in the liver as glycogen. This process ordinarily removes from the extracellular fluid a certain amount of potassium. As the liver becomes deglycogenated in the keto-acidotic patient, this potassium is released. So we now have three processes transferring potassium from the cells into the extracellular fluid; loss of the pump effect, negative nitrogen balance, and deglycogenation of the liver.

The so-called "dehydration reaction" is a fourth cause of potas-

sium loss from cells. These patients become dehydrated, first of all because they are not taking fluids. At the same time, they usually have an osmotic diuresis and continue to lose fluids from the skin and through the lungs. As dehydration progresses, the body tries to maintain the integrity of the extracellular and intracellular fluid as close to normal as possible. Most of the losses are from the extracellular fluid in the initial phase, but ultimately transfers from cells to extracellular fluid occur. A variety of mechanisms bring these transfers about. First, as the tonicity of the extracellular fluid rises because of hyperglycemia, water is drawn out of the cells. Secondly, there is a dehydration reaction which permits the release of potassium from cells and with it a modicum of water. In other words, the transfer of potassium out of the cells reduces the osmolarity of the cells and raises the osmolarity of the extracellular fluid, and therefore water is transferred with the potassium. These mechanisms serve to prevent excessive depletion of extracellular fluid, but at the same time they deprive the cells further of potassium.

That a deficit of cell potassium of sufficient degree produces histologic evidence of cell destruction is clearly demonstrable in heart and skeletal muscle. Interference with normal cell function by potassium depletion is recognized in electrocardiographic changes, and in altered function of the nervous system, the gastrointestinal tract, and the kidneys. But more important than any of these is that potassium deficits within the cell are associated with increased mortality. This is amply demonstrated in animal studies and has its counterpart in the clinical situation.

Serum Potassium Levels

Although the patient with diabetic keto-acidosis is markedly depleted of potassium, the initial level of serum potassium is often high. This is because, during the development of keto-acidosis, potassium has been transferred from cells into the extracellular fluid, and as dehydration and decreased renal blood flow diminish the urine output, potassium may not be well excreted. With fluid replacement and insulin treatment, potassium will quickly re-enter the cells and the serum potassium may drop sharply during the first few hours of treatment. In children, the initial serum potassium levels are not so often elevated, but may be normal or occasionally low. The reason may be that in children there is possibly a greater osmotic diuresis and a more rapid excretion of the potassium that has passed from the cells into extracellular fluid. In either case a low initial serum potassium level should alert one to the presence of very severe potassium depletion and the danger of severe hypokalemia developing in the course of treatment.

Sodium Loss, Dehydration, and Shock

With respect to sodium, some of the comments already made concerning potassium apply. The intake of this electrolyte is cut off, and further losses occur through vomiting and from renal loss as part of the osmotic diuresis. All these losses of sodium result in sodium depletion. When extracellular sodium is reduced by 25% a prompt decrease in circulatory efficiency occurs. If sodium is lost from extracellular fluid in excess of water, hypo-osmolarity of the extracellular fluid results. This causes water to move into the cells. This by itself has no particular significance, but the loss of circulating volume from the extracellular fluid, either by loss to the exterior or by transfer into cells, results in circulatory inefficiency. With the reduction in plasma volume the hematocrit rises. There is slowing of the circulation, with diminished venous return, decreased cardiac output and increased peripheral resistance. The end result is circulatory collapse, just as real as that which can follow hemorrhage, extensive trauma, or any other cause.

It is very important to recognize the occurrence of sodium deficits. Such deficits are invariably present but the signs of circulatory collapse may not be. I think surely all of us now realize that we can have circulatory inefficiency with a normal blood pressure. As the blood volume falls, the blood pressure can be maintained for a while by arteriolar constriction, but this will lessen the delivery of blood to the tissues, which in turn interferes with cell function.

THERAPY

Insulin

The treatment of diabetic keto-acidosis begins with insulin. Generally this can be given in the home before the patient is referred to the hospital. Time is of the essence and one has to make sure that valuable time is not lost transporting the patient to the hospital, getting him admitted, finding out about hospital insurance, etc., and moving him to his bed. How much insulin, what route of administration, frequency of dosage etc., you and I could discuss for a long time. I think it is interesting to recall that some 20 years ago, Rabinowitz, in Montreal, routinely administered 200 units of insulin on admission and gave no further insulin, and in that particular series of patients all of them recovered. You and I are more apt to approach this problem in a gradual fashion, so to speak. We back into a final decision. Of course we can be a little bit more scientific if we call it "the method of successive approximations toward the need," but fundamentally "chicken" is a better term. I think it is better to remember that you can quite safely give too much insulin because you can counteract this subsequently by administering carbohydrate. But if you do not give enough insulin, the one thing that you cannot recapture is time. So, if you are going to make a mis-

take, do so in a very bold fashion. Experience indicates that ordinarily 300 or 500 units of insulin in the first 24 hours have proved to be adequate. This does not mean that there are not going to be patients that require a good deal more. Also you will have patients who will do well on a smaller quantity. This is an average figure and ordinarily in this "chicken" fashion, you will first administer 100 units as soon as the patient comes into the emergency room. This gives you a chance to get a little information as to the level of blood sugar, the decrease in "CO_2," the presence of plasma acetone, and the status of the circulation.

Fluids

After withdrawing blood from one vein, you start an infusion of 0.9% sodium chloride solution. There are many choices of solutions. We still prefer sodium chloride. First it is generally available. Secondly, all of the solutions that are offered represent confusion in a sense. If you use Ringer's lactate solution, it has a little bit of bicarbonate in it and it has a little bit of potassium and you may think you are doing something, but you are only deluding yourself. So we recommend beginning fluid replacement with sodium chloride. It is a useful rule of thumb to keep in mind that an adult diabetic coma patient comes in with a water deficit equal to 10% of the body weight, a sodium deficit of 10 mEq/kg, a chloride deficit of 10 mEq/kg, and a potassium deficit of 5mEq/kg. This means that in an adult weighing 70 kg, on admission there is a deficit of 7 liters of water, 700 mEq of sodium, 700 mEq of chloride, and 350 mEq of potassium. Our goal is not to replace these deficits at once. Our goal is one of turning the patient around and starting him toward recovery and away from death. The administration of sodium chloride following the initial dose of insulin provides an adequate beginning in most instances. Ordinarily it will be sufficient to give two liters of sodium chloride, which contains approximately 18 g, or 308 mEq of sodium and of chloride. Please note that we are not trying to replace the total deficit of 700 mEq at once. We are giving part of it over the course of several hours. We recognize that during these several hours some of what we have administered will continue to be lost in the urine or by other routes. But it is enough just to turn the patient around. At the end of the 2 liters of saline, which will probably take some 3 hours to administer, one will have further laboratory data. At that point it may very well be that the laboratory indicates that the serum potassium is now down to normal or below normal, and at this point one can start therapy with potassium. Also laboratory reports will often indicate that the blood sugar is decreasing. At this point the potassium can be administered in 5% glucose. Generally it is desirable to use potassium phosphate rather than chloride. The reason for this is that we are using sodium chloride which has 154 mEq of chloride which is higher than the concentration normally present in extracellular fluid. We do not want to give KCl because we will be further adding to the chloride load and in some patients a hyperchloremic acidosis may result. The second reason is that patients with diabetic keto-acidosis develop deficits of phosphate from lack of intake and from loss of this solute in the urine. This phosphate does not come from the extracellular fluid; it comes from the cells. Some of it comes from protein breakdown, but the majority of it represents the breakdown of high-energy phosphate compounds such as ATP and creatine phosphate which are not being rebuilt because carbohydrate metabolism is reduced. No one has ever succeeded in demonstrating that these huge deficits of phosphate do any harm. Nonetheless, it does seem logical to give the potassium replacement as buffered phosphate, both to help somewhat in replacement of phosphate, and to avoid adding to the chloride load. How much potassium would you give? If the total deficit is estimated to be 350 mEq, it would probably be enough to set as a goal the administration of approximately one third of that over 3 or 4 hours, at the rate of approximately 40 mEq per hour.

Glucose

There has been great controversy in the past as to whether glucose should be given in the initial phase of treatment. Glucose solutions given even at the start of treatment do no harm except possibly to contribute further to the osmotic diuresis. Glucose does help to replete liver glycogen and diminish the ketosis, but many prefer not to begin glucose administration until there is definite evidence that the blood sugar has begun to fall with treatment. We should remember that even an initial blood sugar of 500 mg% may not represent more than 50 or 60 g of total glucose in the extracellular fluid, and this amount can be put back into cells fairly quickly once enough insulin is given. It is imperative that glucose be provided as the blood sugar falls, in amounts adequate to cover the large doses of insulin that have been given, and at a rate rapid enough to prevent hypoglycemia.

Dextran and Alkalis

It is a good rule in seriously ill patients to consider two additional elements in the early therapy. The first of these is the use of dextran, or less desirably, the use of whole blood or plasma. Whole blood or plasma is less desirable because of the problem of hepatitis. In patients on the verge of circulatory collapse or in actual circulatory collapse, a unit of dextran is a kind of insurance and I would rather give it needlessly to 99 patients than fail to give it to the one who needs it. The second item is the use of alkali

solutions shortly after admission. I like to reserve these for patients who have a reduction of the pH down to seven or so. The routine administration of alkali interferes with the use of "CO_2" (bicarbonate) as a precise index of improvement. It is very reassuring to find that a bicarbonate of 5 mEq/liter has risen after several hours of treatment to 8 or 9 mEq/liter. I know that the patient is clearing ketone bodies and is responding to insulin. I cannot tell this quite as precisely when one uses the plasma acetone or the urine acetone as the sole index. This index is lost when 6 molar lactate or sodium bicarbonate is administered. On the other hand if the pH is reduced sufficiently, we know that this by itself threatens survival, and under these circumstances one should give alkali.

Use of Fructose

Another point that deserves mention is the use of fructose instead of glucose. Theoretically there are several advantages to fructose. First of all, it can enter the glycolytic cycle without the intervention of insulin. Secondly, it is an excellent glycogen former and, as we have indicated, hepatic glycogen is depleted. Thirdly, the Tm for glucose and the Tm for fructose are independent and non-additive. The kidneys reabsorb glucose and fructose independently, and therefore one can carry higher blood sugar levels with less glycosuria. All of these are cogent arguments, but from the practical point of view, they are not significant. Fructose further complicates therapy and there may be some hazard because in children fructose causes massive deposition of glycogen in the liver which itself might be harmful. The liver becomes greatly distended and you have the feeling that only the capsule is preventing it from bursting.

I have said nothing about lavage of the stomach or passage of a stomach tube. Life is already complex when you have a keto-acidotic patient to look after, and passing a tube into an unconscious patient is not the easiest thing to do. The stomach tube should be put down only in those patients who continue to vomit. Most patients will not continue vomiting if you do not give anything by mouth. Whatever is in the stomach and gastrointestinal tract will be absorbed as therapy continues, so generally it is reasonable to avoid this additional complication.

MANAGEMENT AFTER THE FIRST FEW HOURS

We have come now to the sixth, seventh or eighth hour and the patient is responding to treatment in a satisfactory fashion. We have seen some decrease in the blood sugar, some rise in the "CO_2," some decrease in the acetonemia. The urine continues to contain sugar; it still contains ketone bodies but perhaps in reduced quantities. By this time the patient is partially restored to consciousness, perhaps asking for food and fluids by mouth. We can begin to relax a little, but we should not take the needle out of the vein. The patient can be started at this point on some intake by mouth. If vomiting ensues, this should be discontinued. One can alternate tea fortified with glucose and sucrose and lactose with 0.5% sodium chloride broth. The real problem is encountered between the 12th and 24th hour. The difficulties stem from the fact that the house staff has been working all night long on the coma patient; morning arrives, and it is time to have the report and to make rounds. So everyone relaxes as far as attention to the patient goes. Or, if the house staff has worked all day, it is midnight and time to go to bed. The nurses are very considerate, so they do not report promptly when the glucose infusion is not working properly. There are two problems that develop. One is hypoglycemia and the other is hypokalemia. Twenty percent of the patients who are in the 12th to 24th hour of therapy develop blood sugars which are in the hypoglycemic range. Approximately 20% develop hypokalemia with potassium levels below 3.5 or 3.0 mEq/liter. These are the two sequelae which undoubtedly account for unexplained deaths in comas that have been otherwise treated very successfully. When the patient reaches the 24th hour of treatment, usually we put him back on his usual dosage of insulin or on regular insulin. With resumption of a normal dietary intake, the remaining deficits are made up.

MORTALITY

There is no question that some centers have a better record than others. Certainly the Joslin Clinic record is most impressive with mortalities of 1%, 2%, or 3%. It is recognized that these low mortality rates represent a very selected type of experience, under unusually favorable circumstances. The Joslin Clinic has a laboratory that is set up to look after keto-acidosis seven days a week. Unfortunately, in many other centers the mortality is still high. It ranges between 15% and 25% in adults. The mortality in pediatric diabetic coma is much less. Indeed, you hardly ever see a death in childhood provided the diabetes had been recognized previously, the patient is under therapy, and the coma is treated in a qualified institution. But there are still deaths in children which result from previously undiagnosed diabetes terminating in coma, or that result from the assumption that all hospitals are equivalent in terms of their ability to treat diabetic keto-acidotic coma. Properly treated, keto-acidosis in children and adults should be nothing but an event, certainly an avoidable event in many cases, in the life of the diabetic.

The Management of Diabetes in Children

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I think the time will come when we will all agree that diabetes mellitus is indeed the most common endocrinopathy, and that if we live long enough, at least 25% of the people in this room will develop diabetes. I believe that diabetes has manifestations both as a homozygous and heterozygous state, and that the heterozygous state or so-called carrier state becomes clinically manifest as we get older. Now I am not sure that such diabetes has the same significance as diabetes coming on earlier in life. It may be a benign type of diabetes, but at any rate, it is common.

The problem of diabetes of childhood onset is of tremendous importance because here we see diabetes in its most florid state, and here we see most clearly its devastating end results in certain patients. Here, at this moment, we stand by helplessly watching the evolution of some of the problems.

INCIDENCE AND DIAGNOSIS

It has been estimated that 5% to 10% of the total diabetic population has the onset of diabetes during childhood. I do not know how accurate these figures are since we do not know how common diabetes is. Diabetes in children, in contrast to adults, is characterized by the presence of symptoms. Adults, as you know, can go for years and not know they have diabetes because it is asymptomatic and often demonstrable only by glucose tolerance tests. This is not true in children.

In looking over the records of several hundred children with diabetes, one finds that polyuria, polydipsia, weight loss, polyphagia and fatigue are present in 90% or more of the children. These are the classical symptoms that we ordinarily associate with diabetes, although they are not present in the majority of adults. About 20% of childhood diabetics are first diagnosed when admitted to the hospital with diabetic acidosis. Often the diagnosis of diabetes is not suspected early and is actually made in retrospect. Practically everything else may be done in the case of a youngster who is having anorexia, nausea, and vomiting, including a gastrointestinal series, but not a blood sugar determination or a urinalysis. The recurrence of bed-wetting in a previously trained child pointed to the presence of diabetes in 13% of these patients.

More than half the children with diabetes are diagnosed in the first 30 days. That is because the disease is symptomatic. However, there are some who apparently go on for periods of months or perhaps for as long as a year or two without diagnosis. January is the month in which diabetes is diagnosed most frequently and one wonders why this is so. Of course in the North one can say that it is the time of year when respiratory infections are present and this would make diabetes worse. There are those of us who might feel that overindulgence, particularly at Christmastime, has something to do with it.

There is a fairly symmetrical distribution curve of the age of onset of diabetes in childhood. The youngest diabetic on record is one diagnosed by urine test within an hour or two of birth. The youngster did have permanent diabetes and still has it, but is doing well now some 10 or 12 years later.

Diabetes occurs in families. Particularly one finds that the grandmothers of a diabetic on both the maternal and paternal side have diabetes. This does not necessarily mean that there is such a striking difference between grandmothers and grandfathers, but it probably reflects the fact that grandmothers live longer than do grandfathers. At the time the diabetes is diagnosed, one can obtain a history of known diabetes in some relative in approximately 20% of the patients. If one waits a period of five years and surveys the group again, this percentage increases to 60%. What happens is probably that other members of the family are tested, or with the passage of time, diabetes appears in the others.

THERAPY

Diet

Once the diabetes is diagnosed, one is faced with the problem of therapy. There are many choices open to us. With regard to diet, in general we take the attitude that children will eat, and that if children are properly brought up, they will eat the same kind of diet that we would prescribe. Indeed this is the custom that we follow. We begin with an approximation based on calories per kg, starting at birth

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with 125 calories per kg, and decreasing to 40 to 45 calories per kg when the body weight reaches 60 kg or 130 lbs. One can use this approximatation as a starting point. If the youngster says he is hungry, we give him more food. If he cannot eat it all, we give him less. When we get through, actually the youngster is selecting his diet. Not everyone practices this approach, and indeed we do not try to do this with every patient. There are some patients or families who derive tremendous reassurance from a program based on careful measurement of food intake. But by and large, most patients over the long pull object to a precise regimen. This represents not necessarily a yielding to their wishes, but rather an attempt to "custom-tailor" the program to meet the needs of the majority of children with diabetes.

The diets outlined by the American Dietetic Association provide a large number of calories from fat, as high as 45% to 50% of the total calories. We think that all Americans eat too many calories, too much fat, and too much saturated fat. A better diet for us, diabetic or non-diabetic, would be one that restricted calories, restricted the amount of fat to some figure around 30%, and increased the proportion of unsaturated fat. This may or may not have any relationship to the problem of atherosclerosis, but it would seem reasonable to adjust our diets in this direction.

Insulin

Virtually all children require insulin, in contrast to adults. The reason, of course, is that they require insulin not only for energy purposes, activity and so on, but also for growth. The mean dosage of insulin is approximately 1 unit per kg body weight, but this is just an average dose, and does not apply to every patient with diabetes. You must give a quantity of insulin sufficient to meet the need. There is no rule of thumb that we can give to the house officers as much as they love the one plus, 5 units; two plus, 10 units, and so on. This is not a rational way of treating diabetes at any age, and certainly not in the case of children.

When diabetes begins, it is possible to demonstrate in approximately two out of seven patients a responsiveness to the sulfonylurea oral drugs. But at the end of a year or two, virtually all of them are no longer responsive. In other words, it is most unusual to find a child with diabetes who does not need insulin, and who can be maintained on diet alone or diet and oral hypoglycemic agents. I do not say that there may not be a place for phenformin (DBI) in the treatment of some diabetic children. This drug, used in conjunction with insulin, will often smooth out the lability which so characterizes juvenile-onset diabetes.

PROBLEMS IN REGULATION

The problem of "brittle" diabetes is often a vexing one in juvenile diabetics. Many patients are sent to us who swing between hyperglycemia or ketosis and hypoglycemia. When I see these patients, the first thing I look for is a "brittle doctor." Often the physician has the idea that children with diabetes should be so perfectly regulated that all urine sugars are negative and the blood sugar normal at all times. This goal is perfectly reasonable in many adult diabetics, but you cannot do this with children. If you try, you are forcing a square peg into a round hole. The child will inevitably have hypoglycemic reactions, with rebound hyperglycemia and often acetonuria afterwards, and his diabetes will really be "brittle." You will most often have to let the child spill some sugar to avoid hypoglycemia at other times.

The next consideration with the "brittle" diabetic is the patient himself, or his family. Are they so obsessed with the goal of sugar-free urine tests as to bring on hypoglycemic reactions with the same consequences.

Then we look for inadvertent overinsulinization. This can sometimes be demonstrated by taking the patient who is receiving 90 or 100 units per day and reducing the dose to 30 units. Sometimes you find that he does just as well, or just as badly, and sometimes you find that he does a great deal better. Repeated insulin shocks, sometimes unrecognized, may be making the diabetes worse, and this can be corrected by lowering rather than increasing the dose.

And we also look for liver disease which is occasionally a cause of brittleness, because the liver cannot adequately store glycogen to buffer the blood sugar level.

By the time we have considered all these possibilities, the brittleness has usually disappeared. If you remember that even precise regulation of diabetes does not guarantee freedom from vascular disease, you can begin thinking of your patient not as a diabetic, but as an individual, with the same problems as anyone else, of growing up and becoming a useful citizen. Please understand that I am not promulgating the idea that you should ignore the blood sugar or the glycosuria, or that you should not regulate the diabetes as well as you can. I am saying that when you strive for perfection in this regulation, you may defeat your own purpose. The price you pay may be too great for the product you get. Indeed, you may get nothing at all.

A true physician does not really alter many things. Often his role is that of an observer, a confidant, a philosopher. If you admit this to yourself, and can approach the problem of regulation of diabetes in a child without preconception or emotional involvement, it is sometimes amazing to see how the tension is relieved in a household, and how much better a youngster does when you get away from urging him to a goal he cannot reach.

GROWTH AND DEVELOPMENT OF THE JUVENILE DIABETIC

Once the patient is started on diet, insulin, and urine testing, we have to consider growth and development. When the diabetes is diagnosed you will note that the diabetic patients are generally just about as tall or sometimes a little shorter than their non-diabetic peers. This is interesting because it used to be said that children are taller when they develop diabetes than their non-diabetic peers.

After treatment for a period of 5 or 10 years, we find that the diabetics are shorter than their peers even though they start off approximately the same. This is not a new observation. Prior to the advent of PZI insulin in 1936, diabetes in children was the commonest cause of dwarfism. With the use of PZI insulin and more adequate programs of regulation, frank dwarfism disappeared. Apparently this tendency to be shorter than the population as a whole is still left. Whether this is nutritional or genetic I am not sure.

In contrast to adults, diabetic children seldom present the problem of obesity. Usually the children are of average or below average size, and they continue to maintain this position relative to non-diabetic children.

An interesting finding is that if you obtain gastrointestinal x-rays on 100 youngsters with diabetes, you will find abnormal patterns in the duodenum in approximately 18. Twelve of these will represent duodenal deformities that appear to be inactive and six of them will represent an active ulcer. This is a surprising finding, although pediatricians are finding more peptic disease in children generally than was formerly suspected. It has some importance because when a diabetic child begins to have nausea and vomiting, we think of diabetic acidosis, but rarely think of an acute ulcer.

EMOTIONAL IMPACT OF DIABETES IN THE CHILD

Another aspect of therapy which is exceedingly important has to do with the emotional patterns of these diabetic children. Any family that has a diabetic child, or indeed any child who is in any way less than perfect, experiences a sense of guilt. Now this sense of guilt may be manifest by projection upon the professional people around them. These are the people we find difficult to deal with, but we can succeed in winning them over. The mother and father may become overprotective about the child. They will team up with a pad and pencil and they will mark down every single event in the life of this child. When they take the child to the doctor, both parents are often present and are anxious to do exactly the right thing.

The youngster has one of several choices. One choice is to comply; this is perfectly acceptable up to the time of adolescence. But adolescence normally includes a period of rebellion which is a normal manifestation of growing up. The child has to disavow his family so that he can set himself up as an individual. He can come back into the family circle afterwards, but if he is overprotected and does not rebel, he does not mature. Experience indicates that diabetic children, as a group, are emotionally immature. You have to be very careful because you can be confused into thinking that they are well-organized and mature, because they are asked to assume responsibilities such as urine testing and abiding by diets and administering their own insulin. Teachers and everyone around them think they are maturing very well. They may be maturing physically, but not emotionally. This is manifest later on in life by poor scholastic records, by poor employment records, and by poor marital records. This is one pattern that evolves.

Another pattern is one of undue rebellion on the part of the youngster, because there is no more effective weapon than an insulin hypoglycemic convulsion or a diabetic keto-acidosis to extract practically anything that one wishes from parents and those about him. This is the type of youngster who is best handled by removing him in every way except environmentally from parental supervision. The physician should deal with him on a kind of man-to-man basis, pointing out that this attitude could mean self-destruction. This kind of behavior may also be present in adults who did not develop diabetes in childhood.

SPECIAL COMPLICATIONS

I should like to turn to some of the incidental events that occur in the lives of these children. Let us

consider diabetic keto-acidosis and coma. In our experience these youngsters develop coma once in five years. Now this does not mean that they have to. Some patients never develop it, and we have had some that have coma every month for 12 months in a row. There should be a low mortality associated with keto-acidosis and coma in a child that is known to have diabetes. The deaths that have occurred have invariably occurred in previously undiagnosed diabetic children, who, as I have indicated, are often admitted to a hospital and studied for all types of entities other than diabetes. When the diabetes has reached the point of no return, the diagnosis is made and they are transferred to a medical center, but it is too late then. Another difficulty is that they sometimes get into hospitals where the staff is not experienced in dealing with keto-acidosis in general, especially in children, and mortality ensues. There are about 200 deaths a year from diabetic keto-acidosis in children in the whole country.

The big problem we are left with is that these youngsters are heir to small blood vessel lesions which involve the kidneys and the eyes, and possibly the blood supply to the nervous system. This microangiopathy, or tri-angiopathy, consisting of retinopathy, glomerulosclerosis, and neuropathy, is present in every single child that has had diabetes for any period of time. One of these, glomerulosclerosis, is present at the time diabetes is diagnosed. In these patients, there is a thickening of the capillary basement membrane, which we recognize as diffuse glomerulosclerosis, and it is present at the time the diabetes appears. Indeed it can antedate the carbohydrate disturbance. Studies demonstrate very clearly that in identical twins, one of whom has already developed diabetes and the other still has a normal glucose tolerance test, such changes in the basement membrane of the glomeruli are already present in the non-diabetic twin.

We cannot, therefore, speak of prophylaxis when something is there before we know that the patient has diabetes. Fortunately, this is not meaningful in terms of survival in the majority of the youngsters. However, it is true that after 15 years of diabetes, some 40% of them have proteinuria. The commonest cause for this is glomerulosclerosis. But the damaging statistic is that after 25 years, 25% of them have died from uremia on the basis of the Kimmelstiel-Wilson syndrome.

The other problem, that of retinopathy, is equally devastating, but only in a minority of the youngsters. After 7 or 8 years there is tortuosity and dilatation of the retinal veins, and after 9 or 10 years microaneurysms may appear. After 15 years, the incidence of microaneurysms is 80%, and after 25 years, it is 100%. Microaneurysms are nothing to worry about; they can come and go and they need not concern us. The dilatation of the retinal veins is unimportant. What we are concerned about is the appearance of neovascularization (new blood vessel formation), and of retinitis proliferans, with resultant scarring. Finally there occur preretinal hemorrhages, and hemorrhages into the vitreous, resulting from the neovascularization and the retinitis proliferans. The end-result is blindness. I cannot give you any specific figures as to how many diabetic youngsters ultimately develop blindness, but it is well known that diabetic retinopathy is the most common cause of blindness of recent onset in young adults in the United States today.

The third member of the triad of small blood vessel lesions is neuropathy. We think that this may have a vascular basis also. A large percentage of the youngsters will ultimately have evidence of neuropathy at some time, but there are usually no clinical manifestations. You can show changes in vibration perception, or absence of the ankle reflex in some, but these have no meaning.

We cannot promise any of these patients that if they abide by an optimal regimen they will be freed from these hazards. I would not want to say that their chances of avoiding these hazards are not improved by a strict regimen, but we cannot be sure of this. Statistics supposedly bearing on this question are very difficult to interpret.

The last point I want to make has to do with atherosclerosis. With the survival of these children into young adulthood and into middle age, we are faced with the early onset of atherosclerosis, and its more extensive presence, with the hazards of myocardial infarction, peripheral vascular disease, and perhaps strokes. These complications may occur when the juvenile diabetic reaches young adulthood, or later. If we are on the right track with regard to atherosclerosis in the population as a whole, perhaps changing the diet given to these youngsters or to diabetics in general will make a difference, as we hope it will in the non-diabetic population.

As time goes on it becomes more and more apparent that there is a merging of atherosclerosis and diabetes. There is increasing evidence that the patient who comes in with a myocardial infarction has often been an unsuspected diabetic. In tackling the problem of diabetes in both adults and in children, you are not only dealing with a devastating illness, a metabolic disturbance, which affects a minority, but at the same time you are working with a problem which will ultimately afflict the majority of any population group.

The State of Insulin in the Blood*

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In discussing the state of insulin in the blood, I should like to review briefly the regulation of insulin secretion and what is known about its manner of synthesis and release. Since some of the insulin in the blood may be in an ineffective or inactive state, I shall refer to active insulin as *effective* insulin.

METABOLITE STIMULATORS

The stimulus acting on the pancreas that controls the level of effective insulin in the blood is probably related to more than one metabolite. For many years glucose was considered the only substance capable of insulin stimulation, but recently it has been shown that keto-acids (Mebane and Madison, 1962) and certain amino acids such as leucine and arginine (Floyd et al., 1965; Merimee et al., 1965) can also stimulate insulin release. There is need to learn whether this has physiological significance before assigning it a specific role in the checks and balances of human metabolism. Intravenous studies using arginine will be followed by oral feedings of appropriate animal proteins to determine whether or not there will be an increase in the level of serum insulin without a rise in blood sugar.

SENSING-RELEASING MECHANISMS

The manner in which glucose or other metabolites bring about the secretion of insulin is unknown. It is reasonable to postulate that a sensing device must be present that recognizes the amount of the specific stimulator present and informs the pancreas that insulin is needed. This immediately raises the possibility that a pathologic state could exist wherein a faulty sensing device would fail to inform the pancreas of the need, and insulin would not be secreted despite the presence of normal quantities of insulin in the pancreas. Studies with the sulfonylurea drugs may perhaps be interpreted as bearing on this question. It is clear that insulin can exist within the islet cells quite unaware of the hyperglycemic blood flowing past and that sulfonylurea drugs can bring about the release of this insulin. These drugs may activate a sensing device. It is equally possible that they may activate a releasing mechanism for we cannot separate these two postulated functions clinically. In individuals with adequate pancreatic stores of insulin that are not responsive to elevated levels of glucose, the sulfonylurea drugs bring about a more normal response to the stimuli. There is increasing evidence that there is carbohydrate intolerance that advances with age (Andres, 1966, in press) and again it seems likely that this relative insensitivity comes about through a failure either of the sensing device

* The schema presented here is the result of much discussion involving all members of the endocrine division at the Johns Hopkins Hospital. Dr. Kenneth Zierler, Dr. David Rabinowitz, and Dr. Thomas Merimee are especially cited in the formulation of these concepts.

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or releasing mechanism. Perhaps other conditions which alter insulin release, such as the glucose intolerance following fasting, may relate to these mechanisms.

SYNTHESIS AND STORAGE

Although we can say little about the mechanisms of release of insulin, we are indebted to the beautiful studies by Lacy (1961) with the electron microscope for an exposition of the migration of the insulin granule across the beta-cell to the cell surface. On reaching the cell surface, the envelope of the beta granule appears to coalesce with the surface membrane where upon the beta granule is discharged into the extracellular space. At this point, unfortunately, the resolution of the electron microscope does not allow further physical view of the discharged granule. After discharge of the previously stored insulin, empty sacks are again seen in the beta cell; these are frequently surrounded in part by a protein believed to be ribonuclear protein. The ribonuclear protein granules clustered about the sack slowly disappear as the amorphous material fills the empty sack, and it is easy to presume that we have witnessed the synthesis of insulin on a template. The amorphous material in the sack is next seen to condense into a storage form that is typical of the beta granules previously discharged. The discharge of these granules in response to known stimuli such as glucose and sulfonylurea drugs adds further to the circumstantial evidence that we are in fact witnessing the synthesis and release of insulin.

Randle and his associates (*see* Coore and Randle, 1964) have been able to show that insulin can be released from pancreatic slices in vitro by the addition of glucose to the medium. In this system, epinephrine inhibits the release of insulin by both glucose and the sulfonylureas. Perhaps the most important observation has been that he has been able to prevent the release of insulin from the pancreas by the addition of manoheptulose when glucose is added to the medium, but manoheptulose does not prevent the release of insulin under the stimulus of the sulfonylureas. This is the first time that anyone has been able to separate the release mechanisms associated with glucose from those related to the sulfonylureas and parenthetically this suggests that the release mechanism rather than the sensing device is the site of action of the sulfonylureas in human subjects.

CIRCULATING INSULIN

In considering the state of insulin in the blood, we must deal with certain direct questions: What is its form? How is it transported? And what is the material being measured which we call "insulin?" These are fundamental questions, but our answers must be incomplete.

From the work of Sanger (1960) we have the precise structure of the insulin molecule, and the molecular weight is known to be approximately 6,000. It has not been possible to be certain of the form taken by circulating insulin. It probably circulates as a double molecule or dimer with a molecular weight of 12,000, but it may circulate in aggregates of three or four molecules (Prout, 1963). There is some evidence that the insulin may be transported in the blood attached to a carrier protein, but this cannot be definitely proven at this time.

Insulin is measured in biologic fluids on the basis of its biologic effect or its immunologic properties. In general, there are two types of biological assay, one measuring the effect of glucose uptake or glycogen deposition in a rat hemi-diaphragm and the other measuring the incorporation of C^{14} from labelled glucose into glycogen or CO_2 by the rat epididymal fat pad. Both of these tests measure a net biological effect which may be altered as a result of several modifying factors either potentiators or inhibitors. For this reason, the activity thus measured is referred to as the "insulin-like activity" or ILA. The immunoassay of Berson and Yalow (1960) identifies immunologically active insulin quite specifically and with considerable sensitivity; it is, of course, able to tell us nothing about the biological activity of the thing that is measured. About these two types of assay have grown up two schools of thought which divide the investigators interested in this field.

Faced with this dilemma, it is of some comfort to consider the number of ways in which the ILA as measured by the diaphragm and the immunoassay give parallel results (table 1). By both tests the blood insulin is low in the fasting subjects but rises after glucose or after administration of the sulfonylureas. By both tests the blood insulin is high in patients with insulin secreting islet cell tumors. In obese patients both assay techniques reveal increased insulin levels. The levels may be high by both assay methods in certain adult diabetes, and most importantly immunologically active insulin and ILA as tested by the rat hemi-diaphragms are both

TABLE 1
Similarities in the Assay of Insulin in Whole Serum by the Rat Diaphragm and by the Immunoassay

1) Low insulin levels in blood of fasting patients
2) Rise of insulin after glucose administration
3) Rise of insulin after sulfonylurea administration
4) High levels of insulin in hyperinsulinism
5) Elevated levels of insulin in some obese subjects
6) Suppression of insulin in vitro and in vivo by specific insulin antibodies
7) Disappearance of insulin after pancreatectomy
8) Absence of insulin in serum of patients in diabetic keto-acidosis

suppressed by anti-insulin antibodies either in vitro or in vivo. Finally, the insulin measured by either method disappears when the pancreas has been removed. In these respects both assays would appear to be measuring the same material.

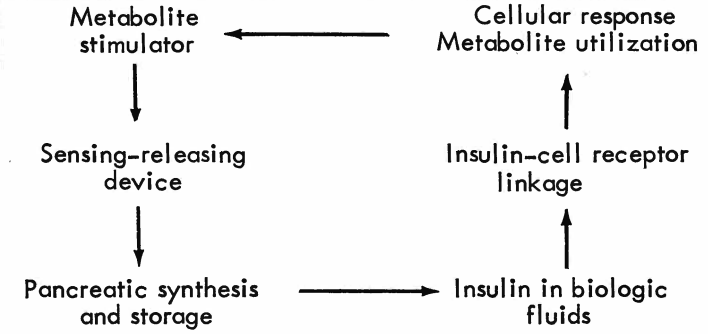
The observation that insulin-like activity measured by the fat pad was several fold that measured by the diaphragm or the immunoassay turned attention to the question of whether or not a circulating form of insulin existed which had lost, or perhaps had never had, immunologic identity. By means of a cation exchange resin column, Antoniades and his associates (1964) separated a form of insulin-like activity that could be measured initially by the fat pad but not by the diaphragm or immunoassay. This was called "bound" insulin as opposed to the "free" form. Others have found insulin-like activity that is "atypical" (Samaan et al., 1963) or "non-suppressible" (Froesch et al., 1963) because the activity unlike that of crystalline insulin is not inhibited by anti-insulin antisera added to the test medium. We can conveniently consider together these various types of "bound," "complexed," "non-suppressible," or "typical" insulins and contrast them to insulin that is measurable by the other methods (table 2).

One difficult problem confronting the proponents of atypical insulin in that some "atypical" insulin seems to persist in the blood for considerable periods of time after pancreatectomy (Goldberg and Egdahl, 1961). Before attempting to give clinical relevance to ILA of the "atypical" type, a second observation requires physiologic explanation. We are asked, for example, to believe that ILA measured only by the fat pad is circulating in excess quantities in patients with decompensated diabetes in whom the principle evidence of decompensation is failure of insulin to act normally upon fat synthesis (Steinke et al., 1961). These criti-

TABLE 2
Differences Between "Typical" and "Atypical" insulin

	"Typical"	"Atypical"
Assay	Measured by diaphragm fat-pad and immunoassay	Measured by fat-pad
Effect of antiserum	Inhibited	Not inhibited
Effect of pancreatectomy	Disappears	Remains
Origin	Pancreas	Unknown
Keto-acidosis	Absent	Present in large quantity
Other unresolved questions	Biologic activity of insulin measured immunologically is not known	Cannot be converted reproducibly to typical form

TABLE 3
The Feed-back Mechanism of Insulin Synthesis and Release



cisms have lead many to deny that "atypical" insulin has any real relationship to true pancreatic insulin. Despite these difficulties, it is theoretically possible that some form of insulin may exist which is different from the insulin measured immunologically and by its biologic effects on muscle and further study of the problem will be necessary.

A FEED-BACK MECHANISM

We can now picture the glucose insulin regulating mechanism as a feed-back system (table 3). A metabolic stimulator, usually glucose, is measured by a sensing device which tells the pancreatic cell to release and re-synthesize insulin in relation to metabolic need. After circulating insulin has arrived in the blood, it is picked up by a specific cell receptor and initiates a cellular response. The cellular response not only serves a metabolic need but also removes from the blood some of the metabolic stimulator that initiated the cycle. As a result of the fall in the metabolite, no further stimulation for insulin release is given, and the feed-back mechanism is satisfied. Various other factors can presumably inhibit or potentiate the different steps of this process.

In this framework the diabetes with which we have been most familiar in the past is associated with failure of insulin release from the pancreas. This is most typically exemplified as the pancreatic exhaustion of juvenile diabetes. It is also true of the pancreas that has been destroyed by pancreatitis, hemochromatosis, or removed by the surgeon's knife. It may be seen where pancreatic exhaustion results from metabolic stresses such as hyperthyroidism, multiple pregnancies, or long-standing obesity. In all cases the pancreas is no longer able to respond to demand, and clinical diabetes is seen. In true pancreatic exhaustion the sulfonylureas are, of course, ineffective.

We should also note that a state of functional low insulin output exists where there is either dulling of the sensing device or interference with insulin release; either of these mechanisms impairs the ability of the pancreas to deliver insulin on demand. In these instances, the sulfonylureas release insulin. Epinephrines and the thiazides inhibit release of insulin.

The new concept that must be brought into this scheme is the clinical situation in which metabolic abnormalities of the type seen in diabetes are present in spite of high circulating levels of insulin. A state of impaired carbohydrate intolerance in association with a high level of plasma insulin can be understood if the insulin present is ineffective. It is also possible to recognize the clinical syndrome in which normal high levels of insulin compete with antagonists such as growth hormone, acromegaly, or adrenal steroids. A similar though less well defined impairment of insulin is seen in association with obesity. Here again we may see impaired carbohydrate tolerance in the presence of high circulating levels of insulin (Karam et al., 1963). In this state it appears likely that the impairment to insulin function is located primarily at the level of cellular response. The same may be true in carbohydrate induced hypertriglyceridemia, a condition closely allied to diabetes but not necessarily true diabetes. There is some evidence that the lipoatrophic form of diabetes may be characterized by high levels of circulating insulin that are rendered ineffective by an insulin antagonist (Louis et al., 1965).

"Prediabetes" may take one of two forms. It may be a state in which high levels of insulin are put out to overcome peripheral impairment or circulating antagonists but in which carbohydrate intolerance cannot be demonstrated by ordinary techniques. This state is readily understood within the present framework. "Prediabetes" may also be present in a patient who shows

evidence of the "complications" of diabetes before carbohydrate tolerance is lost. There is some evidence that different tissues react to different levels of insulin and by presumption that levels of insulin adequate for the metabolism of some tissue would be ineffective for others. This may well be the reason why it is possible to see degenerative complications in the retina that is typical of diabetic retinopathy in some patients who have no carbohydrate intolerance. The same may be true of patients who develop vascular disease in the absence of alterations in carbohydrate utilization. Perhaps the future study will allow us to demonstrate that tissue sensitivity in such patients is the cause of the degenerative complications. There is abundant evidence that complications may be seen in the absence of carbohydrate impairment, and we can no longer accept the frequently stated belief that control of carbohydrate metabolism in diabetes will prevent all other forms of the "complications."

Much of the theme presented here can be verified, but much of it still remains speculative. It is probably possible to place all variants of the diabetic state somewhere within this cycle so that diabetes will eventually become better understood as a complex metabolic disorder involving all tissues and all metabolites rather than the simple derangement of carbohydrate utilization.

SUMMARY

Diabetes mellitus has been reviewed as a group of conditions with impaired function of one or more portions of a feed-back system involving the release and utilization of insulin. It is hoped that this may form a useful scheme by which we can study and understand a number of complex metabolic states which we must still collectively refer to as diabetes mellitus.

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Insulin Antigenicity

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I would like to begin with a brief historical review of the subject of insulin antigenicity before I discuss its clinical significance.

After the discovery of insulin, a little over four decades ago, some of the early preparations of insulin were relatively crude; and, as might be expected, a number of reactions occurred. In one of the first studies on insulin allergy utilizing pure crystalline insulin, Tuft (1928) established that it was the insulin itself which caused the skin reaction and not the protein of the animal from which the insulin came. He further demonstrated that the material causing the skin reaction could be passively transferred to the skin of a normal individual by an intradermal injection of serum from the insulin-allergic individual. He also showed the presence of a precipitin against insulin in the serum of the insulin-allergic patient and demonstrated that the skin-sensitizing antibody remained in serum long after the precipitin was lost. He presented some evidence of an increased insulin requirement in the patient when the precipitin was present and suggested that antibodies to insulin might be associated with insulin resistance. Other workers confirmed the fact that insulin was antigenic (Prout, 1962) and Sir Frederick Banting (1938) made the observation that psychiatric patients receiving insulin for shock therapy required more and more insulin to produce shock as time went on. He demonstrated that serum from these patients protected mice from convulsions when injected with insulin and later showed that the anti-insulin material was located in the serum globulin rather than the albumin.

In 1944 Lowell defined the two kinds of antibodies against insulin, one a reagin which was heat labile and caused skin sensitization, and the other a heat-stable factor that prevented the hypoglycemic effect of insulin in vivo.

Loveless and Cann (1955) showed that the heat-stable precipitin, the material with anti-insulin effect in the intact animal, could in fact act as a blocking antibody for the skin-sensitizing reagin or the heat labile factor. These antibodies traveled in two distinct areas on serum electrophoresis; the blocking antibody was a γ-globulin, while the skin-sensitizing reagin traveled with the β-globulins.

Up to this time insulin was thought to be rarely associated with host reactions except for the occasional local reaction to injection. It was Berson and his associates (1956) who showed that insulin antigenicity was a common phenomenon. In patients who have been treated with intermediate or long-acting insulin, 80% have antibodies in the serum that are measureable by techniques utilizing insulin labelled with iodine 131 (table 1).

Most of the clinical manifestations of the skin-sensitizing reagin are straightforward. Some of the rarer forms of sensitivity reaction attributable to insulin are difficult to substantiate (e.g. thrombocytopenia and gastrointestinal upset), but the skin reactions to insulin are not at all unusual. It is quite common to have local reactions to insulin in the first few weeks after insulin injections are started. In

TABLE 1
Insulin Antigenicity

	Skin Sensitivity	Insulin Resistance
Tuft (1928)	Passive cutaneous transfer	Precipitin in serum
Banting (1938)		Mouse protection by globulin of insulin-resistant patient
Lowell (1944)	Heat-labile	Heat stable. Related to resistance. Possibly species specific
Loveless and Cann (1955)	Separated with β-globulin	Separated with γ-globulin. "Blocking antibody"
Berson (1956)		Insulin-binding antibody

TABLE 2
Saturation in Insulin-binding Antibodies*

Daily Insulin	% Retention in Serum 60 min	% Free Serum Insulin 5 min
45 u/day	83	2.1
90 u/day	72	3.3
190 u/day	48	17.6

*The relationship between daily dose of insulin and saturation of insulin-binding antibodies is shown by these results. Free insulin is increased and becomes available for peripheral use. The increase in daily insulin does not stimulate the over-production of antibodies in this type of patient.

treating the patient with local reactions, it is essential to be certain that the patient is injecting himself properly, that he is using a clean syringe and not injecting alcohol. Some physicians advocate that syringes and sites of injection be changed or that the insulin be warmed or even boiled; after several weeks in which several techniques have been tried, the local reactions subside. I suspect that this is not related to the ingenuity of the therapeutic maneuvers, but to time that has been consumed while waiting for the blocking antibodies to block the skin-sensitizing antibody. The patient has been desensitized in precisely the same way that he has been desensitized for ragweed antigen, and the important part of therapy has been the continuation of injections until the patient is desensitized.

Other phenomena at the injection site are of great interest although it is not proven that they are related to insulin antigenicity. These are the insulin-induced fat atrophy and/or fat hypertrophy. Their cause remains an enigma. I have wondered whether insulin may become fixed to adipose tissue at the injection site and set up a tissue-fixed antigen-antibody reaction with circulating antibodies. The time sequence suggests the validity of this possibility and on occasions a change to insulin of a different species has coincided with the end to fat atrophy. I am currently trying to improve these demonstrations and determine their significance. These phenomena may well relate to the effect of insulin on fat metabolism, but thus far the reasons for both fat atrophy and fat hypertrophy are obscure.

The clinical significance of the heat-stable antibody to insulin found in the γ-globulin is more easily determined. If we study the insulin-binding capacity of the serum of patients attending a diabetes clinic, we find that all patients taking intermediate insulin develop antibodies in six to eight weeks.

In general the titre of antibodies is low, and as a group the patients who have been on insulin the longest period of time have the higher titres. There is, of course, great variability. There are several interesting exceptions to this generalization. Insulin antibodies have been noted to disappear in patients receiving steroid for sarcoidosis. In other patients having the proteinuria of Kimmelstiel-Wilson syndrome, insulin-binding antibodies are often lost along with other proteins. Part of the insulin sensitivity seen in patients with this syndrome is probably related to the loss with the proteinuria of the buffering effect of the antibodies. In such patients the antibody titre seen in the serum is low even through the patient had been on insulin for more than 20 years.

As Berson (1956) demonstrated, the presence of antibodies is readily shown in vivo. In patients with little or no antibody, there is rapid disappearance from the blood of insulin labelled with I^{131} following an intravenous injection. Patients with insulin resistance show a marked prolongation of the half-time of labelled insulin in blood, and it is easy to show that the insulin I^{131} continues to circulate because it is bound to the γ-globulin.

Let me give an illustration of the clinical significance of this. A man previously controlled on 40 units of insulin developed ketoacidosis without obvious cause. He was treated successfully and discharged on his previous dose of 40 units daily. In a short time he returned again with ketoacidosis. An insulin effect had been obtained and the acidosis had been treated successfully, but this effect was promptly dissipated when he returned to his maintenance dose that was less than his daily needs. It was postulated that by saturating the circulating antibodies with larger daily doses of insulin the anti-insulin effect of his antibodies could be neutralized. It was first demonstrated that approximately 90% of the injected insulin I^{131} remained in circulation for more than two hours while he was on an inadequate dose of insulin. We then progressively raised his insulin dose, and he began to come under better control. Now we found that injected insulin I^{131} disappeared from the blood more quickly, presumably because some of the binding sites of the insulin-binding antibody were being occupied by the daily dose of insulin he was receiving. As his insulin dose was increased during the next week, he showed progressive shortening of the half-time of insulin in his blood and reciprocally a greater amount of the insulin was free to be utilized in the periphery. Insulin bound to antibody is preserved not only from peripheral use but also from peripheral degradation. The results of these studies of insulin-I^{131} over this period are shown in table 2. As the increased daily dose of insulin occupied more of the binding sites of the insulin-binding globulin, more of the daily insulin dose was free to exert its physiological effects, and the control of his diabetes was thereby improved (Prout and Katims, 1959).

Insulin resistance is not always related to insulin-binding antibodies, of course, and in the differential diagnosis of this problem a number of other conditions must be considered (table 3). Obesity is usually associated with relative insulin resistance. Obese patients who have never received insulin may require three or four times as much insulin to produce the same fall in blood glucose on an insulin tolerance test as their colleagues of normal weight. Obese diabetic subjects who have not followed their prescribed diet and who hence are not controlled may require 50 to 60 units daily at the onset to achieve control, although they are not dependent on insulin to prevent ketoacidosis.

Moderate degrees of insulin resistance are seen in acromegaly, Cushing's syndrome, hyperthyroidism, and with steroid treatment.

Cyclic resistance associated with the menstrual cycle has been reported. None of these states are related to antibodies and are all relatively mild forms of resistance for the most part.

Infection, of course, is the most common cause of insulin resistance and resistance quickly disappears as the infection is brought under control. Although an increase in insulin-binding antibodies with infection would appear likely, we have not found a significant rise in circulating antibodies of any of these patients' studies, the most remarkable of whom has been reported by Knowles and his colleagues (*see* Tucker et al., 1964).

Peripheral or tissue resistance to the effects of insulin has been postulated and there are remarkable instances reported of severe resistance on this basis that are unrelated to insulin antibodies (Field, 1962). Another cause of apparent insulin resistance is the so-called Somogyi effect or paradoxical hyperglycemia (Somogyi, 1959). This refers to the patient who appears to need more insulin but in whom control becomes more difficult despite the increase in his insulin dose. Hypoglycemia that often goes undetected is followed by rebound hyperglycemia and the patient and the physician are likely to increase the dose further unless the paradoxical hyperglycemia is recognized. The proper treatment is to decrease rather than increase the insulin dose after which the apparent insulin resistance disappears.

Evidence that the antibodies are not the result of high insulin dosage used in insulin resistance rather than a cause is difficult to find. I had an opportunity to study one patient who has helped to answer this question. A woman had had diabetes for a number of years and had developed insulin resistance with requirements of insulin exceeding 1,500 units per day. Her physician had told her that insulin was useless for her and the patient had discontinued her injections. When seen, she had been off all treatment for four years. During this time, she had had constant glycosuria and had developed severe peripheral neuropathy. We measured her insulin-binding capacity after four years on no insulin and found an insignificant amount of binding still present, about 50 microunits per ml. We began insulin in relatively low doses and at the dose of 60 units of insulin per day, an insulin effect was seen. Her urine became free of glucose for the first time in four years. On the eighth day after beginning therapy she was again found to be extremely resistant to insulin and impossible to control; her insulin-binding antibodies had increased ten fold. An attempt was made immediately to saturate the high level of circulating antibodies by giving her 500 units of insulin intravenously which, under these specific circumstances, was quite safe and no effect of this insulin was seen on the blood glucose. Insulins from different species were tried as well as steroids; but in spite of this, on insulin in doses up to 1,500 units daily, she did not respond. After oral agents became available, hyperglycemia was controlled to some degree. This patient was found responsive to insulin in moderate doses before the recurrence of insulin resistance. Antibodies developed before massive doses of insulin were used and resistance became clinically significant with the rapid rise of antibodies.

What steps do we take when confronted with an insulin-resistant patient? Let us assume that the obvious causes of insulin resistance, such as obesity or infection, have been ruled out and that the insulin requirements are in excess of 200 units per day. First we should determine whether the patient is really insulin dependent. The two phenomena do not necessarily go hand in hand. Insulin dependency is related to the presence or absence of retrievable insulin from the pancreas. Insulin resistance is related to response to injected insulin and may develop in patients still capable of responding to oral agents. The patient just described illustrates this. If the patient is not insulin dependent, an oral hypoglycemic agent may be effective. If this fails, and insulin therapy is mandatory, one may attempt to saturate the antibodies by rapidly increasing the insulin dose as I have described above. This can sometimes be best accomplished by using crystalline insulin in multiple doses throughout the day; this is always more effective in patients with a large amount of insulin-binding antibody than is intermediate or long-acting insulin. If this does not succeed, insulin from different species, usually pork insulin, can be tried.

TABLE 3
Differential Diagnosis of Insulin Resistance

1) Obesity	Relative resistance easily overcome.
2) Endocrine states:	
a) acromegaly b) Cushing's syndrome c) hyperthyroidism d) menstrual cycle	Mild resistance. Usually less than 100 units/day of insulin required unless other complications are present.
3) Peripheral resistance	Unusual condition difficult to prove. Very high quantities of insulin used with little effect.
4) Infection	Commonest form of resistance. Rapidly reversed with treatment of infection.
5) Antibodies to insulin	Demonstration by in vivo or in vitro techniques.

TABLE 4
Treatment of Insulin Resistance Related to Insulin-binding Antibodies

1) Determine insulin dependency
2) Antibody saturation
3) Change to insulin of another species (pork, fish)
4) Adrenal steroids or ACTH
5) Anti-metabolites not recommended
6) Time and continued treatment with insulin in crystalline form

Antimetabolites such as 6-mercaptopurine theoretically might help these patients by suppressing formation of antibodies. This has been tried on several occasions without any great success (Merimee, 1965).

Adrenal steroids are relatively low on the treatment list for insulin resistance. It is better to have a patient maintained on 300 units of insulin a day than to have him on steroids for life. Steroids can sometimes be used to decrease insulin resistance but the resistance frequently returns when steroids are tapered and stopped, and long-term steroid treatment may be required. Steroids must be used, as elsewhere in medicine, with circumspection.

Not the least important in the treatment of insulin resistance due to insulin binding antibodies is the use of time. If the resistant patient can be maintained on a high dose of insulin required for control, eventually the resistance may disappear in the same way it came, indeed, with less explanation. Continuation of insulin, especially as crystalline or regular insulin, is essential in such patients (table 4). Interruption of insulin therapy may in fact be one of the settings in which relative insulin resistance occurs when insulin is restarted.

Thus we have seen that evidence of insulin antigenicity in one or more forms is present in most individuals receiving intermediate insulins for six weeks or longer. A number of clinical manifestations of insulin antigenicity and their treatment have been discussed.

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Insulin Antagonists

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Ten years ago, in 1955 the "Metabolic Establishment" first began to hear what might be called the "Great Diabetes Paradox:" impaired glucose tolerance can occur side by side with normal concentrations of blood insulin or insulin-like activity. This sounded like endocrinologic heresy but it has been confirmed by almost every worker in the field, using different assay methods. Since the paradox is true, it is provocative, for it suggests that an important truth may be hidden beyond it.

One line of approach to this problem has been to look for insulin antagonists which might prevent normal amounts of insulin from accomplishing their physiological tasks. Much work has been done in this area, some of it controversial, all of it exciting. It is not easy to prepare a critical evaluation without beginning to seem to be against progress. But true progress requires that controversy be resolved.

INSULIN ANTAGONISTS

In 1954, John Vallance-Owen and Barbara Hurlock described a method for the assay of insulin-like activity (ILA) in plasma, using as an index of response the amount of glucose disappearing from the medium in which was incubated a rat hemi-diaphragm. These workers found a low level of ILA in fasting normals, with a brisk rise after glucose ingestion. Crystalline beef insulin added to plasma was recovered quantitatively.

The next year Vallance-Owen and co-workers (1955) reported similar values in obese diabetics requiring no drug treatment, but found no detectable ILA in the plasma of uncontrolled, insulin-requiring diabetics; crystalline insulin added in vitro had little or no effect. Later these authors showed that if plasma from such patients were diluted 1:4, ILA could be again demonstrated and added insulin recovered quantitatively. They concluded that such plasma contained ILA all along, but that some other plasma component antagonized the action of both the ILA and added crystalline insulin (Vallance-Owen et al., 1958a). It has never been clear why the antagonism disappears when both ILA and the antagonist are diluted to the same degree.

The next step was to isolate and identify the antagonist (Vallance-Owen et al., 1958b). Fractionation of serum proteins showed the antagonist to be associated with albumin and because it could be eluted off the albumin on column chromatography, it was called "synalbumin antagonist." Serum albumin from both normal and diabetic patients antagonized 1,000 μu per ml of beef insulin when added in a 3.5 to 5.5% concentration to the medium containing rat hemi-diaphragm. When the same albumin fractions were added in only 1.25% concentration, there was no inhibition with normal albumin but persisting, almost complete, inhibition with diabetic albumin. A fair appraisal would be that everyone has synalbumin antagonist, but that insulin-requiring diabetics have more of it than others.

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Other disease entities were soon admitted to the not-so-exclusive ranks of synalbumin excess. In 1961, obese maturity-onset diabetics and pre-diabetics with normal glucose tolerance were shown to have antagonist at the 1.25% concentration in blood (Vallance-Owen and Lilley). In 1963, synalbumin antagonist was found in 19 of 28 patients with fresh myocardial infarction and no family history of diabetes. This finding persisted after recovery from infarction, and contrasted with an incidence in only 6 of 28 control patients without vascular disease or positive family history (Vallance-Owen and Ashton). Then the antagonist was found to be present in 6 of 10 grossly obese women without diabetic "chemistries" or family history (Vallance-Owen, 1965). Further, Alp and Recant (1965) have demonstrated the presence of synalbumin antagonist (at levels between 1.25 and 3.50%) in ten pregnant women in the third trimester, again without family history of diabetes.

EFFECT ON METABOLISM IN ADIPOSE TISSUE

It was soon learned that synalbumin antagonist did not antagonize the effect of insulin on adipose tissue (Vallance-Owen and Lilley, 1961; Lowy, Blanshard, and Phear, 1961). Vallance-Owen has emphasized this (1964a, 1964b), and has speculated that obesity may be a manifestation of diabetes rather than the other way around. Investigation of this phenomenon by Alp and Recant (1964) revealed that the synalbumin antagonist, like insulin, actually stimulated the oxidation of glucose by adipose tissue. The similarity was particularly close in that anti-insulin antibody could abolish this effect, a finding considered by many to be proof of identity with insulin. Furthermore, the effect of crystalline insulin was enhanced by the presence of synalbumin. Fourteen diabetic albumin samples in 1.25% concentration produce on the average 86% inhibition of the effect of 1000 μu per ml of insulin on rat diaphragm. The same albumin contributed on the average 41% of the stimulation of glucose uptake by adipose tissue which was ascribed to insulin-like activity. It is perfectly clear that such a metabolic picket line could divert a great deal of blood glucose away from muscle and into fat.

These divergent actions have not been investigated by other workers, who have concentrated their efforts on the study of the diaphragm effect. Sherman (1965) has recently reported confirmation of the findings of synalbumin antagonist in normal and diabetic plasma in the same concentration as originally noted. Using the Stadie technique, Davidson and Goodner (1965) found that after diaphragm was dipped in solution containing synalbumin antagonist, no amount of washing would enable it to respond properly to insulin. Conversely, prior dipping in an insulin solution partially but not completely prevented subsequent action of the antagonist. They also found that a huge excess of insulin did not wholly overcome the effects of a small amount of synalbumin, and inferred that the inhibition is not competitive, contrary to the report of Alp and Recant (1965) that it was partially competitive. Of special interest was the finding that synalbumin also antagonized the insulin effect of intracellular accumulation of aminoisobutyric acid, and to a lesser degree of glycogen synthesis, which actually tended to increase proportionally as overall glucose utilization declined. Both antagonistic human serum albumin and non-antagonistic beef serum albumin depressed the incorporation of glycine-2-C^{14} into muscle protein. Davidson and Goodner concluded that the synalbumin antagonist either binds strongly to the cell membrane, precluding contact with insulin, or irreversibly alters the membrane's biochemical response to insulin.

CHEMICAL IDENTITY OF ANTAGONIST

During the last three years, Vallance-Owen and his colleagues have been attempting to identify synalbumin. Preliminary studies suggested that it was probably a polypeptide. In 1963, Ensinck et al. found that when insulin is cleaved enzymatically in vitro, the 30-amino acid B chain appears to associate with albumin. Ensinck and Vallance-Owen (1963) reported at the same time that purified B chain readily unites with non-antagonistic albumin in vitro, and thereby restores the usual antagonism to 1000 μu per ml. They have demonstrated 10 biochemical similarities between isolated synalbumin antagonist and B chain, with no reported dissimilarities (Vallance-Owen, 1964b). In 1964, Ensinck et al. incubated I^{131}-labelled insulin with the hepatic enzyme that cleaves insulin, glutathione-insulin transhydrogenase. They dialyzed the material and found that most of the radioactivity remained attached to the albumin on electrophoresis. In 1965, Ensinck, Mahler, and Vallance-Owen repeated this study with non-labelled insulin in order to test the effects of various alkylating agents. Reduced or sulfated B chain was antagonistic as usual, but if the molecule were oxidized, or its thiol groups alkylated with iodacetamide or N-ethylmaleimide, the antagonism disappeared. It is generally accepted that the insulin molecule attaches to a receptor site on the cell membrane by forming disulfide bonds. Reduced B chain, with its own "dangling" disulfide bonds, could conceivably attach to the cell membrane and effectively compete with insulin for attachment sites by the mechanism of steric hindrance. Ensinck et al. (1965) have found that albumin-B chain complex incubated with diaphragm or cell-free muscle extracts

become non-antagonistic, so apparently B chain has a greater affinity for cell membrane than for the albumin molecule.

Vallance-Owen (1946b) has presented the idea that hepatic glutathione-insulin transhydrogenase cleaves insulin to a greater or lesser extent corresponding to the activity of the pituitary-adrenal axis, but concedes that there is no direct support for this theory. As indirect support he cited earlier work on cats; ordinarily cats do not have the synalbumin antagonist (Vallance-Owen and Lukens, 1957), but, it can be demonstrated after pancreatectomy, although not after combined pancreatectomy and hypophysectomy.

ROLE IN PATHOGENESIS OF DIABETES

The presumed role of synalbumin antagonist in the pathogenesis of diabetes mellitus can now be traced as follows: Due to a genetic predisposition, there is excessive hepatic glutathione-insulin transhydrogenase activity (perhaps due to decrease in inhibitor), which is exaggerated by pituitary-adrenal hyperactivity. Insulin secreted by the pancreatic B cells reaches the liver via the portal vein and much of it there is cleaved to the A and B chains. The B chain binds to albumin, circulates in the blood, and detaches from albumin at the cellular level in order to attach to membrane binding sites. In adipose tissue the B chain actively supports the uptake of glucose; in muscle it merely inhibits the attachment of the intact insulin molecule. Therefore, glucose tolerance diminishes, blood sugar rises, the cells become initially hypersecretory and eventually exhausted, and permanent pancreatic diabetes ensues (Vallance-Owen, 1964a and b).

Vallance-Owen has been quite interested in using the presence of synalbumin antagonist as a biochemical marker for the genetic diabetic predisposition (1964a). Most recently (1965), he studied 94 people in 9 families. Of these 38 had normal amounts of antagonist, and 56 had an increased amount equivalent to that found in diabetes; 18 of these had frank diabetes, and 3 more had spontaneous hypoglycemia. He feels that the diabetic predisposition is inherited as a Mendelian dominant, that perhaps 25% of the world population is constituted as diabetic, but that probably only 10% of this segment will develop frank diabetes during life.

CRITICISMS OF ROLE OF ANTAGONIST

This review summarized a body of evidence assembled over a twelve-year period. On the other side of the argument, there is the following evidence:

1) Berson and Yalow (1965) have challenged the experiment using I^{131}-labelled insulin and the hepatic enzyme (Ensinck et al., 1964), on the grounds that the radioactivity bound to albumin can occur without enzymatic intervention and probably represents damaged insulin as a result of irradiation.

2) Some workers have found that albumin is not antagonistic to glucose uptake by muscle (Cameron, Keen, and Menzinger, 1964) or, if it is, only to an extent that could be explained by the association of free fatty acids (Buse and Buse, 1964).

3) A more troublesome question is to explain the presence of synalbumin antagonist in pancreatectomized animals who do not possess the antagonist in the intact state? Vallance-Owen (1964b) has explained this by saying that previously secreted insulin still circulates and contributes B chain to form the antagonist. He argues that hypophysectomy prevents this by suppressing the activity of the hepatic enzyme that cleaves insulin, and that administration of steroids reverses this suppression. It is difficult to understand how a metabolite of insulin could appear only after insulin production has been extinguished.

4) One feels uneasy about the basic premise of this concept of diabetes; can we reasonably base our entire theory on the presence of a factor which can only be demonstrated as something in *human* plasma which antagonizes the effects of *beef* insulin on *rat* diaphragm? This is several steps removed from the clinical situation, and is subject to criticism since beef albumin does not antagonize beef insulin under these conditions (Davidson and Goodner, 1965).

5) The same objection might be made to a specific pathogenetic role of an antagonist which occurs in such a large segment of the population. If everyone possesses synalbumin antagonist, as demonstrated on rat diaphragm, and 25% possess an excessive amount, why should only 2.5% ever develop even chemical diabetes? Explaining this selectivity is really not much easier then explaining the incidence of clinical diabetes without ever invoking synalbumin at all. A factor which is invoked to explain not only diabetes, but also myocardial infarction, obesity, and the third trimester of pregnancy does not really explain anything.

6) Even if the synalbumin antagonist were of metabolic importance to man, how would its excess lead to diabetes? According to Alp and Recant (1964, 1965), the increased glucose uptake by adipose tissue ought to help counteract the decreased uptake by muscle, especially as the bulk of adiposity increases. If so, should not progressive obesity lead to progressive improvement in glucose tolerance? And in that case, why should cell secretion become exhausted? On this point the theory does not agree with clinical facts.

7) Berson (1965) has recently quoted Mirsky as showing that continuous intravenous infusion of reduced B chain in dogs had no effect on glucose tolerance.

CONCLUSION

In conclusion, the synalbumin antagonist exists, and may be important in the pathogenesis of human diabetes, but its role has not been proved. The proof will require elucidation of the problem of species specificity, and ability to measure accurately the levels of synalbumin antagonist.

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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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Treatment of Diabetes With Oral Hypoglycemic Drugs

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Oral hypoglycemic drugs now available are of two types. The biguanides, of which phenformin (DBI) is the only one available, increase glucose utilization by muscles. The sulfonylureas, tolbutamide (Orinase), acetohexamide (Dymelor), and chlorpropamide (Diabinese), stimulate the pancreas to produce and release more insulin. All three sulfonylureas have the same effect in responsive patients, but they differ in potency and in duration of action.

THE SULFONYLUREAS

Tolbutamide is rapidly metabolized into an inactive chemical that is promptly excreted in the urine. Because the blood half-life is six hours, this drug should be given two to four times each day. On cessation of treatment the hypoglycemic effect is promptly dissipated.

Acetohexamide has a blood half-life of six hours, but the metabolic product has hypoglycemic activity that lasts for several hours before it is excreted in the urine. In patients with poor renal function, the metabolite may accumulate in the blood and cause prolonged hypoglycemia after a small dose. This drug is usually given twice daily.

Chlorpropamide is not metabolized but is excreted in the urine over a period of four days. Because the blood half-life of this drug is 36 hours, the entire daily dose can be given at breakfast. Since there are occasional reports of cholestatic jaundice after large doses, chlorpropamide should not be used in patients with known or suspected liver disease.

Comparative studies of these three drugs shows that chlorpropamide has the greatest overall effectiveness with the best diabetic control, the smallest number of secondary failures, and the lowest cost to the patient. The difference between the three drugs is so small that each physician should routinely use only one but learn to use that one well.

The sulfonylureas are most effective in patients who develop diabetes after the age of 30, who have few diabetic symptoms, and who are near normal weight. Younger patients and those who have ketonuria, weight loss, and the classical symptoms of diabetes usually require insulin. A few symptomatic patients who require insulin for initial control may later respond to a sulfonylurea.

The sulfonylureas are usually of no value in juvenile patients. On rare occasions when diabetes was detected during the asymptomatic phase, it has been possible to achieve satisfactory control for several months with the sulfonylureas. Because this response is always temporary, it is essential that the patient be followed closely so that insulin may be started promptly when needed.

FAILURES OF ORAL HYPOGLYCEMIC AGENTS

"Primary failure" refers to lack of response to the oral agent from the beginning of therapy. "Secondary failure" describes the loss of

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diabetic control after initial satisfactory control for more than a month on an oral drug. The exact incidence of secondary failure will depend upon how freely the drug is used initially and how strict are the criteria of control. If the drug is used only in those patients expected to have an excellent diabetic response, the incidence of primary and secondary failure will be low. If the drug is used in younger patients with moderately severe diabetes, there will be a higher incidence of failures. Some patients classified as secondary failures initially were not under good control and should be classified as primary failures. Many obese patients follow their diet initially, but later eat excessively, gain weight, develop hyperglycemia and are classified as a secondary failure. Some patients develop poor control during a transient period of stress and must be changed to insulin. If the sulfonylurea is continued with supplemental insulin during the period of stress, the oral drug may later be successful. In our series, the clinic patients who had a fasting blood sugar over 200 mg per 100 ml after being on the maximum dose of the drug for one week were classified as secondary failures. The highest incidence of failure is in the first few months, but true secondary failure may develop after several years of excellent diabetic control. A patient who is under excellent control is less likely to develop secondary failure than is one who is under fair control. Patients who required large doses of insulin have more secondary failures than do those who require no insulin. The longer the duration of diabetes, the greater is the incidence of secondary failure. The true incidence of secondary failure is probably about 0.25% during each month of treatment with a sulfonylurea. The exact rate makes little difference, as long as physicians are aware that this condition can occur at any time.

CONTRAINDICATIONS TO SULFONYLUREAS

When they were first introduced, the sulfonylureas were not recommended for patients with infection, surgery, pregnancy, or neuropathy. These precautions are still included on the package inserts. However, many patients have successfully undergone major surgical procedures while taking these drugs. Excellent diabetic control was maintained in the post-operative period, but a few patients required supplemental injections of insulin for two or three days. In the presence of infection, the insulin requirements rise and supplemental insulin may be needed until inflammation has subsided. In a group of 20 pregnant patients treated with oral drugs, there was no evidence of any deleterious effect that could be attributed to the drugs, even though there were only 13 live babies in the group.

Many physicians have used the sulfonylurea drugs in patients with very mild diabetes. Theoretically, if hypertrophy and hyperplasia of the β-cells is produced, the eventual use of insulin could be postponed. However, sufficient data to substantiate this is not yet available. Patients with minimal diabetes are more responsive to the sulfonylurea drugs, and may easily develop hypoglycemia. There is little justification for the use of any drug in patients who have a normal fasting blood sugar, even though the postprandial blood sugar is elevated.

PHENFORMIN

Phenformin (DBI) is a different type of chemical that acts on muscle and liver cells in an undetermined manner to increase glucose uptake. This drug will lower the blood sugar of any diabetic if a large enough dose is given, but it does not lower the blood sugar of non-diabetics. It is effective in many patients who do not respond to a sulfonylurea. It is also used to increase the effectiveness of both sulfonylureas and insulin.

Obese patients taking phenformin usually lose one pound each month. Because no other method of treating diabetes causes such consistent weight loss, this is the preferable drug for obese diabetics. The average therapeutic dose is slightly less than 1 mg per lb of body weight, but there is a narrow therapeutic margin. If the dose is raised too high in an effort to produce anorexia, the patient may interpret nausea as hunger and overeat. When an excessive dose is given, any patient will develop such side effects as metallic taste, foul breath, anorexia, vomiting, diarrhea, abdominal cramps, and malaise.

These side effects are readily controlled by stopping the drug, or reducing the dose. The incidence of side effects is less with the use of the time dispersal (TD) capsules than it is with the tablets. Severe side effects are now rare, and true toxic effects are of little consequence. The tablets have a four-hour duration of action and are usually given three to four times daily. The TD capsules have a longer (12 hours) effect, and are usually given at breakfast and supper.

There have been reports of lactic acidosis in patients taking large doses of phenformin. These patients usually had hepatic, renal, or severe cardiac disease with shock and tissue hypoxia. They were seen only after symptoms of toxicity had been present for several days. In our experience lactic acidosis has not been a problem. It is essential that all diabetic patients be followed closely regardless of the method of treatment used.

COMBINED USE OF ORAL HYPOGLYCEMIC DRUGS

There are some patients who improve but do not attain good control with a sulfonylurea drug with phenformin alone, but who achieve satisfactory diabetic control on both drugs together. The average dose for the combination is 500 mg of chlorpropamide and 150 mg of phenformin each day, but the dose of either drug must be varied in order to produce the desired control in each patient.

INSULIN PLUS PHENFORMIN

There have been reports stating that brittle diabetics can be stabilized if they are given one of the oral drugs in addition to insulin. In our study using tolbutamide with insulin, and then a placebo with insulin, there was no difference between the two groups. Most diabetics are made unstable by physicians who prescribe too much insulin, resulting in hypoglycemia and rebound hyperglycemia. When the insulin dose is reduced, there is less hypoglycemia and consequently less rebound hyperglycemia. If the patient is given another drug at the same time the insulin dose is reduced, the new drug is credited with the improvement actually produced by the insulin reduction. Some authors who have reported good results with this combination have not used placebo controls. The combination of insulin plus a sulfonylurea is worthless, but the supplemental use of insulin in patients taking a sulfonylurea is helpful during transient stress.

The combination of insulin and phenformin has been widely advocated to stabilize brittle diabetics. In our study only 2 out of 37 patients on this regimen showed improvement. The other 35 were no better controlled than they were on insulin plus a placebo. The two patients whose control improved possibly ate less because of the mild anorexia produced by phenformin. Patients who need insulin usually do best when they are given nothing but insulin.

Following the introduction of oral drugs, the fear was expressed that the simplified treatment would result in an epidemic of degenerative complications. This fear has not been borne out, and as long as satisfactory control is achieved, there is probably no contraindication to the use of oral hypoglycemic drugs.

CONCLUSION

The sulfonylurea drugs stimulate the pancreas to produce more insulin and are effective in patients with mild diabetes. Because it is excreted more slowly, chlorpropamide is four times more potent, and acetohexamide twice as potent, as tolbutamide. Chlorpropamide gives the most effective and most economical diabetic control. Phenformin increases the use of glucose in the muscle cells and is effective in many patients who do not respond to the sulfonylurea drugs. The average dose of phenformin is slightly less than 1 mg per lb body weight. If excessive phenformin is given, the patient will develop reversible gastrointestinal side effects. Phenformin is the only drug associated with consistent weight loss, and therefore is the drug of choice in the obese diabetic. Continued use of phenformin and chlorpropamide is effective in many patients who do not achieve satisfactory control with either drug alone. A combination of sulfonylurea and insulin is worthless, and a combination of phenformin and insulin is rarely valuable. Surgery, pregnancy, infection, or degenerative complications are not absolute contraindications to oral drugs, as long as the diabetes is well controlled. There is no evidence of increased incidence of degenerative complications in patients controlled by oral hypoglycemic drugs.

Some Surgical Problems in Diabetic Patients

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To illustrate some of the surgical problems in diabetic patients, I would like to present three patients. The first patient has been taking insulin longer than many of the people in this audience have been living. He is the oldest living juvenile diabetic in the United States. He had diabetes at birth. His mother took him to Boston in 1922 at the age of 17 months, in very bad shape. He was seen by Dr. Joslin and was worked up by a young intern whose name was Priscilla White. He began to get insulin in very small doses because there was not very much insulin available at that time. He has been taking insulin ever since, and at present he takes 40 units a day. He has gotten along extremely well with very few complications or difficulties until about three or four years ago when he began to have intermittent claudication. When this first came on, he could walk about six to eight blocks before he began to have pain in his calves. Later this progressed to the point where he could walk only 75 feet. It was at that point that we came in contact with him and he was admitted to the hospital here. Work-up included various arteriographies and these demonstrated blocks in both iliac systems and in both of the superficial femoral arteries. He underwent a bypass graft from the aorta to both femorals and a bypass graft from the femoral on the left to the popliteal on the left. Since this time he has been getting along very nicely. I asked him just this afternoon how well he could walk and he said he could carry a 75 pound tool box five blocks without any difficulty at all. So he seems to be pretty well over his claudication.

The next patient I would like to present is a woman of 33 who has been a diabetic since the age of 6. She has been taking insulin since the age of 6 and now takes about 65 units a day. She is a graduate nurse, so that sterile techniques have been no problem to her, and she got along very well with few complications until about two years ago. At this time on a routine checkup it was noted that she had albuminuria. Her BUN was 37 mg%. No specific treatment was undertaken. She went along doing her housework and not having any particular difficulty until December 1964, about a year ago. At this time she noted that she was tiring much more easily than she had and was feeling weak. She again consulted her doctor who discovered that her hemoglobin was down to 5 gm% and her BUN had now risen to well over 100 mg%. She obviously had severe renal disease. Later she was admitted here for study as a possible candidate for transplantation. Her renal disease had advanced to the point that her creatinine clearance was below 2 cc per minute. She was dialyzed in preparation for transplantation and a transplant was carried out about eight months ago, using a cadaver transplant because we were uncertain as to the outcome in a diabetic patient and did not want to use a living donor. Since this time she has been getting along quite well. We did not take out her kidneys at the beginning because, although

there were very small quantities of urine being formed, it was desirable to get a little bit of urine to follow her diabetic status. One of the most serious problems was that it was very difficult to dialyze her because as a rule a dialysis bath contains 2,000 mg% of glucose, and every time she was put on dialysis, her blood sugar rose to 2,000 mg%. She would be given more insulin and the next thing you knew the blood sugar was down to about 15 mg% and she was in insulin shock. Dr. John O'Brien and the other people in renal physiology finally came up with a formula which worked very nicely. They reduced the glucose in the bath to 200 mg% and used suction on the bath to extract the fluid instead of relying on the osmotic effect of excess glucose. With experience they were able to maintain her pretty well on dialysis, although this was really a major feat. She has gotten along very nicely since the transplant. She did remain somewhat hypertensive. We did not take out her own kidneys prior to the transplant, but because she was still hypertensive, she came back about a month ago, and had both her own kidneys taken out. Since that time, she has continued to stay on her insulin dosage. She is living at home and is getting along nicely. Her BUN is down to 17 mg%, her serum creatinine is 0.8 mg%, and her creatinine clearance has risen to 100 cc per minute. Her blood pressure is still elevated somewhat, but not as much as it had been prior to the nephrectomy and it is gradually coming down. Her eyegrounds at the present time are essentially normal. One of the problems is that she is on prednisone, which has made the management of her diabetes a little more difficult than usual and it also has had some tendency to keep her blood pressure elevated more than it would be otherwise. I think that as we decrease her prednisone, which we are gradually doing, her blood pressure will come down. She is now on 15 mg a day and is only taking 5 more units of insulin than she did before.

My third patient is 67 years old. She has had a great deal of difficulty with vascular disease. She is not a severe diabetic. She developed her disease only a few years ago and has been treated pretty well with tolbutamide (Orinase). Four months before she came in, she developed gangrene in the second toe on the right foot which had become severely infected. A month before she came in, she developed an ulcer between the fourth and fifth toes of the same foot and had severe rest pain in bed. She had an arteriogram and underwent a femoral-popliteal bypass graft on the right. After this the second toe healed up and she was able to walk very nicely. She also had rather severe arteriosclerotic heart disease with angina and was taking nitroglycerin and had some EKG changes of myocardial ischemia, but no definite recent myocardial infarct. She came back in April 1963 with gangrene of the fourth toe on the right foot at the margin of the previous ulcer. This had to be amputated. The base of the toe bled nicely and the amputation healed promptly without difficulty. She then came back in January 1964, this time with an ulcer on the left heel. This was a rather large ulcer. Sometime between April 1963 and January 1964, she had suffered a myocardial infarction which was easily demonstrable on her EKG. She had severe angina and was in congestive heart failure. Some people thought that perhaps the ulcer on her foot was a neurogenic ulcer and it was felt that she would not tolerate any operative procedure because of her severe cardiac state. It was recommended that no treatment be carried out at that time for her leg and foot. However, she was not able to walk because of the ulcer, which was large and dirty, involving almost the whole heel. She was having a lot of pain and was beginning to have ascending infection from the ulcer. We went ahead and carried out a femoral-popliteal graft on the left. After this she did very nicely. She was discharged and followed in the clinic and the ulcer finally healed completely. Ever since this time, she has been able to get along very well. She walks as far as she wants to, has not had any pain at rest, claudication, or further difficulty with ulceration.

These patients illustrate some of the more perplexing and challenging surgical problems in diabetic patients. There are many others, but these are particularly gratifying because only a few years back the circulatory problems in the lower extremities were treatable only by high amputation, and in the case of kidney disease with renal failure, there was no other treatment at all.

The Pregnant Diabetic

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At present, more diabetic females of childbearing age are going through pregnancy, and more diabetic children are living beyond maturity. The outlook for the pregnant diabetic has improved greatly but the infant mortality rate of diabetic children remains relatively high. My remarks are based on observations on 105 pregnant diabetics from my private practice.

Pregnancy imposes a strain, not only on the heart and circulation, but also on the carbohydrate metabolism of the body. Insulin needs of the pregnant diabetic often change, and certain pregnant women have a temporary increase in the blood sugar levels, accompanied by glycosuria; blood sugars return to normal between pregnancies. Some of these patients may present with full-blown diabetes after several pregnancies. Some workers suggest that control of this temporary diabetes with each pregnancy may prevent, or at least postpone, diabetes in an appreciable percentage.

The goal in following the diabetic pregnant woman through pregnancy is to see that she remains in good health and delivers a normal baby. The delivery of a live infant is not sufficient. Of four babies delivered from 26 to 30 weeks of pregnancy, all were born alive but died in a few hours. Of the 10 babies delivered from 30 to 34 weeks, 9 were born alive and the 10th was delivered just under 34 weeks of a 41-year-old woman with severe acidosis. Of these 60% in the neonatal stage died. To attain our goal, we must try to treat the mother and deliver the baby at such a time and in such manner to guarantee the good health of the baby and the mother.

GLYCOSURIA AND ACIDOSIS

I shall mention a few factors that influence treatment of the mother. The lowering of renal threshold for sugar is bothersome but not serious. More frequent blood sugar determinations are needed, greater attention to clinical observations is imperative, and prompt treatment for untoward findings is in order. The renal threshold may be expected to drop in 25% of cases, reaching below 120 mg in 11%. These figures are based on blood sugar determinations at certain times after meals, as correlated with urine sugar in specimens voided at the same time the blood is drawn.

The ease with which acidosis occurs in the pregnant diabetic woman is well recognized. Acidosis can develop quickly and advance rapidly in patients with blood sugar levels that are rarely associated with acidosis in the non-pregnant diabetic. Any acute infection, e.g., gastroenteritis, that seems trivial otherwise, poses a threat to the life of a diabetic.

FETAL SURVIVAL

The survival of fetuses of diabetic mothers has not increased significantly in the last 30 years. The time of delivery appears to have a definite influence; the 37th week was associated with the best sur-

vival rate, whereas all of those younger than 30 weeks died *in utero*. Excessive weight gain was associated with a higher fetal mortality. If pregnancy had progressed to the 34th week, the fetal survival rate was not seriously affected by episodes of acidosis, but acidosis occurring earlier in pregnancy accounted for many still-births.

NEED FOR INSULIN

During pregnancy the insulin need is apt to rise, although some doctors seem to believe that the baby's pancreas will supply insulin to supplement that of the mother. In only two of our patients did the insulin need drop, one from 60 units to 34 units with a subsequent rise to 54 units in a case of fetal death, and the other from 35 units to zero in a case with fetal survival. In 38% of the series, there was no appreciable change in the insulin need, but in 50%, the need increased to as much as 100 units. Fetal survival seemed uninfluenced if the dose was changed as indicated.

At the time of delivery, in those patients in whom insulin need had increased during pregnancy, the insulin need dropped abruptly the day of delivery to the prepregnancy level or lower. If such a reduction in the insulin dosage is not made, one may expect severe hypoglycemia.

The method of delivery in primipara is chosen the day of delivery. If the cervix is soft and somewhat dilated, and there are no other contraindications, vaginal delivery is performed if labor progresses satisfactorily. Otherwise, Caesarian section is indicated unless death of the fetus seems obvious. Over half the patients are delivered by Caesarian section and the fetal survival seems better, 91% as opposed to 76% with pelvic delivery. This difference may be due in part to the fact that Caesarian section is done only when there is an apparently living fetus.

SUMMARY

All diabetic mothers survived pregnancy in this series. If the mother's diabetes was well controlled, her weight gain is less than 16 pounds, and delivery occurs at about the 37th week, the baby has about a 90% chance of survival. This may be improved if prompt delivery is carried out when the insulin need drops 10 units or more. However, since the fate of the baby appears to depend on whether delivery should be made on a given day or three days later, obviously we lack some fundamental knowledge about the pregnant diabetic. It seems worthwhile to emphasize the need to reduce the dose of insulin the day of delivery to a level that is at least as low as the prepregnancy need of the mother.

Diabetic Glomerulosclerosis*

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I would like to show first the glomerulus of a 92-year-old man who did not have diabetes. It is perfectly normal. I want to emphasize that in the glomerulus there is not necessarily any ageing phenomenon per se. With the electron microscope there may be a slight increase in the thickness of the basement membrane of the glomerular capillary, but it is not visible by light microscopy.

In the normal glomerulus the afferent arteriole breaks up into capillary loops which spread out to form the lobules of the glomerulus. The central portion of each lobule or group of capillary loops is called the mesangial area (fig. 1). The capillary loops themselves are lined with endothelial cells, consisting of nuclei which protrude into the lumen, and a widely spread-out thin layer of fenestrated cytoplasm lining the capillary lumen. The endothelial cell is separated from the epithelial cell by a thin layer of basement membrane, and this basement membrane connects with little processes of similar material between adjoining mesangial cells. Outside the basement membrane are the epithelial cells, each with a wide extension of foot processes, forming a network around the capillary, with a tiny canaliculi between each foot process.

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The mesangial area is the central area of each lobule and is separated from the blood by the endothelial cells. The mesangial cells are frequently surrounded by a little bit of basement membrane material. The mesangial cells have a more abundant cytoplasm and are better equipped with mitochondria and endoplasmic reticulum than the endothelial cells, but it seems likely that the mesangial cells are derived from the same group of cells as the endothelium. If endothelial cells are damaged, the mesangial cells can proliferate to form new endothelial cells. Also, I believe that the mesangial cells normally produce basement membrane material and pump it out in some fashion along the capillary wall to form the basement membrane of the periphery of the capillary loop. There are practically no mitochondria or endoplasmic reticulum in the cytoplasm of the flattened endothelial cells, and it seems very unlikely that they could be producing the basement membrane material. Others have suggested that the epithelial cells form basement membrane, but this seems unlikely as some capillaries do not have such cells.

In the diabetic, the mildest change is thickening of the basement membrane (fig. 2). The basement membrane of the normal capillary loop measures 2,000 to 3,000 Å in thickness, by our methods. In diabetics, the thickness is from 6,000 to 15,000 Å. There are occasional exceptions—diabetics who show only normal thickness of the glomerular basement membrane—but the great majority of diabetics show a very definite thickening. In the early stages there is an abnormal accumulation of basement membrane material in the mesangial area. Gradually over many years this basement membrane material of the mesangial area increases until it appears to fill up the glomerulus. The material is PAS-positive. In the early stages, this lesion is diffuse glomerulosclerosis. This lesion is not specific for diabetes, and at this stage the pathologist cannot positively identify this as a diabetic process. It seems quite clear, however, that the development of nodular glomerulosclerosis, the Kimmelstiel-Wilson lesion which is specific for diabetes (fig. 3), is simply a further progression of the same process.

The little strands of basement membrane which normally separate the mesangial cells are called mesangial matrix. In the diabetic where this material is greatly increased, we call this material hyalinoid matrix. We now think it may be of a slightly different character. So we now have three basement membrane-like materials to think about in the glomerulus: *basement membrane proper,* the thin strands of normal *mesangial matrix,* and the pathologic material found in this area in diabetics, called *hyalinoid matrix.*

In the diabetic, as the basement membrane material accumulates, it piles up, particularly in the mesangial area, as hyalinoid matrix (fig. 2). This may form large

masses or nodules in which mesangial cells appear to be trapped. This is the so-called Kimmelstiel-Wilson nodule of nodular glomerulosclerosis, and it is specific for diabetes. The basement membrane of Bowman's capsule also becomes thickened, and shows a laminated structure. It is of interest that the basement membrane of epithelial structures show a laminated thickening, whereas that of the capillaries usually shows a diffuse thickening.

In the beginning of this process, the foot processes of the epithelial cells are not affected. As diabetes progresses, the normal foot processes are progressively fused until they may be totally absent. The disappearance of foot processes is apparently associated with proteinuria, and this is found in the neophrotic syndrome from any cause. In the diabetic, the foot processes may not be lost until the Kimmelstiel-Wilson lesion is well advanced, and this correlates quite well with what we see clinically. The diabetic may go for years without proteinuria, then rather abruptly develop a nephrotic syndrome with heavy proteinuria, hypoalbuminemia, and edema. The Kimmelstiel-Wilson lesion itself probably has nothing to do with it. It is a reactive phenomenon of the glomerulus, with loss of the epithelial cell foot processes.

There are several other changes commonly seen in the kidney in diabetes. One is the so-called exudative lesion or hyaline-fibrinoid lesion. These occur in the glomerulus and are most often seen in far advanced diabetes. Similar lesions are seen in other diseases; in some of the collagen diseases for example. At times they appear as almost solid hyaline masses; at other times they have vacuoles or even become quite foamy. The first are composed of a hyaline material, while the latter contain a high percentage of fat. They may fill the capillaries adjacent to the Kimmelstiel-Wilson nodule. They occur beneath the thickened basement membrane of the capillaries, and in Bowman's capsule adjacent to the thickened basement membrane.

Another interesting phenomenon has been known for many years. Hypertension in the non-diabetic is associated with arteriolar hyalinization and sclerosis in the afferent arteriole of the glomerulus but not in the efferent. In diabetes —and as far as we know only in diabetes—when there is hypertension one finds hyalinization and arteriolar sclerosis not only in the afferent but also in the efferent arteriole. Whatever the pressure is within the glomerulus of the diabetic with hypertension, it must be higher than the pressure in the glomerulus of the hypertensive patient without diabetes.

There is also thickening of the basement membrane of the renal tubules in diabetes. It is important to realize that in any patient, atrophy of the tubules from any cause will be accompanied by thickening of the basement membrane. This is a nonspecific change. But in diabetes, the basement membrane of otherwise normal tubules becomes thickened. There is a lamination of this. As was mentioned above, the basement membrane of epithelial structures, when it becomes thickened in diabetes, shows a laminated structure.

Certain other findings in the diabetic kidney are well known. You

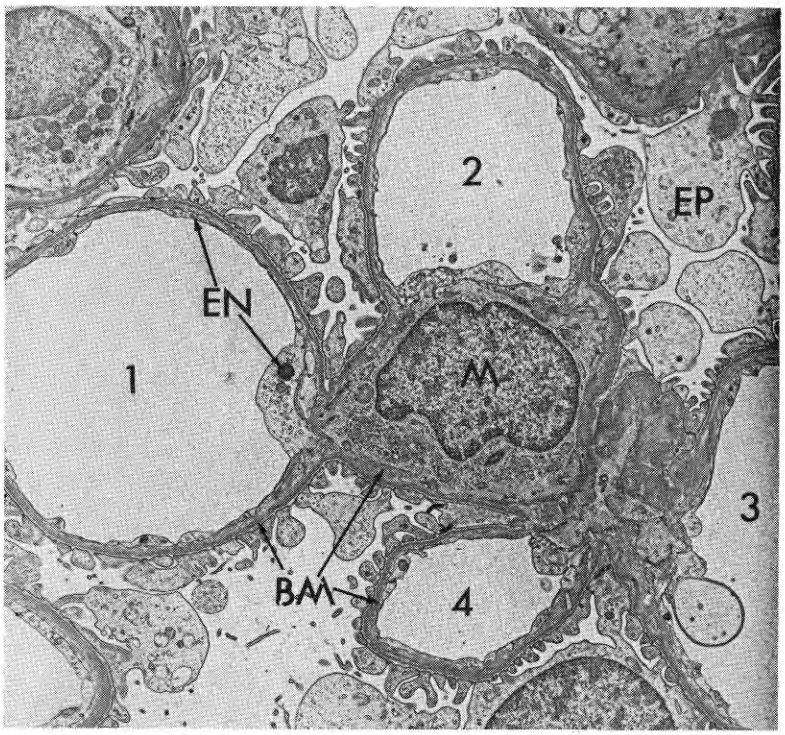

Fig. 1—Electron micrograph of a glomerular capillary tuft from a non-diabetic patient. The tuft is composed of a central mesangial area which is usually limited to a single mesangial cell (*M*) surrounded by several capillary loops, in this case four. Each capillary lumen (*1, 2, 3, 4*) is surrounded by a very thin layer of endothelial cytoplasm (*EN*) which is frequently fenestrated. The endothelial cytoplasm is, in turn, surrounded by a gray basement membrane (*BM*). External to the basement membrane are various processes of the epithelial cells (*EP*) which are called foot processes and are separated from each other by canaliculi (4000 ×).

are familiar with the yellow spots sometimes found in the medulla of the kidney in diabetes. This is renal papillary necrosis. It often occurs in association with pyelonephritis, but histologic examination shows that it is really a small infarct of the renal papilla, with necrosis in the center and inflammatory reaction around the edge. Although it may be associated with a highly virulent ascending pyelonephritis, there is obviously a vascular factor here. Pieces of infarcted and necrotic papilla can break off and be passed in the urine, and often these are sent to the pathologist for examination.

Pyelonephritis itself is a very common finding in diabetic patients, as is well known. Mention should also be made of the glycogen deposition in the renal tubular cells, the Armanni-Ebstein lesion, formerly a pathologic hallmark of uncontrolled diabetes, but no longer the common finding it once was.

I would like to describe briefly my findings in experimentally-produced diabetes in dogs. Ten dogs were made diabetic, five by alloxan and five by injections of bovine growth hormone. The dogs were maintained on insulin, but in a severely diabetic state, for one to six years. All the animals manifested diffuse glomerulosclerosis, and seven developed nodules of the classical Kimmelstiel-Wilson type, as found in human diabetics. The

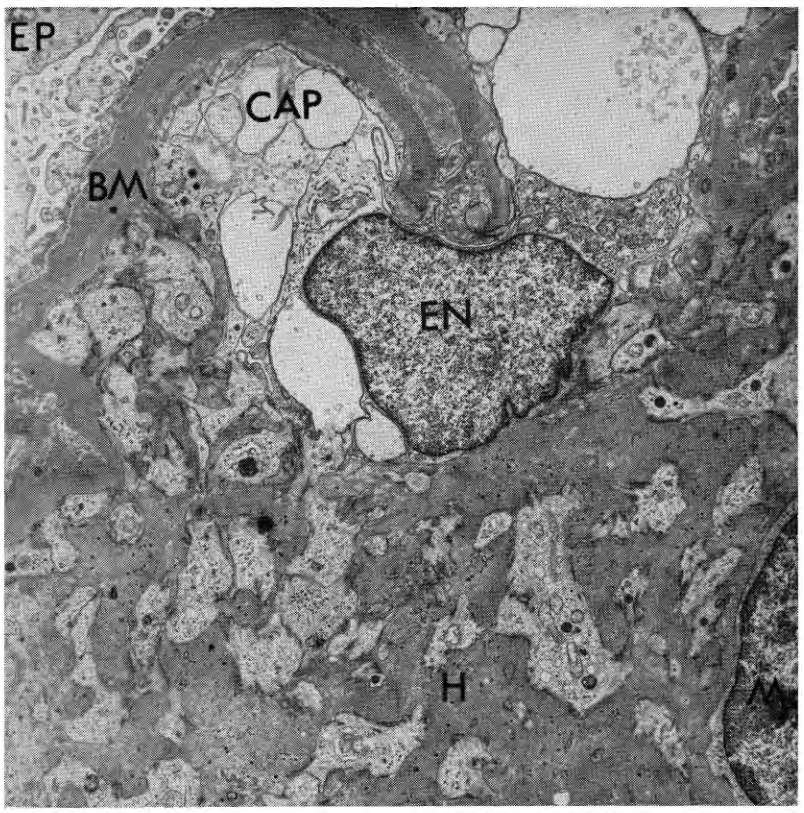

Fig. 2—Electron micrograph of a portion of a glomerulus from a diabetic patient comparable to that shown in Figure 1. The mesangial area has been markedly expanded by large amounts of hyalinoid matrix (*H*), or basement membrane-like material. The capillary lumina (*CAP*) are almost completely obliterated by swelling of endothelial cytoplasm and pressure by the hyalinoid matrix. The basement membrane (*BM*) is markedly thickened. The epithelial cell (*EP*) foot process structure is distorted and the canaliculi obliterated by fusion of foot processes (5100 ×).

exudative glomerular lesions, arteriolar sclerosis and thickening of the basement membranes of capillaries and tubules were present. Three long-term dogs also demonstrated diabetic retinopathy and thickening of peripheral capillary basement membranes.

From here on, I would like to speculate about the pathogenesis of these glomerular lesions. I have already stated that I believe the mesangial cells produce the basement membrane material. It is difficult to be sure of this in the normal state, but in the pathological states my colleagues and I are reasonably certain the mesangial cell is producing the hyalinoid matrix which surrounds it, and we have postulated that some of the basement membrane-like material from the mesangial area may migrate out into the periphery of the capillary loop to form its basement membrane. Why should the mesangial cell produce excessive quantities of this material? It is our theory that the mesangial cells are damaged or irritated in some way, and that this stimulates the cell not only to proliferate but also to produce more of this basement membrane-like material.

Why should the mesangial cells be irritated? We recently observed in some diabetics black deposits beneath and on both sides of the basement membrane. These appear quite similar to deposits seen in and around the basement membrane in glomerulonephritis and in lupus nephritis. I do not know for sure what they are, but theory says that in glomerulonephritis they probably represent antigen-antibody complexes. There is some evidence to support this. One would assume that in diabetes they might be the same thing. Or they might be some other atypical plasma protein which results from the abnormal pattern of diabetic metabolism. I do not know. I believe this substance may be trapped by the basement membrane. It may be an abnormal substance that is trapped, or it may be an abnormal basement membrane that traps it. As this material is trapped, it is irritating to the mesangial cells and causes them to proliferate and secrete more of the basement membrane-like material. This material gradually fills up the glomeruli, and causes them to become non-functional, ultimately leading to uremia and death. It is of great interest also that these same processes are observed in experimentally-produced diabetes in the dog, a non-hereditary form of diabetes. This would seem to favor a metabolic rather than a genetic origin for the vascular defect.

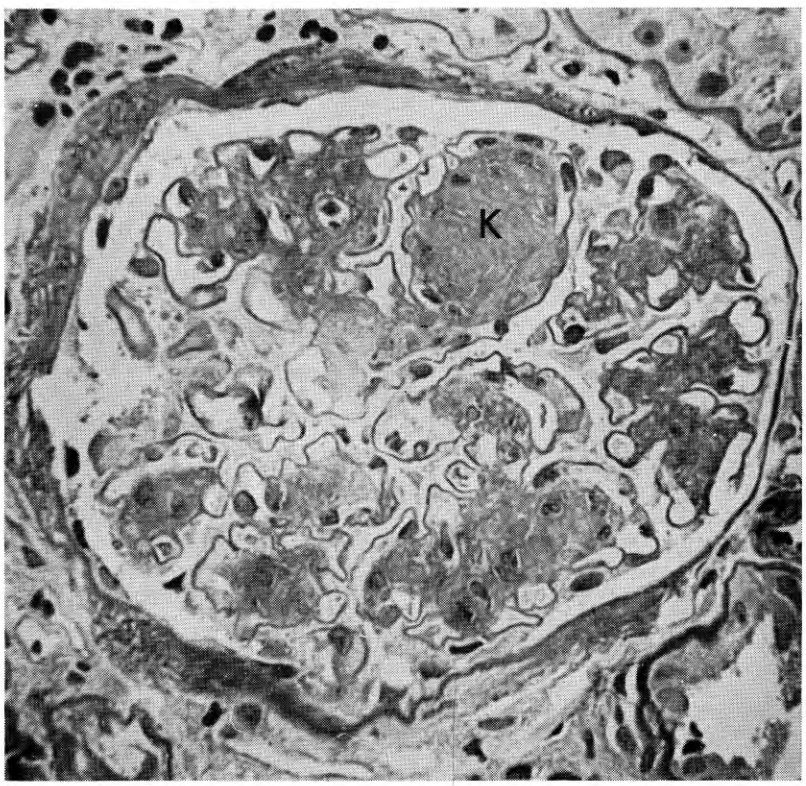

Fig. 3—Light micrograph of a glomerulus from a diabetic patient showing typical Kimmelstiel-Wilson nodules (*K*) and diffuse thickening of the remaining mesangial stroma (430 ×).

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Diabetic Microangiopathy*

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Microangiopathy is the term applied to the abnormal state of the capillaries, arterioles, and venules found in the diabetic patient. It is characterized principally by thickening of the basement membrane of these small vessels. It might be worth mentioning that while we are concerned here with the smaller blood vessels, diabetic patients also show thickening of the basement membrane beneath the endothelium of arteries of all sizes. Also, the basement membrane-like material that surrounds each smooth muscle fiber in the wall of arteries shows similar thickening in diabetic patients. With this thickening, there is an increased glycoprotein content of the arterial wall.

Diabetic microangiopathy is associated with well known clinical disturbances in the retina and in the kidney, but involves as well capillaries throughout the body.

Let us consider the structure of the normal retinal capillary as revealed by the electron microscope (fig. 1). The lumen of the capillary is lined by endothelial cells. The nuclei of these endothelial cells protrude into the capillary lumen, but elsewhere the cytoplasm of these cells is spread out in a continuous thin layer around the capillary to form its inner wall. In turn, a layer of basement membrane completely surrounds each endothelial cell. External to the single layer of endothelial cells are cells whose cytoplasm extends like tentacles around the capillary. These outside cells are the pericytes, although Dr. Cogan in Boston (1961) prefers to call them mural cells. Whatever they are called, they give support and strength to the capillary wall. Projections of basement membrane extend out between the cytoplasmic projections of the pericytes, and around the body of the pericytes.

One difference between retinal capillaries and other capillaries is that the retinal capillaries are intimately surrounded by the elements of the retina, the nerve fibers, and the glial cells. These structures are right up against the retinal capillaries and perhaps support them to some extent. At times the basement membrane material of the capillary appears to trail off into the adjacent nerve fibers or glial cells.

If we examine that retinal capillary of an elderly man or an elderly dog, we can observe two changes. There is some thickening of the capillary basement membrane, and in the outer layers of the capillary wall it has developed vacuolization, giving a Swiss cheese appearance. These changes occur with age in man and in the dog, but not in the elderly rat. It is of some interest that retinopathy will develop in the diabetic man and the diabetic dog, but apparently not in the diabetic rat.

Let us examine the retinal capillaries of a diabetic human with the

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electron microscope. The mildest change noted is the thickening of the basement membrane. The normal basement membrane is 700 or 800 Å in thickness, by our method; that of the elderly human a little thicker; but that of the diabetic much thicker, from 1100 to 3600 Å. The diabetic shows the Swiss cheese type of vacuolization of the outer portion of the basement membrane, and in addition in the diabetic the vacuolizations seem to be filled up with some kind of debris. Sometimes, the thickened basement membrane of the diabetic appears slightly laminated with similar osmiophillic debris between the layers. Another finding in the diabetic is the occurrence of collagen fibrils within the thickened layer of basement membrane.

The internal structure of the endothelial cells and the pericytes appears entirely normal in the diabetic. One sees normal nuclei and organdelles; that is, normal mitochondria, normal pinocytic vesicles, normal endoplasmic reticulum and ribosomes.

Let us now turn to the more classic light microscope findings in diabetic retinopathy; the microaneurysms, exudates, hemorrhages, and changes of retinitis proliferans. We really do not know whether these are related to the ultrastructural abnormalities seen in the capillaries or not. For one thing, the ultrastructural capillary changes are generalized throughout the retina while the microaneurysms and exudates are spotty, tending to occur mostly around the nerve head.

In the diabetic, the degenerative changes in the capillaries begin shortly after birth and progress throughout life, similar to the changes accompanying ageing in the non-diabetic. We see collapsed, acellular capillaries composed of basement membrane material in which are interspersed the processes of glial cells. This is evidently the end stage of the capillary degeneration. Whether it has something to do with the development of microaneurysms we do not know.

Microaneurysms tend to occur in focal groups or clumps (fig. 3). They will occur in one group of capillaries coming off an arteriole, but not in another group of capillaries coming off the same arteriole. There must be some focal factor that we do not understand.

Microaneurysms occur only in the inner half of the retina, which is the only part supplied by retinal capillaries. They occur in the ganglion cell layer just beneath the nerve fibers or as deep as the outer molecular layer, but not in the deeper structures such as the rods and cones.

Microaneurysms can be divided into the thin-walled type and the thick-walled type. Actually all of them have thicker walls than the normal capillary. The thin-walled microaneurysm appears as a great ballooning out of the capillary into a globular shape with the capillary entering at one end and coming out the other. I think this is the first stage, and the thickening of the wall comes later.

There is no change in the structure of the wall of the capillary at the point where it begins to balloon out to form a microaneurysm. The endothelial cells are intact and appear healthy (fig. 4). The basement membrane is thicker than usual and has debris in it, and may contain some collagen fibrils. These findings are diffuse and cannot explain the microaneurysm. The basement membrane material of the aneurysm must have been produced in increased amount to allow this ballooning out, with still an increased thickness. Also, there must have been proliferation or hypertrophy of the endothelial cells to allow them to continue to line the greatly enlarged surface of the aneurysm. This seems to suggest a vital, living process going on.

Cogan and his group in Boston (1961) found certain large capillaries with hypercellularity of the endothelial cells, but with unhealthy appearing or dead pericytes

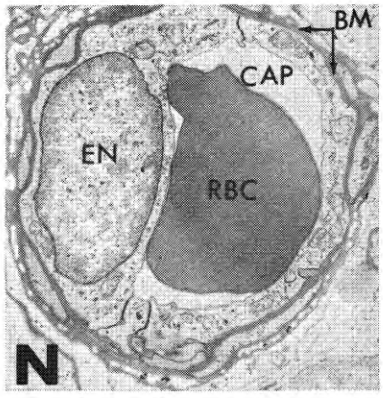

Fig. 1—Electron micrograph of a retinal capillary from a non-diabetic human patient for comparison with Figure 2. The capillary luman (*CAP*) contains a red blood cell (*RBC*). The lumen is surrounded by a thin layer of endothelial cytoplasm which, to the left of the lumen, contains a nucleus (*EN*). The endothelial cytoplasm is, in turn, surrounded by an irregular basement membrane (*BM*) (4200×).

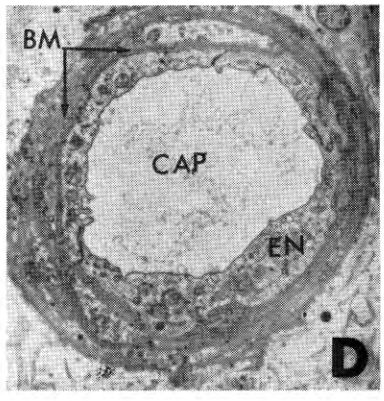

Fig. 2—Electron micrograph of a retinal capillary from a diabetic patient. The capillary lumen (*CAP*) is surrounded by a thin layer of endothelial cytoplasm (*EN*). The cells appear intact, and the usual organelles are present. Nuclei are absent at this particular level. Peripherally, there is a basement membrane which is considerably thicker than in the normal, and also contains a great deal of osmiophillic debris between the layers (6200×).

(or mural cells), which he calls "ghost cells." He believes that it is the pericyte that gives strength to the capillary, and that when this is damaged or dies, the capillary dilates. He calls this type of damaged vessel a "shunt vessel," and it is from these that microaneurysms develop. Adjacent capillaries may show no blood and no cells, only a basement membrane, and occasionally atrophied remnants of cells and glial fibers. I cannot find enough of these large, hypercellular "shunt vessels" to explain even a small portion of the total changes seen in diabetic retinopathy. I would be inclined to consider them as another phenomenon seen in diabetic retinopathy, but not as the basic etiology of the microaneurysms.

The thick-walled microaneurysms have a lot of glial cells around them and usually show accumulations of platelets. These collect along the endothelial lining, but some platelets may be seen within the vessel wall, along with red blood cells and fibrin. It seems evident that the thick-walled aneurysm is leaking, and the thickness results from the blood elements trapped in the wall and the glial reaction about the vessel.

The second classic finding of diabetic retinopathy is the exudate. The smallest exudates are those that appear immediately around microaneurysms, and represent leaked plasma constituents. They can hardly be distinguished from the aneurysm itself on ophthalmoscopic examination. The larger, waxy exudates are large collections of PAS-positive material, usually in the plexiform layers. Under the electron microscope, the exudate has a fine granular component and a fibrillar component. We believe this is a mixture of plasma proteins including fibrin that has leaked from the capillary. Apparently capillary leaks can occur in all eyes, but they are vastly more frequent in diabetic eyes. Around these exudates we may see glial cells attempting to

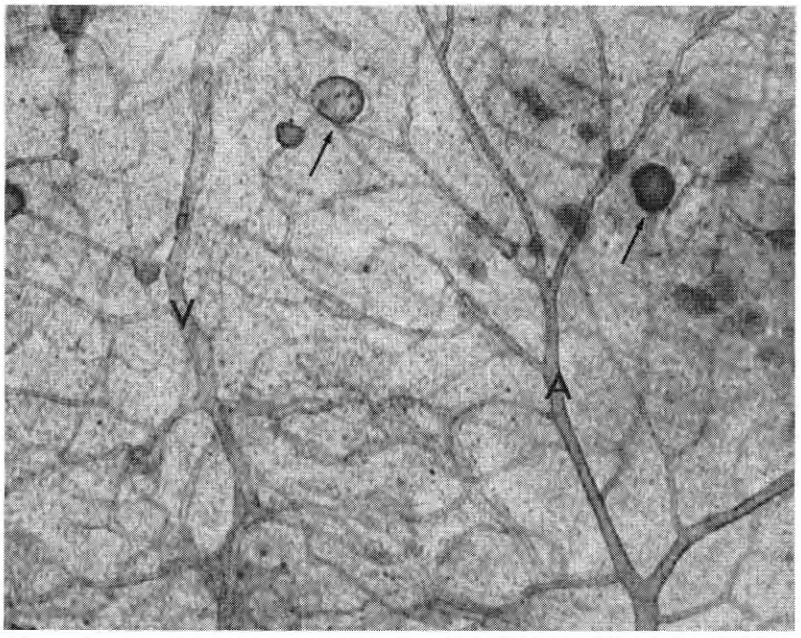

Fig. 3—Flat preparation of the retina from a diabetic patient. Note the artery (*A*) and vein (*V*) between which there is a capillary plexus. Numerous microaneurysms (arrows) are present on the capillary network. At the right of the photograph, the dark gray areas represent exudates associated with the microaneurysms in this area (90×).

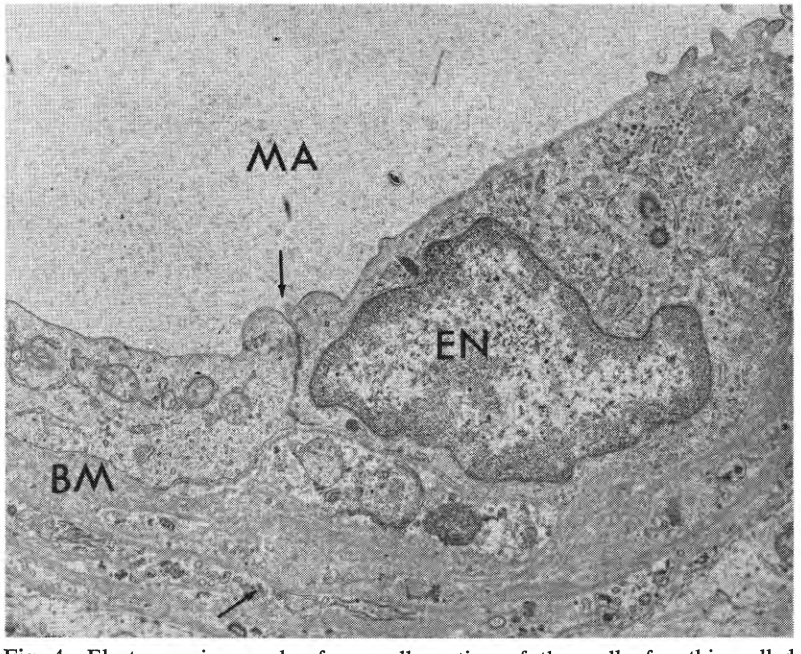

Fig. 4—Electron micrograph of a small portion of the wall of a thin-walled microaneurysm from the retina of a human patient. The lumen of the microaneurysm (*MA*) is surrounded by portions of two endothelial cells (*EN*). There is a cell junction at the upper arrow. Note the normal intercellular organelles in these cells which appear viable. They are in turn surrounded by a multi-layered basement membrane (*BM*). Note the osmiophilic debris and collagen-like material located between the layers of basement membrane, especially at the lower arrow (9600×).

phagocytize them. Apparently they can be phagocytized and removed eventually.

Hemorrhages are of two major types. The small, round hemorrhages occur in the deeper layers, from rupture of or leakage from microaneurysms. These are reabsorbed in a few days and probably cause no appreciable damage. Larger hemorrhages occur superficially, and may leak into the vitreous or may dissect beneath the retina and cause detachment. Strands of fibrin are laid down in the vitreous, and new blood vessels grow into these. These delicate new capillaries are easily disrupted, with further bleeding, and a vicious cycle is set up. This is the situation known as retinitis proliferans, the principle cause of blindness in diabetic patients.

Along with these vascular changes, there seems to be some degeneration of ganglion cells. In the ganglion cell layer, there seems to be a dropping out of cells and some of the remaining cells appear atrophic. In some areas, special stains reveal a swelling and fibrillar fragmentation of the nerve processes.

The cotton wool plaque looks like a mass of debris replacing a portion of the inner layers of the retina. It appears to be a microinfarction. Attempts at revascularization are seen. These structures are not specific for diabetes.

Evidence of microangiopathy may be seen in patients who have just developed diabetes, and in prediabetics with no demonstrable abnormality of carbohydrate metabolism. This had led some people to think that the changes of microangiopathy are due to an inherited defect in the capillary itself, inherited in parallel with the defect in metabolism. I think our evidence is definitely against this view. There are a fair number of examples of microangiopathy in humans with non-hereditary diabetes. In dogs made diabetic with alloxan or with growth hormone, I have seen all forms of microangiopathy, including retinopathy, with all the features described in human beings. I think

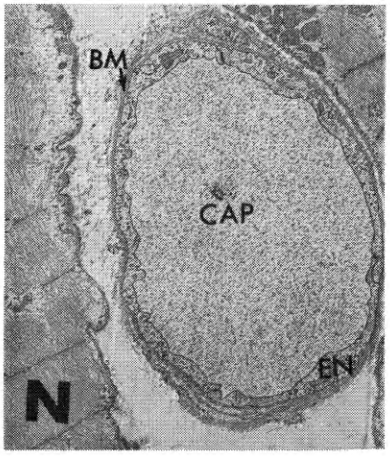

Fig. 5—Electron micrograph of a muscle capillary from a non-diabetic patient. The capillary lumen (*CAP*) is surrounded by a thin layer of endothelial cytoplasm (*EN*). Numerous pinocytic vesicles are present within the cytoplasm. The cytoplasm is, in turn, surrounded by a thin, gray basement membrane (*BM*). Compare with Figure 6 (5800×).

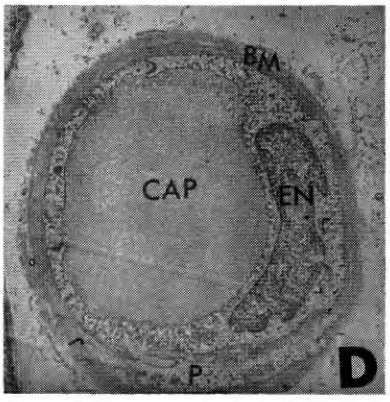

Fig. 6—Electron micrograph of a muscle capillary from a diabetic patient. The capillary lumen (*CAP*) is surrounded by several endothelial cells. The endothelial cell at the right contains a nucleus (*EN*). The endothelial cells are, in turn, surrounded by an unusually thick, gray basement membrane (*BM*). A portion of a pericyte (*P*) is separated from the endothelial cell by portions of basement membrane (6300×).

the microangiopathy results from some abnormality of metabolism that we are not just yet able to measure. I think we will some day find out what this is.

I would like to point out that most of the other capillaries in the body of the diabetic show the same thickening of the basement membrane. Muscle capillaries (compare figs. 5 and 6) show this, as do capillaries from the skin, ear lobe, toe, uterus and mammary gland. The one exception is the capillaries in fat tissue which show no thickening of the basement membrane in diabetes. This is true in the diabetic dog as well as in the diabetic human being. This must have some real importance, but we do not know the explanation. It might be related to differences in the utilization of insulin by muscle and fat, but this remains to be determined.

I should mention the work of Dr. Siperstein (1964 and 1965), who found thickening of the muscle capillary basement membrane in his diabetics and in prediabetics, but did not find any increase in thickness with age in the non-diabetic. I think there is an increase in the basement membrane thickness with age in non-diabetics, and am not sure the increased thickness he reports in his prediabetics is significant. He reports about 1,200 Å for his normals, 1,500 Å for his prediabetics, and around 2,500 Å for the diabetics. The error inherent in the method of performing basement membrane measurements is rather large.

Blumenthal and his associates at St. Louis have reported the finding of proliferative lesions in the capillaries and small vessels of the diabetic. Three pathology laboratories, including my own, have studied this problem and have concluded that these changes are not specific for diabetes. They apparently occur in areas of trauma and infection, as around the edges of the gangrenous area in a diabetic leg. The importance of these lesions remains speculative.

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Diabetic Neuropathy

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Diabetic neuropathy is becoming increasingly recognized because of its frequency and the severity of its manifestations. There is no domain in the field of medicine or surgery that is not at some time concerned with diabetic neuropathy.

Neuropathy in diabetes may be divided into somatic and visceral types. I will discuss chiefly visceral neuropathy, but I should first say a few words about somatic neuropathy, which is the commoner of the two.

PERIPHERAL (SOMATIC) NEUROPATHY

We hear much about the lower extremities in diabetic neuropathy, but relatively little about the upper extremities. One of the important manifestations of diabetic neuropathy is involvement of the motor nerves to the hands. Marked atrophy of all the interosseous muscles may occur; it is usually most marked in the first interosseous space and is bilaterally symmetrical. There is also atrophy of the thenar and hypothenar eminences. When this is seen without other evident neurological explanation, the odds for its being on a diabetic basis are overwhelming. This finding may be the first clue to the diagnosis of diabetes, as it can occur in the absence of overt aberration of carbohydrate metabolism.

There is also a sensory form. A man had an ulcer of the left heel, which he soaked in "warm" water, but it turned out to be "hot" water and he developed a third-degree burn of the heel for which he was hospitalized. The first night in the hospital, during sleep, his hand slipped over the left side of the bed and unfortunately landed on top of a radiator. He received a third-degree burn on the hand which was entirely painless because of marked sensory involvement of the hand by diabetic neuropathy.

Two manifestations of diabetic neuropathy deserve special reference. The first is the Charcot joint or neuropathic arthropathy. A Charcot joint can develop only when there is sensory impairment without motor loss, present over a long period of time. This combination of circumstances does occur with diabetic neuropathy and with syphilis, and hardly with anything else. This lesion has nothing to do with circulation, which is usually good. Repeated minor trauma over a long time in a joint without sensation, but still in active use, can lead to tremendous destruction of the bones of the joint. In syphilis this most often involves the knee or hip, the upper extremity, or the spine. In diabetic neuropathy the involvement is almost always in the foot. The most satisfactory treatment is rest of the joint, and this is best accomplished by a walking cast.

The other lesion of neuropathy in the lower extremity is the neuropathic ulcer or mal perforans. With neuropathy involving the lower limbs there is often muscle wasting and weakness, which may upset the normal stability of the foot and thrust excessive weight bearing on areas poorly adapted for it. A callus results, which eventually breaks down revealing a sharply circumscribed round ulcer beneath. The ulcer is entirely painless because sensation in the area is lost. The circulation is grossly normal although there may be disturbance in the capillary-tissue exchange because of microangiopathy. Sometimes infection occurs beneath the callus, but this is not necessary for the ulcer to develop. In the diabetic these neurotropic ulcers always develop in a weight-bearing area. Treatment includes measures to clean up infection, debridement of the callus, and elimination of weight bearing on this area. Local surgery can be performed as necessary because the circulation is good. The prognosis for healing is very good. Orthopedic measures to shift weight bearing elsewhere are necessary to prevent recurrence.

In regard to the peripheral form of diabetic neuropathy, I would like to say that the absence of ankle jerks is *the* most reliable objective manifestation of diabetic peripheral neuropathy. If you examine a patient and find bilaterally absent ankle jerks after reinforcement, in the absence of any other obvious neurological explanation, diabetes must be considered first. Again, neuropathy manifested by absent ankle jerks may be the first clinical manifestation of diabetes in the absence of any overt disturbance of carbohydrate metabolism.

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One of the classical manifestations of diabetic neuropathy is extra-ocular muscle palsy. This most commonly involves the sixth, third, and fourth nerves in that order of frequency. The paralysis is almost always ushered in by pain. The pain occurs on the side on which the paralysis is to appear. The pain always follows the distribution of one of the three branches of the trigeminal nerve, usually the first (ophthalmic) division. After three to seven days of pain, the paralysis appears. In the old literature, the association of pain and extra-ocular muscle paralysis always brought to mind the syndrome associated with aneurysm of the internal carotid artery, and many of these people have been subjected to arteriograms which are not to be taken lightly in the diabetic with fragile blood vessels. If you recognize the syndrome of pain and extra-ocular muscle palsy without other associated neurological phenomena, this in all probability is a diabetic neuropathy. More important, one can afford to relax about it because, of all the diabetic neurological manifestations, this is the one that has, by far, the best prognosis. Almost invariably these paralyses clear spontaneously in about 6 to 12 weeks. It affords the clinican a wonderful opportunity to reassure his patient who is really scared. The doctor can relax and the patient can relax. Whatever therapy is given will be effective because the condition clears spontaneously.

Postural or othostatic hypotension can occur as a result of neuropathy involving sympathetic vasomotor nerves. A dilated peripheral or mesenteric vascular bed fails to constrict when the patient stands, with pooling of a considerable amount of blood in that vascular bed, resulting in hypotension.

VISCERAL NEUROPATHY

The various manifestations of diabetic visceral neuropathy have been lumped together into a syndrome called "pseudotabes diabetica" for the obvious reason that it mimics the manifestations of luetic tabes in almost every degree, including the site of the pathological involvement. Sir William Osler used to say, "Know syphilis, know medicine." Today with syphilis hopefully on the wane and diabetes certainly increasing by leaps and bounds and diabetic complications increasing in parallel fashion, we can safely paraphrase William Osler and say, "Know diabetes, know medicine." There is no field in medicine or surgery where diabetes and its complications do not play a significant role today. The name "tabes" means wasting. There may be marked wasting of every muscle system in the body, the shoulder girdle, the gluteal muscles, and the lumbosacral muscles. This of course results from the accompanying somatic neuropathy.

THE GASTROINTESTINAL TRACT

Let us now turn to visceral neuropathy and consider first the gastrointestinal tract. Involvement of the stomach is not uncommon. This is characterized by delayed emptying of the stomach with marked retention, and with evidence of marked hypersecretion. It leads to a variable and unpredictable rate of absorption which in turn interferes with proper control of the diabetes. In the small bowel one finds what is called "diabetic diarrhea." I want to stress that the diabetic may get every kind of diarrhea that nondiabetics are subject to, but in addition, there are two types of diarrhea which are fairly specific for the diabetic and merit further discussion. The first, "diabetic diarrhea," I prefer to call "diabetic enteropathy" because it localizes the site of pathology. Diabetic enteropathy is characterized by spontaneous remission and exacerbations. The diarrhea is usually most marked at night, and not infrequently is associated with fecal incontinence. It may show postprandial exacerbations. Post-breakfast diarrhea is one of the more common manifestations of diabetic enteropathy. It is associated with perfectly normal pancreatic secretion as determined by the secretin test. It is always associated with diabetic neuropathy and has a fairly characteristic, though not specific, x-ray picture of the small bowel. The x-ray appearance is that of disordered motility. There are areas of widening and of narrowing of the bowel, and scattering and puddling of the barium, the typical disordered motility pattern of the small bowel. This was once thought to be due to vitamin deficiency but we know now it is not. The small bowel biopsy in diabetic enteropathy is perfectly normal.

There are several other interesting clinical aspects to diabetic enteropathy. These patients, in spite of severe diarrhea at times, rarely show malnutrition. The diarrhea is not associated with infection; there is no pus or blood in the stool. The patients do not lose weight and ordinarily there is neither vomiting nor abdominal pain. The treatment for this condition is not too rewarding. For some reason, a fair number of these patients respond to antibiotics, particularly chloramphenicol, and at other times, neomycin. Why this is so, I do not know, but it remains a practical clinical empirical point and these patients are certainly entitled to a trial of antibiotic treatment.

Another form of diarrhea in the diabetic, which may or may not be coincidental, is the diarrhea of the malabsorption syndrome. The patients show the classical malabsorption syndrome with flat vitamin A tolerance test, low fasting vitamin A, low fasting blood carotene, abnormal d-xylose excretion test and, of course, marked steatorrhea, and marked fat excretion in the stool. These people also have perfectly normal external pancreatic secretion, so it is not a manifestation of pancreatic dysfunction. In these patients the small bowel biopsy is markedly abnormal and is char-

acteristic of that seen in the sprue syndrome. There is complete loss of the delicate villi, marked clubbing of the villi, tremendous edema and cellular infiltration, with many eosinophils as are seen in sprue. This is more than an academic differentiation. It is tremendously important to recognize that this occurs in diabetics and to differentiate it by appropriate tests from the diabetic diarrhea. Whereas on the one hand the therapy of diabetic diarrhea leaves much to be desired, therapy here with either corticosteroids or a gluten-free diet as in sprue, offers a really dramatic response. The patients, almost overnight, become tremendously improved. The steatorrhea disappears, appetite picks up, malnutrition vanishes, and in a few days there is complete symptomatic recovery. (I might state that there is no contraindication to the use of corticosteroids in the diabetic when there is a specific clinical indication. The worst that could happen is that the insulin requirement increases so that the patient takes a few more units of insulin.)

I should also mention that true pancreatic diarrhea can occur in the patient with chronic pancreatitis and diabetes. The small bowel biopsy is again perfectly normal and not like that in the true malabsorption syndrome. This condition has to be differentiated from the malabsorption syndrome, because there is steatorrhea in both. By the use of the I^{131}-labeled oleic acid and triolein tests, pancreatic diarrhea may be readily distinguished from the primary absorptive defect of the malabsorption syndrome.

THE GENITO-URINARY SYSTEM

Let us turn to the genito-urinary tract for another fascinating aspect of diabetic neuropathy. Neurogenic vesical dysfunction, or neurogenic bladder paralysis, is one of the least recognized aspects of diabetic neuropathy. It is a pity because here again we have definite therapeutic measures available to help these patients. Perhaps the chief reason that it is missed is because its clinical manifestations are so insidious. The bladder slowly distends as it loses its sensitivity and its responsiveness to the normal stretching by urine. The bladder dilates and empties poorly, and finally there is more and more residual urine until the patient presents with an "abdominal tumor of unknown etiology," or there is the classical overflow with incontinence. Much worse, all these patients eventually develop infection and renal failure. They present with severe sepsis and azotemia and everybody gets busy treating the azotemia and the sepsis, and may forget all about the cause.

The patient with the neurogenic bladder may have no symptoms whatever. A full bladder may be palpated, or an x-ray taken for some other reason may reveal a full bladder. The degree of bladder distention may be tremendous, with a capacity of 3,500 ml or more. The flat cystometrogram and the cystogram itself are the hallmarks of the diagnosis. Intravenous pyelography may show dilatation of the ureters and beginning dilatation of the calyces and renal pelvis. Visualization may be faint because of the tremendous dilution of the dye, and also because of impaired renal function.

Besides azotemia and sepsis, one other complication of the neurogenic bladder is pneumaturia, caused by fermentation in the bladder urine. This does not occur except in the presence of neurogenic vesical paralysis. The diagnosis may be made by the roentgen picture, or by tympany on percussion of the lower abdomen. On passing a catheter there is passage of urine followed by an explosion of gas through the catheter.

How do we treat this type of neurogenic bladder? Some patients respond to simple catheterization, with removal of the residual urine for a period of ten days or so. Some patients do not respond to this, and after appropriate catheter drainage, still have residual urine in the bladder. It is the sensory arc of the bladder reflex that is interrupted in diabetic neuropathy so that the stimulus for motor contraction is gone. After the bladder becomes more and more distended, the motor arc also disappears. The internal vesical sphincter controls the emptying of the bladder. The external sphincter is separated and actually is not an anatomical part of the bladder. The bladder and internal sphincter are innervated by sympathetic and parasympathetic nerves from the lumbar and sacral segments of the cord. These nerves are involved in diabetic neuropathy. The external sphincter, however, is innervated by a voluntary nerve, the pudendal, which is usually not involved in diabetic neuropathy. The neurogenic bladder is so paralyzed it does not have the force to propel the urine through the internal sphincter. These patients respond dramatically to surgery. The operation is based on equalizing the two forces, by removing the internal sphincter. The external sphincter is anatomically distinct and separate from the bladder, and its innervation remains intact in diabetic neuropathy; hence it can continue to exert sphincter control, and one does not get incontinence. Fortunately, in the male, if the diagnosis is missed, it is called "prostatism." The prostate is removed and the internal sphincter is always destroyed in the process, so we get the same result. In the female the internal sphincter is resected transurethrally, with excellent results.

Impotence is a frequent symptom of neuropathy in the male diabetic patient. Unfortunately the prognosis for this complication is poor.

The Natural History of Diabetic Retinopathy

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Since the discovery of insulin and its use in the management of diabetes, the occurrence of diabetic retinopathy appears to have increased (Vogelius, 1949). In 1923, the incidence was 14.6% and in 1953, it had risen to 46% (Portsmann and Wiese, 1954). The progressive increase has been attributed to the longer survival of diabetic patients, in whom retinopathy usually develops after having had diabetes for 15 to 25 years (Ashton, 1958).

Although diabetic retinopathy is a common cause of blindness (Bradley, 1965), the etiology of the associated retinopathy is still unknown. From reports in the literature (Scott, 1951; Ehlers, 1953; Cogan, 1961; Lawrence, 1951; Mooney, 1963; Dobree, 1964) and recent clinical observations made on diabetic patients at the Medical College of Virginia, two types of diabetic retinopathy can be distinguished. They differ noticeably in two clinical aspects; the rate of visual deterioration, and the ophthalmoscopic findings during the early stages of the retinopathy (table 1).

TYPE I DIABETIC RETINOPATHY

This is the commoner variety. It is characterized by a slowly progressive course of visual deterioration and ophthalmoscopic changes. Caird reported in 1963 that approximately 14.5% of patients with this type of retinal pathology become blind within five years after the onset of first signs of retinopathy. The diagnosis of this disorder is based on the detection of micro-aneurysms, round hemorrhages, and waxy exudates which are characteristically found in the posterior polar region of the eye (fig. 1).

Microaneurysms

The earliest abnormality to be noted is usually microaneurysms which are situated predominantly in the macular area, and in most cases are adjacent to the venous end of the capillaries. These aneurysms appear as small red dots, 20 to 30μ in diameter, and are highly suggestive of diabetes (Ashton, 1958). They are visible in 55% of patients with diabetic retinopathy (Scott, 1951). Histologically, a microaneurysm is an aneurysmal dilatation of the capillary wall. The etiology is still unknown, although many theories have been proposed. Wise (1956) suggested that microaneurysms are an abortive form of neovascularization. Ashton (1958) demonstrated histologically that aneurysms develop from capillary loops. The opposing walls of the loops become fused and exudates form a cap on the aneurysm. Cogan (1961) found that in the diabetic retina the mural cells, which are normally present in the capillary wall, show degenerative changes, and the microaneurysms appear to begin at the sites of these cells. However, Bloodworth (1962) suggested that the initial lesion is the degeneration of neurons and glial cells, followed by aneurysmal dilatation of the capillary wall. Wolter (1962) noticed a significant increase of intervascular mesodermal

strands connecting the retinal capillaries, and suggested that microaneurysms may be due to traction of these strands developing within the process of pathological neovascularization.

Round Hemorrhages

Microaneurysms are located in the inner nuclear layer of the retina and hemorrhages commonly occur at the site of these aneurysms (Ashton, 1958). Ophthalmoscopically, the retinal microaneurysms in diabetes may be visible for many months in contrast to hemorrhages, which disappear within weeks. Round hemorrhages are intra-retinal bleeding spots located deep in the outer plexiform layer. The blood is confined by the retinal fibers, which are arranged in the anteroposterior axis of the eye, and hence the hemorrhagic areas appear round. Hemorrhages of this type are seen in 85% of patients with diabetic retinopathy (Scott, 1951).

Waxy Exudates

The white or yellowish patches are exudates, consisting of lipoid and PAS-positive material, thought to be mucopolysaccharide. These substances seep through the walls of the blood vessels and eventually accumulate in the outer plexiform layer of the retina (Ashton, 1958). These well-defined waxy exudates form a characteristic ophthalmoscopic picture and are found in 76% of patients with diabetic retinopathy (Scott, 1951). Many small exudates tend to coalesce to form larger plaques. In advanced cases, this formation of larger plaques can result in a circular pattern surrounding the macula which may be referred to as *circinate retinopathy*.

Fig. 1—Diabetic retinopathy, Type I, early stage. Photograph of macular area of fundus of 54-year-old diabetic, showing microaneurysms near the venous end of capillaries (arrow 1). Larger lesions with ill–defined borders are "round" hemorrhages (arrow 2). The well-demarcated white lesion is a waxy exudate (arrow 3).

Vitreous Hemorrhages and Retinitis Proliferans

During progression of the retinal lesion, hemorrhages into the preretinal space and the vitreous can occur, and this may be followed by retinitis proliferans, which is a product of the proliferation of fibrous tissue in varying amounts associated with new fine vessels (Hanum, 1938). This advanced retinopathy marks the final stage of useful vision.

TYPE II DIABETIC RETINOPATHY

This proliferative type of retinopathy is characterized by a rapid progression of visual loss and ophthalmoscopic changes. Recently, much has been written on this type of retinopathy, with special reference to the visual prognosis, the evolution of the retinal lesions and the fundoscopic changes following hypophysectomy (Beetham, 1963; Dobree, 1964; Root, 1959).

The incidence of proliferative diabetic retinopathy was recently found to be as high as 30% in diabetics with visible retinal changes. About 50% of this group of patients had fairly good vision and 30% had visual acuity of less than 20/200 in the better eye. The progression of this retinopathy from onset to "legal" blindness took an average of three years (Beetham, 1963).

Venous Engorgement, Vascular Proliferation, and Connective Tissue Condensation

In the early stages, the ophthalmoscopic signs are venous engorgement, vascular proliferation and connective tissue condensation. The

most important diagnostic features are the neovascularization and connective tissue condensation which are found initially around the optic disc. Smaller collections of new vessels are also seen in the superficial retinal capillary plexus and the vitreous (fig 2). Vision and the retinal details may be blurred by larger proliferative lesions which project into the vitreous. The proliferative vessels sometimes assume a veil-like structure and wave in the vitreous at slight movement of the eye.

TABLE I

Comparison of two types of diabetic retinopathy based on clinical observations.

	Type I	Type II
Age of onset	(5th or 6th Older decade)	(Before 4th Younger decade)
Visual deterioration	Relatively slow	Relatively rapid
Fundus Early	Microaneurysms, round hemorrhages, waxy exudates	Vitreous* hemorrhages Venous engorgement, vascular proliferation, connective tissue condensation
Late	Fibrosis (retinitis proliferans), retinal detachment	

* Vitreous hemorrhages may occur in either type at any time during progression of retinal lesion.

Vitreous Hemorrhages, Retinitis Proliferans, and Other Complications

Bleeding from fragile vessels gives rise to subhyaloid and vitreous hemorrhages which are liable to occur during exertion as in bending, stooping, or severe vomiting (Dobree, 1964). When absorption of blood takes place, the vision improves, only to be followed by repeated episodes of sudden blindness caused by recurrent vitreous hemorrhages. Eventually, severe retinitis proliferans develops (fig. 3). The latter, as with Type I, is the final stage, and the already blind eye may be further complicated by occlusions of the retinal vessels, retinal detachment, and secondary glaucoma.

COMMENTS

Despite the differences observed clinically, the proliferative retinopathy may be a variant of the more common, slowly progressive type (Cogan, 1961). The complex ophthalmoscopic picture of the former can be superimposed on a background of Type I diabetic retinopathy which may be of any degree of severity (Dobree, 1964).

It is significant to note that in spite of the relatively malignant course in visual deterioration with the proliferative retinopathy, spontaneous regression occurs in 10 to 15% of patients, some of whom

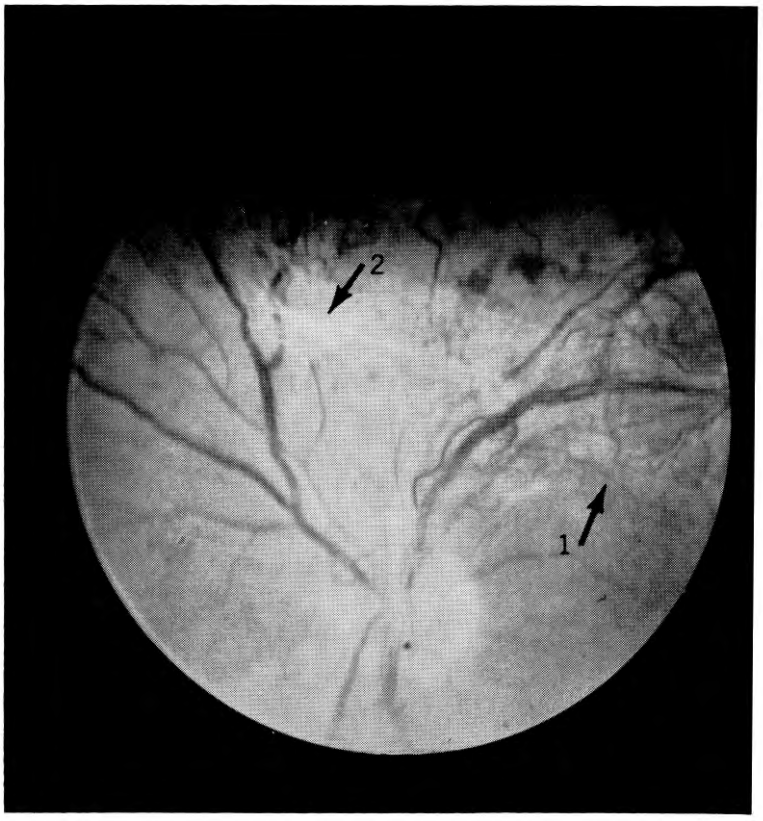

Fig. 2—Diabetic retinopathy, Type II, early stage. Optic disc and adjacent re of 42-year-old diabetic, showing growth of fine, tortuous brush-like vessels tending into the vitreous (arrow 1). White strands surrounding new vessels connective tissue condensations (arrow 2).

enjoy improvement of vision for as long as 10 years (Beetham, 1963; Dobree, 1964; Bradley, 1965).

It is of interest that, with maximal medical management fewer than 30% of patients with Type II retinopathy showed overall stabilization of retinal pathology and visual improvement, whereas following pituitary surgery, 50% or more had a favorable response (Bradley, 1965).

SUMMARY

Diabetic retinopathy is a common and increasing cause of blindness. The higher incidence of retinopathy is related to the longer survival of the diabetic patient.

The etiology of diabetic retinopathy remains unknown. However, two varieties appear to exist:

Type I retinopathy, characterized by a slowly progressive course and ophthalmoscopic findings of microaneurysms, round hemorrhages, and waxy exudates; and Type II retinopathy, associated with a more rapid loss of vision, in which the main findings are venous engorgement, vascular proliferation, connective tissue condensation, and recurrent vitreous hemorrhages. Both types may result in retinitis proliferans and blindness. In the proliferative (Type II) diabetic retinopathy, regression of the vascular element, but not the fibrous tissue, may occur spontaneously or after hypophysectomy.

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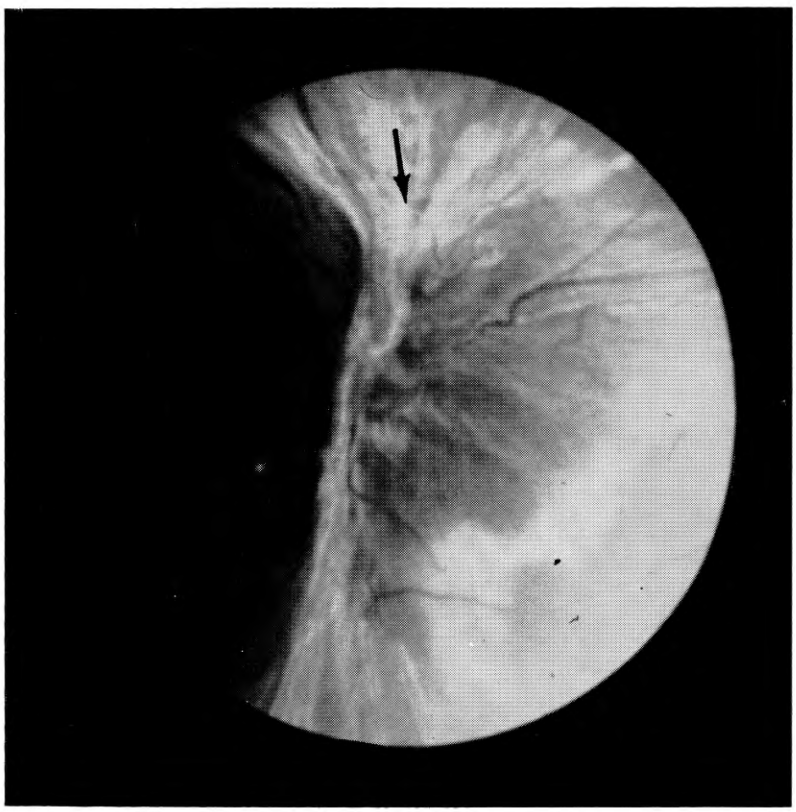

Fig. 3—Diabetic retinopathy, Types I and II, late stage. Retinitis proliferans (arrow), consisting of whitish bands of fibrous tissue and fine vessels.

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Pituitary Ablation for Diabetic Retinopathy*

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Ablation of the pituitary gland appears to alter the course of diabetic retinopathy in some patients. This is purely an empirical form of therapy. It developed mostly from the observation in a patient with advanced diabetic retinopathy who, following pregnancy, hemorrhage, and the onset of Sheehan's syndrome (or hypopituitarism), showed marked regression of the retinopathy. This observation was made by Poulsen (1953). Shortly thereafter, Luft, Olivecrona, and Sjögren, (1955), in Stockholm, performed surgical hypophysectomy in a group of patients with rather advanced diabetic vascular disease and diabetic retinopathy. The results were not very good on a long-term basis, but did demonstrate that in some of these patients the course of the diabetic retinopathy apparently was altered favorably. It has now been confirmed by several workers that removal of the pituitary gland can alter the course of the changes just described by Dr. Chan.

* These studies have been carried out in collaboration with Drs. W. F. Collins, Jr., C. N. Shealy, C. I. Thomas, and B. Kaufman, and were supported by grants from the U. S. Public Health Service, CA 05197-06, FR 80-02, and the American Cancer Society, T 46 F.

SURGICAL RISK OF HYPOPHYSECTOMY IN DIABETICS

The idea for this therapeutic measure goes back to Houssay's observation that removal of the pituitary gland has an ameliorating effect on diabetes mellitus. There were a few early attempts to do hypophysectomies before these more recent observations, but they were probably premature because the replacement hormones necessary to maintain the hypophysectomized patient were not available and these patients all succumbed quickly. It also became very apparent that in carrying out surgical hypophysectomy in diabetic patients, there was a major threat to life. Of the first 20 patients operated on by Dr. Olivecrona (1955), about a third died in the immediate post-operative period. In other clinics, Dr. Bronson Ray began to do hypophysectomies about 1955. In his first 14 patients, there were two operative deaths. Dr. William Collins and I started our experience with the procedure about 1960 in Cleveland, and in a group of eight patients, we had one operative death. So it became apparent that although surgical hypophysectomy can be performed in other types of patients with very

little mortality and morbidity, the problem was quite different in the diabetic patient. Those patients of Dr. Luft (1962) who survived had convulsions and periods of stupor in the post-operative period. It became apparent therefore that the brain behaved quite differently in the diabetic patient. It was obvious that there must be a more subtle way of changing the hormonal environment of these patients.

BENEFICIAL EFFECT OF HYPOPHYSECTOMY; RELATION TO GROWTH HORMONE

Many studies have been carried out to try to determine by what mechanism hypophysectomy could alter the course of this disease. I think we can say emphatically that we still have no inkling. It is apparent that hypophysectomy does ameliorate the metabolic defect in the diabetic patient, in that there is a marked reduction in insulin requirement. In the juvenile diabetic, the dose of insulin drops to about a third of its previous level. Adult diabetics frequently do not require insulin after hypophysectomy. The amelioration of the diabetic defect may be due to withdrawal of growth hormone, since administration of human growth hormone to diabetics produces a marked exacerbation of the diabetic state.

More recently the ability to measure growth hormone in the serum of patients has permitted an evaluation of whether the hormone levels are normal or abnormal in the diabetic patient. Preliminary studies seem to indicate that blood growth hormone levels are perfectly normal in diabetics, including those who have diabetic retinopathy. With insulin-induced hypoglycemia, growth hormone levels rise very much as they do in normal subjects. So, a superficial look at growth hormone in these patients would seem to indicate that there is no basic abnormality such as is seen in acromegaly and in the diabetes that may be associated with acromegaly. However, I think further data are needed because although diabetic patients may have normal growth hormone levels, these levels may be too high in relation to the elevated blood sugar. There may be fluctuations of growth hormone levels during the period of the day which may be quite abnormal in the diabetic patient as compared with the non-diabetic. But this information has not helped us really. The incidence of diabetic retinopathy in acromegalic patients does not seem to be any higher than, and certainly not as high as, in patients with ordinary diabetes mellitus, although definite microangiopathy has been seen in acromegalic patients and particularly in those who have a diabetic tendency.

EXPERIENCE WITH HYPOPHYSECTOMY BY YTTRIUM^{90} IMPLANTS

To study further the clinical response of patients to hypophysectomy, it seemed worthwhile to try another approach to ablation of the pituitary gland. Dr. Forrest and co-workers (1959) in Scotland has been working on the implantation of radioactive materials into the pituitary via a trans-nasal, transsphenoidal approach. The early results were not very satisfactory but about five or six years ago, he adopted a technique in which he introduced two yttrium rods attached to a stainless steel screw into each side of the pituitary gland. The stainless steel screw was designed to do two things; first, it would fix the yttrium rod which would deliver a necrotizing dose of radiation to the pituitary, so that the accuracy of placement of the rod could be enhanced, and, it would plug the hole that was used to put the yttrium^{90} into the pituitary, thus preventing such complications as rhinorrhea and meningitis.

Dr. Collins and I embarked on this program about three years ago and we have now had experience with this type of implantation in 125 patients. Specifically we have had experience with 32 patients with diabetic retinopathy. We have not been able to confirm Forrest's observations (1959) that this technique is without complications. We have had rhinorrhea in three patients, and meningitis in two; all of these subsided, however, without residual damage. From a surgical point of view, the procedure is indeed a benign one and is useable in patients who are completely unsuitable for surgical hypophysectomy. We have had no mortality in the original procedure in these 32 patients, but we did have one surgical mortality in a patient who was re-operated on a year later. We have seen no significant nerve palsies.

EFFECT ON VISION AND RETINOPATHY

In this group we have studied patients with quite advanced diabetic retinopathy. In two thirds of the patients, we have seen significant improvement in terms of better vision. The most striking change that the ophthalmologist reports is a decrease in edema of the retina, a decrease in hemorrhages, in the neovascularization, and in microaneurysms. The retinitis proliferans shows no change. The fibrous changes remain, but the vascularity of this proliferative disease can regress. I specifically state that there is a decrease in these changes and not a complete disappearance of all of these vascular difficulties. But the clinical response in these patients has indeed been quite remarkable.

Of the group whom we considered to be failures, there were only three who have shown progressive changes in terms of hemorrhage going on to destroy vision. In two of these three, we felt that the hypophysectomy had been incomplete and that one of these had shown transient improvement, followed by a recurrence of hemor-

rhages which went on to destroy vision. Whether complete hypophysectomy is essential for the best results is of course not certain. But some of the data that we have suggests that the more complete the hypophysectomy, the better the results.

Also in the group that we considered to be failures were patients who had bilateral retinitis proliferans with large areas of fibrous tissue covering the disc and extending toward the macular area. A number of these patients had only peripheral vision. Visual acuity was less than 20/200 and yet we reasoned that if we could retain this degree of peripheral vision, the hypophysectomy would have been worthwhile. In five such patients we have seen no significant change except for some decrease in the vascularity of the diabetic retinopathy. But there has been no improvement in vision and these patients cannot be considered successes. It is striking, however, that a number of patients with retinitis proliferans with sparing of the macula and useful vision, seem to have shown no progression of the scarring. We have patients who have gone as long as nine years now without evidence of progression of the retinopathy.

SUMMARY

Our clinical experience and the experience of others seems to indicate that pituitary ablation can induce a significant beneficial effect on the course of diabetic retinitis, even in advanced stages. We have no strict criteria for the selection of patients. When surgical hypophysectomy is being done, the major restriction is whether the patient has a fair chance of getting through the procedure without great risk of death or serious complication. With yttrium-implant hypophysectomy, the risk of death from the procedure itself has been practically eliminated. The morbidity would be much less if the rhinorrhea and the threat of meningitis could be eliminated completely. From our experience, the procedure appears to be futile in patients with severe retinitis proliferans with very little vision left. Where there is useful vision left, even 20/100 or less in one eye, where there appears to be a chance of reversibility, we have seen striking improvement lasting for several years.

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Cryosurgery of the Pituitary Gland*

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I have been asked to discuss neurosurgical methods of altering pituitary function as a means of controlling diabetic retinopathy. Partial or total destruction of the pituitary gland can only be affectively utilized in the therapy of the complications of diabetes if it can be accomplished with low morbidity and mortality. My experience with hypophyseal stalk section and hypophysectomy by frontal craniotomy for palliation of carcinoma of the breast led me to believe that these methods would have low morbidity and mortality in the diabetic patient. However, in contrast to the older, apparently frail woman with metastatic carcinoma of the breast who had little difficulty undergoing craniotomy, the diabetic not only had difficulty with the craniotomy but also had significant morbidity with prolonged general anesthesia. Any complications of either anesthesia or craniotomy often led to a fatal outcome or severe morbidity. Because of this morbidity and mortality, I first attempted, as Dr. Pearson has mentioned, stereotaxic hypophysectomy with Yttrium^{90}, a radioactive isotope. The ease with which the isotope could be placed in the gland with uniformly high incidence of total or near total destruction of the gland led to the series of patients which Dr. Pearson has discussed. A problem in the long-term followup with these patients, namely a 10% to 12% incidence of rhinorrhea and a smaller percentage of late radiation changes in surrounding neural structures, induced our division of neurological surgery at the Medical College of Virginia to attempt another method for producing destructive lesions in the pituitary gland. The method had to be simple in application, preferably able to be done under local anesthesia, and should be relatively innocuous to the ocular motor nerve, the optic nerves, and the hypothalamus, which lie close to the pituitary gland. Our reason for picking stereotaxic cryosurgery was the unique position of the pituitary gland and the reversibility of a controlled cold lesion. The gland is surrounded by bone on its inferior surface, the cavernous sinus on its lateral surfaces, and cerebrospinal fluid on its superior and posterior surfaces. The areas containing the neural structures we wished to protect were, therefore, isolated from the gland by either cerebrospinal fluid or blood, substances capable of rapid heat exchange. The ocular motor and optic nerves are known to cease functioning at approximately 10 C, but do not sustain irreversible damage until cooled 10 to 15 C below this. These factors seemed ideal for cryosurgical techniques.

TECHNIQUE

Cryohypophysectomy at the Medical College of Virginia is done under local lidocaine (Xylocaine) anesthesia with a modification of the Rand-Wells stereotaxic head holder. The coiling instrument is the Cooper-Linde cryosurgical probe which utilizes liquid nitrogen as the cooling agent. For total hypophysectomy we use the 4.4 mm probe and for partial lesions the 2.2 mm probe. The probe consists of three unicentric tubes with an exposed silver tip. The inner tube delivers the nitrogen, the middle tube exhausts it, and the outer tube is a vacuum insulator. After positioning the head with x-ray control, the nasal mucosa is anesthetized and the probe guide is positioned at the floor of the sphenoid sinus. An opening is then drilled through the floor of the sinus and the probe guide advanced to the floor of the sella. After checking the position by x-ray, the floor of the sella is opened with a drill, the capsule of the pituitary gland incised, and the the probe placed in the gland. The usual probe position is just below the equator of the gland and about 2 to 3 mm lateral to the midline. The low position in the gland is to minimize cooling of the pituitary stalk in order to avert significant diabetes insipidus, and the medial position is to protect the ocular motor and optic nerves. Liquid nitrogen is circulated through the probe with thermistor control of the probe temperature, and frequent checks of optic and ocular motor function are made while the temperature is lowered to −180 C. Since there is considerable difference between non-functioning of a nerve and damage, any evidence of malfunction signals the operator to rewarm and reposition the probe. A second lesion is placed in the gland 2 to 3 mm on the opposite

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side of the midline by either slanting the probe across the midline or using the opposite nostril. Each lesion takes approximately 10 min of cooling.

RESULTS

We have performed cryohypophysectomies in 35 patients with no mortality. In six of the patients with carcinoma of the breast who subsequently died of their disease, histological section of the sella has failed to reveal any evidence of remaining pituitary gland. Complete endocrine evaluation has been done pre- and postoperatively on all the patients, and except for a few patients in whom partial destruction was planned, these tests indicate no functioning pituitary. The morbidity has consisted of two cases of rhinorrhea, both of which occurred in the immediate postoperative period and have healed spontaneously. This is in contrast to the delayed onset of rhinorrhea in the radiation pituitary abalation cases. It is difficult at this time to state that stereocryohypophysectomy is superior to stereo-Yttrium hypophysectomy, since both have low rate of immediate complications. As time has passed, the lack of delayed complications in the cryosurgical cases appears to favor that technique.

In closing I would like to state that I believe that with stereocryohypophysectomy we have a simple, effective technique which can be utilized to alter pituitary function. It can be performed under local anesthesia and, is a safe and effective method for aid in the control of diabetic retinopathy.

GOOD TEACHING*

The growing emphasis on research, the availability to academic personnel of external grants which support a wide variety of activities other than teaching, the lure of "freedom from routine duties" (although teaching should never deteriorate into a routine duty), and the use by some institutions of criteria for advancement that seem to overemphasize research or even that superficial evidence, publication—all of these factors have of late tended to underemphasize the role of good teaching.

But what is a good teacher? Is he the popular teacher? Is he the one who gives flashy and spectacular lectures? Is he the one whose students average highest on departmental exams? Is he the one whose presentations are so tidy that note-taking is easy? Is he the good fellow with the best jokes? Is he a disciplinarian, or is he lax about standards and performance? Does he trouble the stupid but inspire the really able?

The answers all depend on the orientation of the one who replies. By all odds the most popular physics teacher I have ever known was a sweet gentleman who just could not bring himself to fail the letters and arts students who flocked to his sections to work off their science requirements. One of the most popular lecturers in a social science subject I have met with was a man whose smoothly presented lectures were almost as well organized as the textbook. He was famous for finishing every lecture with a polished phrase exactly as the bell rang.

On the other hand, one of my own great teachers in high school was an exceedingly strict Latin teacher. Perhaps he was not loved, but he certainly was respected—and 55 years later I can still scan Vergil.

My very greatest university teacher stopped one day, in the middle of a long and complex proof of a fundamental theorem in potential theory, looked at the confused and badly written mess he had put on the blackboard, said "Well, boys, something is wrong" —and walked out, leaving us to save ourselves.

So before you decide whether a teacher is good, ask, good for what? The purposes should vary greatly, from the broad intent of survey courses and the exploratory excitement of introductory courses to the stimulating depth of graduate courses. Is the criterion of goodness the mechanical success with which information is transmitted, the sympathy and warmth with which a young mind is led to unfold—or the influence a great character can have on the whole life of a student?

I do not think a teacher can be judged by weighing publications, but I also think no teacher can be successful unless he is alert to the new knowledge in his field. In many instances it is absurd to expect a teacher to be a scholarly producer of original research; but it is fatal not to require him to be alive to his subject.

I am sure that some evaluations of teachers by students have been made with serious purpose, but I profoundly disbelieve the results. It will not even work to ask alumni —presumably wiser, surely older, and hopefully more eclectic— which teachers they remember with greatest admiration.

I think the only useful judgment concerning university teachers comes from their immediate working colleagues. The administrators should be aware of student opinion, of course, and in some cases it may be useful. But fellow teachers, through their skillful and intimately informed judgments, will come nearest to recognizing good teaching. The immediate colleagues of a teacher will know what the students really think, for they will have obtained this information in effective informal ways, will have available the evidence of student records, will be aware of the general community opinion, and will have put all this information through the sieve of their own competence.

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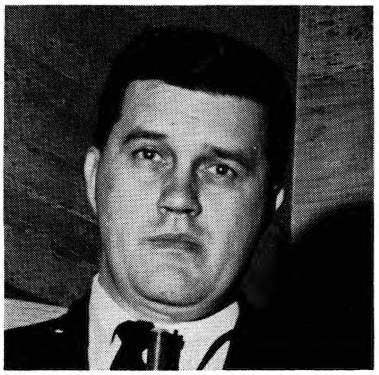

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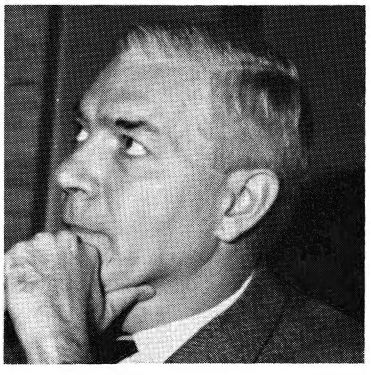

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