Diabetes in Children and Adolescents; Observations on Diabetic Microangiopathy

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You may well wonder why I have combined a talk on diabetes in children and adolescents with one on diabetic microangiopathy when as pediatricians we rarely, if ever, see clinical evidence of the sequelae of vascular disease in our patients. If we see proteinuria in a child, we seek another cause. We may see young teen-agers with a microaneurysm or a trace of protein, but we soon refer them to our internist friends who fall heir to the care of problems that doubtless have their beginning in childhood years. Pediatricians are, therefore, concerned about these problems and the adequacy of treatment they are prescribing for their young diabetic patients.

There is a recent movement to place considerable emphasis again on strict control of blood glucose as a means of reducing complications of diabetes. In an effort to achieve better control many physicians are placing their patients on two injections a day.

I believe we can say that there are few, if any, physicians today who could duplicate Dr. Elliott P. Joslin's success in obtaining patient cooperation in his efforts to control their diabetes. Yet data from his clinic show that only a small percentage achieved what he considered excellent control. Nor did we see a striking difference in the incidence of complications in his patients when compared with that in the general diabetic population.

I do not minimize the need for achieving as nearly optimal control as one can with insulin, but I believe a return to the old emphasis on strict control does a disservice to our diabetic children and adolescents. It misleads them into thinking that controlling the blood sugar adequately *is* possible with present day methods of insulin administration; that if this is achieved, it will prevent or slow down complications; and that if this is not achieved, even with the most conscientious efforts, it is the patient's fault. I believe there is evidence that none of the above is true. Also, this re-emphasis on control and what it does or does not do to the basement membrane, diverts our attention from pursuing other productive avenues of research that may uncover clues and therapeutic approaches. It is with some of these avenues that I would like to acquaint you and stir your interest.

I would like first to address myself to important considerations in the care of the child or adolescent who has diabetes.

It is, of course, fundamental that the patient and the parents be properly educated about diabetes and its control at the very beginning if one is to expect acceptance and participation in a program of good management. We feel this should always be initiated on a hospital ward even if the child is not acidotic. Here the patient and parents can work with a teaching team in a relaxed setting where questions can readily be answered before the family is left on its own. The focus of instruction for the very young child and infant is *both* parents; by 7 to 10 years of age the child can help with urine testing; the 11-year-old can learn to give his or her own injections. In the teens the patient becomes the focus of instruction with parents also learning the facts and techniques. Do not be misled on this point: teen-agers very much need and want the support of their parents in these circumstances.

As soon as the patient has intravenous feedings

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discontinued and is ambulatory the routine that he or she will continue at home is initiated. After the acidosis is cleared the patient is not awakened during the night hours for either urine testing or supplemental insulin.

The educational process continues upon discharge from the hospital, first with phone calls to talk over changes in insulin dosage, and then in weekly visits to the clinic. As confidence and understanding increase, visits are less frequent but are continued with regularity.

What do we teach our patients about diabetes and how it should be managed?

Good management of the diabetic begins with the *physician's* smooth management of the initial ketoacidotic episode, for actions speak louder than words. I believe pediatricians have an advantage here because it can be said with certainty, if not with modesty, that pediatricians have been in the forefront in the proper administration of fluids and electrolytes. One need only recall the names of Gamble, Butler, and Darrow to know that we have had good mentors. Fluids play a most important role in recovery from acidosis; no amount of insulin will rid the patient of the accumulation of hydrogen ion and restore his or her base deficit. Briefly, the initial hydrating solution is a mildly hypotonic solution of sodium chloride free of potassium, containing bicarbonate if acidosis warrants its use. This is followed by a more hypotonic solution including potassium and dextrose, usually around the second hour. We discourage the use of isotonic saline as unphysiologic because of its high anion concentration and the absence of free water. Pediatricians also for many years have been administering small doses of insulin at frequent intervals instead of the large doses prescribed in adults. Indeed, the recent introduction of continuous intravenous administration of low levels of insulin has little if any advantage over our long-used methods of administration. We begin with 0.5 to 1.0 units/kg crystalline insulin, giving half intravenously and half deep subcutaneously. Every hour the dose is reduced by 50% unless the interval reveals no progress in reducing the blood glucose. The previous hour's dose is then repeated.

After intravenous therapy is discontinued and oral feedings initiated, regular insulin is given with meals for one or two days. Lente®, a long-acting insulin, comprised of 70% Ultralente® and of 30% Semilente®, is then given once daily prior to breakfast.

Our goal is to allow a trace or 1+ glycosuria in urines tested prior to meals and at bedtime. The Lente® is increased daily by 2 to 4 units until control is achieved.

We teach the patient to monitor his or her diabetic control through daily urine tests: that is, a double-voided specimen before breakfast, before supper, and at bedtime. After discharge from the hospital we allow time for a pattern to develop in response to the child's home and school routine. If the glycosuria falls to negative levels after discharge as so frequently happens, the patient reduces the Lente® Insulin by 2 units after a day of negative tests, or by 4 units if there are symptoms as well. If glycosuria increases uniformly before breakfast and before supper, the patient increases it by 2 units every three to four days until control is again achieved. If a pattern of glycosuria develops in which all the morning urines are 3+ to 4+ and the pre-supper urines are 0 to 1+, the patient increases the Ultralente® or long-acting portion of the Lente® mixture. Conversely, if late afternoon urines are high in sugar, the patient increases the short-acting or Semilente® portion. In this way we achieve as good control over the 24-hour period as with those who use NPH® twice a day and avoid the use of two injections. For this reason we have abandoned the use of NPH® in favor of the Lentes®. As those of you who follow young children know very well, there frequently is no pattern to the glycosuria, and levels will go from negative to 4+. One may be guided in such circumstances by daily urine volumes and adjust the insulin to keep urine volumes in the normal range.

If acetone appears, the patient is to take *regular* insulin at that time. He or she is asked to take 1/5 of his or her daily dose of Lente® for moderate or large and 1/10 for small amounts of acetone. This is repeated at subsequent testings if acetone persists.

If the child becomes ill and is unable to eat or is vomiting, the Lente® is omitted and small amounts of regular insulin are given. Depending on the nature of the problem, the child will be seen in the Emergency Room, admitted, or followed at home by phone instructions.

The diet we propose for the diabetic is no different from one we propose for the non-diabetic. It consists of a good source of protein as the cornerstone of the diet, carbohydrate obtained mainly from starches, a drastic reduction in refined sweets, a mixture of predominantly unsaturated and saturated fats, and, finally, foods containing adequate rough-

age, minerals, and vitamins. We allow the patient to use his appetite as his guide, warning against gorging or excessive snacks, and to use his weight-for-height gains as a monitor of his progress. If overweight is or becomes a problem in the diabetic, he should be approached as a youngster, not a diabetic, with a weight problem. I see no reason to single out the diabetic in his diet therapy when there is no scientific data to suggest this approach is any more harmful to him than to his non-diabetic peers.

We do not attempt to make gross changes in a patient's lifestyle. We recommend regular exercise for all youngsters, but we do not urge all-out vigorous athletics if that is not the child's habit. If exercise can be anticipated, the morning dose of insulin is reduced. If it cannot, increased carbohydrate intake during and after the exercise is required. We explain to teen-agers the serious effects of smoking on the cardiovascular system and urge them not to begin. We explain the hazards of drinking and urge care in this area if they do indulge.

There are a number of special problems we see in children and adolescents.

First of all, the term "brittle" diabetic is frequently used to describe the majority of juvenile diabetics. I believe this is too broad a use of the term and often reflects only a poor understanding of how to manage youngsters whose exercise pattern is unpredictable and whose increased needs with growth are not properly met. I would reserve the term for the juvenile diabetic who is truly difficult to manage; in my experience such patients are few in number and all have been teen-age girls under severe emotional stress.

In the adolescent years there is both an increase in need for insulin and an increase in binding, with insulin resistance of variable degree resulting. Requirements can often rise at an alarming rate to needs of 140 to 160 units per day. The periods of increased need are variable and unpredictable in their length. When the total daily dose reaches 90 to 100 units the dosage is split; 2/3 is given before breakfast and 1/3 before supper. It is frequently advisable to admit the patient to make these adjustments. We admit the teen-ager to the Children's Rehabilitation Center where both physical and school activities can be pursued so that home conditions are more nearly simulated than on a hospital ward. A schedule is set up in which, again, the patient participates. Pre-meal and two-hour post-meal blood glucoses are obtained, urine volumes are measured, and caloric estimates of the food intake that satisfies the patient's appetite in a normal manner are made. Urine volumes are collected in the following manner: patient voids and discards at 7 AM; Urine #1 is voidings up to lunch; urine #2 up to dinner; urine #3 up to 9 PM, and urine #4 overnite to 7 AM. In this manner grams of glucose/hour spilled in respect to a meal can be calculated. Urine volumes collected periodically at home give the diabetic another index of his control.

True insulin resistance is defined rather arbitrarily as a requirement that exceeds 200 units per day, occurring in the absence of ketosis, infections, or other known stresses. The few cases that have occurred in juvenile diabetics have been predominantly among teen-agers 14 to 16 years of age. Most are due to increased antibody formation and respond either to changing to pork insulin, which is less antigenic than beef, or to steroid therapy. We have recently reported the very rare occurrence of severe resistance to insulin in a 17-year-old girl who does not have excessive antibodies either to insulin or to her insulin receptors and showed no improvement on steroids.[1] She was resistant to as much as 5,000 units in pork regular insulin given subcutaneously, but responded normally to a continuous 24-hour infusion of insulin and was well regulated in 60 to 70 units per day. After 5 months of continuous I.V. insulin she remitted spontaneously and is presently regulated on 85 units Lente® in the morning and 35 units Lente® before supper. Since our report, 5 more females of similar age with the same problem have come to our attention.

Over-treatment with insulin can of course result in hypoglycemia, but it can also result in a curious and unexplained phenomenon called the Somogyi reaction, which usually appears after sudden and excessive increases in insulin. The reaction is characterized by polydipsia and polyuria, sometimes to an overwhelming degree. Unlike the patient in acidosis, however, the CO_2 is not elevated though the glucose values may be very high. The explanation given by Somogyi is that the intense hypoglycemia generated by excessive insulin, usually occurring between 2 AM and 4 AM, causes a discharge of adrenalin and a swift rise in blood glucose to excessive levels. The increased glycosuria in the morning and the excessive polyuria suggest the need for more insulin, and a vicious circle ensues. The patient needs to be hospitalized, taken off long-acting insulin, and regulated on regular insulin before returning to Lente®.

One final problem we encounter, especially in

teen-agers, is noncompliance. This must be dealt with in a sympathetic yet firm manner. One can only have deep feelings of empathy for youths who are struggling to establish their own identity in a world generally hostile to teen-agers, and who are aware that in the not-too-distant future they will be on their own.

Our approach,[2] therefore, is to keep the demands on the patient simple but to work closely with him to follow these simple rules:

1) Double void urine twice a day, test for glucose and acetone, and *record* results so they can be reviewed with the patient.
2) Take insulin without fail each morning.
3) Eat a sound diet at regular time intervals and in amounts that satisfy appetite and maintain normal weight.
4) Keep regular medical appointments at 3-month intervals. This provides an opportunity to review the patient's understanding of diabetes and its control.

I would now like to turn to a discussion of abnormalities in serum proteins, platelets, and red blood cells of diabetic subjects discussed at a conference on Diabetic Microangiopathy held by the Kroc Foundation in April, 1976. The conference was arranged by Dr. Donald McMillan of the Sansum Medical Research Foundation and Dr. John Ditzel of Aalborg, Denmark, and the papers have appeared in the November, 1976 supplement of *Diabetes*.[3]

The abnormalities I wish to describe may play a role in the genesis of diabetic angiopathy or are factors that reduce tissue delivery of oxygen by hemoglobin. These mechanisms can lead to tissue hypoxia and subsequent tissue damage.

First, Dr. McMillan,[4] as well as others, describes significant increases in serum proteins in diabetics. No system of proteins is spared. Studies of newly diagnosed diabetics show increases as great as those in established diabetics. Abnormalities are independent of the presence of sequelae of microangiopathy.

The majority of the proteins elevated in diabetics are acute phase reactants: α_1 acid glycoproteins, α_1 antitrypsin, haptoglobin, ceruloplasmin, C-reactive protein, C3C, C4 and C3 activator, and fibrinogen. Albumin levels are lower than normal. By direct measurement Dr. McMillan has shown that diabetic serum has a greatly increased viscosity which is due to the elevation of these proteins. The abnormal viscosity bears no relation to age, sex, body weight or duration or type of treatment of the diabetes.

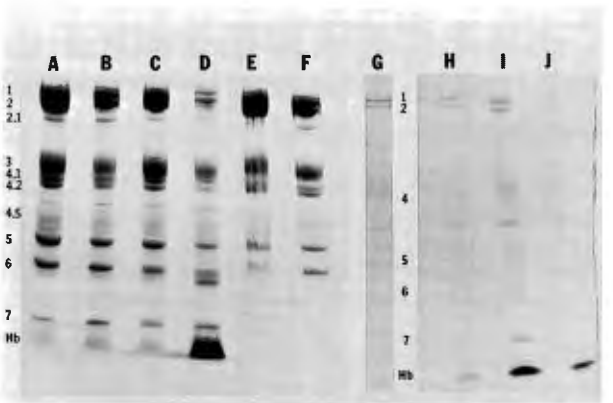
Erythrocyte aggregation is markedly increased due to the increased fibrinogen level as well as to increases in other elongated proteins. Increased erythrocyte aggregation has the added effect of enhancing the coagulation of blood.

Platelet aggregation is also increased in diabetics in the early stages of the disease as well as later. There is a greater sensitivity than normal to aggregating agents such as adenosine diphosphate (ADP), epinephrine, and collagen.

At the same time that intravascular factors are leading to the occlusion of small blood vessels, the fibrinolytic system, the body's defense against vascular occlusion, is decreased. This abnormality is more pronounced in patients with signs of microangiopathy.

We have recently made observations on red cell membranes in diabetics and have noted an abnormal adherence of hemoglobin to the red cell membranes.[5]

Red cell ghosts prepared by the method of Dodge were solubilized in 1% sodium dodecycl sulfate (SDS), separated by gel electrophoresis and stained with Coomassie® Blue (Figure). Increased amounts of hemoglobin were noted in the membranes of diabetics, B, C, and D, compared to those of a non-diabetic child, A. Dislodging the hemoglobin from red cell ghosts with Tris (hydroxymethyl aminomethane), a nonionic buffer, simultaneously



Figure–Membrane proteins of erythrocyte ghosts in 1% SDS separated by polyacrylamide gel electrophoresis and stained with Coomassie® Blue. A to D (untreated ghosts): A, normal 12-year-old; B, 8-year-old on insulin one month; C, top layer of ghosts, pale yellow, D, bottom layer, pink, 15-year-old on insulin five years. E and F (ghosts extracted with 0.01 M Tris, pH 8.2): E ~ A; F ~ B.G to J (Tris eluates): G ~ A, H ~ C, I ~ D, and J ~ B. In D note the doublet of band 6 and the heavy band of hemoglobin, and the appearance of those components in the Tris eluate. The proteins are eluated roughly in proportion to the amount of hemoglobin adhering to the membrane.

removed both peripheral and integral membrane proteins. E and F represent the ghosts after membrane bands 4.1 to 4.5, 5, 6, and 7, as well as the hemoglobin. It is suggested that the tightly adhering and increased amounts of hemoglobin on diabetic membranes interfere with normal erythrocyte deformability because deformability is influenced by the peripheral proteins of the inner aspect of the red cell membrane. Normal deformability is essential for normal blood flow since the diameter of erythrocytes is greater than the diameter of the smallest blood vessels through which they must pass.

Finally there is evidence of disturbance in oxygen transport in diabetics. Rahbar[6] originally described the abnormal increases of the minor hemoglobin components AIa, b, and c in diabetic adults. We have made a similar report in children. In spite of acceptable control of their diabetes, young children, and adults as well, have levels that are twice normal. The important fact about hemoglobin AIc is that it does not react with 2, 3 diphosphoglycerate (2,3 DPG), thus reducing the ability of hemoglobin AIc to yield oxygen to the tissues. Opposing this impairment of oxygen release due to increased levels of AIc, Ditzel has found elevated levels of 2,3 DPG but a lower than normal P_{50}. Phosphate administration to these diabetic children brought their P_{50} to the level of the normal control group. This may be a therapeutic approach toward improving oxygenation of diabetic tissue that warrants further study.[9]

The legitimate question can now be raised as to whether these intravascular abnormalities are not due solely to insulin deficiency and therefore simply reflect inadequate control of the diabetic state with insulin. This may be true. At present we do not know. However, in respect to the increases in acute phase proteins observed in diabetics, studies of protein synthesis of the perfused rat liver by Miller have revealed a very interesting finding.[7] Abnormal alpha cell function is an integral part of the diabetic state.[8] Glucagon secretion continues during periods of glucose plenty and is stimulated by amino acids in the pressure of hyperglycemia. Miller has found that glucagon, either alone or in combination with cortisol, stimulates the acute phase proteins including fibrinogen. The in vitro effects can be abolished with insulin. The possibility thus arises that glucagon excess in a setting of insulin deficiency is the initiating factor of the sequence of events leading to microvascular occlusion. We have begun a prospective study in our young diabetics of the degree of abnormality of glucagon secretion and its progression, and the levels of acute phase proteins, to determine if a correlation exists between them.

I conclude by paraphrasing a well-known slogan, "We want to find a cure for diabetic microangiopathy before our diabetic children leave adolescence," because success of treatment undoubtedly lies in applying it in the trouble-free childhood years.

The figure is reproduced with permission from *Diabetes* (25: 805–930, 1976).

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