DAILY MANAGEMENT OF YOUTH-ONSET DIABETES MELLITUS

AN INTEGRATED GUIDE FOR PATIENTS AND PHYSICIANS

RICHARD SANDLER, M.D.

MICHAEL SANDLER, M.D.

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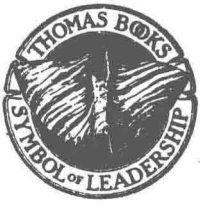
By

RICHARD SANDLER, M.D.
Clinical Instructor in Medicine (Endocrinology)
Tufts University Medical School
Boston, Massachusetts

and

MICHAEL SANDLER, M.D.
Clinical Fellow in Endocrinology
Veterans Administration Hospital
Boston, Massachusetts



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DAILY MANAGEMENT OF YOUTH-ONSET DIABETES MELLITUS

An Integrated Guide for Patients and Physicians

PREFACE

OUR EXPERIENCE IN treating youth-onset* diabetics has demonstrated the need for a book on management, practical in scope, but based on a valid exposition of scientific principles, aimed at both the involved laymen and the managing physician. All too often, patients are ill-equipped to manage their diabetes because they have never received systematic education including both theory and practical application. Unfortunately, their physicians are often only of limited help because they have no intimate appreciation of the daily problems of diabetic life outside the hospital.

We were prompted by the dual conviction that (1) long-term attempts at normalization of the dysmetabolism of diabetes is medically desirable, and (2) the daily management of the disease is chiefly the responsibility of the patient (or parent) himself. The need for education of the patient and of his family concerning the underlying physiologic principles is essential to the maintenance of good diabetic control. The receptive lay person, patient or parent, is generally quite capable of learning and applying clinically relevant information about the disease. Indeed, failure to educate and to involve the patient and his family is a disturbingly common denominator in the histories of poorly-managed cases.

Only by informed and intelligent contribution by the patient to management can we insure metabolic stability and normal growth. To ignore lay participation will leave only two inferior alternatives:

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* In accordance with common usage, we use this term as synonymous with "ketotic prone" (semantic limitations duly noted in Chapter 1). Thus, while this work is directed chiefly at those concerned with children and adolescents, most of it is applicable to adults who are insulin-dependent.

1. The sacrifice of the plasticity of normal daily life for a static, highly regimented, and untenable mode of living.
2. The failure to impose sufficient regulation on daily events, leading to chronic and severe metabolic derangement, which we believe to be medically unjustifiable on the basis of current data.

Although the physician is of central importance in total care, it is obvious that daily management can be carried out only by the patient and/or his family. The doctor must, therefore, distill his body of information into a reasonably accurate but practical and nontechnical education of the family. Thus, the patient and his family act as "doctor surrogates" in regulation of the disease.

One important function of the physician is teaching. An equally important physician responsibility is the more traditional one of continually reevaluating and redirecting the therapeutic program. He does this on the basis of periodic and regular historical reviews, physical examinations, and laboratory testing. A chief concern of this book is the definition of the shared goals, common knowledge, and cooperative interactions among all three parties, which are necessary for optimal diabetic care.

The sections in daily outpatient management are written for both physician and parent/patient because mutual sharing of ends and means are essential to a viable relationship. Separate sections, entitled "For the Physician," are included to present exclusively to a professional readership:

1. More detailed and technically demanding expansions of the basic materials.
2. Discussions of controversial issues.
3. Discussions of inhospital management problems.
4. Discussions of modification of treatment programs based on periodic office evaluations.

The preceding lays the groundwork for answering the question of why we undertook the difficult task of writing a single work for both layman and physician. The answer is that our experience reaffirms that we are dealing with people with a complex but controllable chronic illness. And control requires

daily decisions and long-term goals, executed by mutually cooperative laymen and physicians, who play complementary roles, share common information, and possess the identical ultimate objectives.

R.S.
M.S.

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DAILY MANAGEMENT OF YOUTH-ONSET DIABETES MELLITUS

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Chapter 1

WHAT IS DIABETES MELLITUS?

DURING THE YEARS, more and more detailed knowledge about the condition called diabetes mellitus has been accumulated, and many once-accepted principles have been critically re-examined, and some rejected. However, the belief that the physiologic basis is a *deficiency of insulin* is almost as widely-accepted today as it was more than a half a century ago. Because the hormone, insulin, influences a large number of vital cellular processes, it follows that the immediate consequences of diabetes involve virtually all areas of metabolism—mineral, water, fat, carbohydrates, and protein.

Therefore, it is not surprising that a multitude of diverse functions, involving the entire body, are directly or indirectly affected *acutely* in diabetes. Many *chronic* tissue changes in diabetes may be viewed as the result of these immediate consequences integrated over long periods of time. These points are emphasized to discredit the common misconception that diabetes is just a disorder of sugar metabolism.

FOR THE PHYSICIAN

In the last decade, much attention has been given to the possibility that diabetes may be mediated not simply by insulin deficiency, but by inappropriately high levels of one or more diabetogenic hormones. Considerations of this potential bi- or multihormonal nature of diabetes have centered chiefly on **growth hormone** and **glucagon.** At present, it is fair to state that, although such research may have uncovered important **contributory** roles for these hormones in the total picture of diabetes, the **primacy** of insulin deficiency in its pathogenesis has not been diminished.

The deleterious effects of growth hormone on carbohydrate tolerance have been known since the classical physiologic studies of

Houssay. As recently summarized by Lundbaek,[1] careful studies have shown higher and more labile levels of growth hormone in youth-onset diabetes. Yet growth hormone can have only a **permissive** effect on the development of diabetes, since carbohydrate tolerance is diminished in less than one half of acromegalics.

The fact that high growth-hormone levels tend to **fall** with improvement in control suggests that they **result** from the metabolic deficit (intracellular glucopenia) rather than cause it.[1, 2] Growth hormone may have a special contribution to the pathogenesis of retinopathy, as evidenced by correlations between the incidence of retinopathy and growth-hormone levels in diabetics;[3] and by the favorable effects of pituitary ablation on the progression of retinopathy.[4]

However, no serious thoughts of prophylactic hypophysectomy have been entertained. Even if growth hormone secretion could be effectively blocked by the development of clinically useful preparations of somatostatin, the problem of growth retardation in young diabetics presents a formidable obstacle to its clinical application.

With the advent of a radio-immunoassay for glucagon,[5] numerous subsequent studies appeared to define an important role for the hormone in the pathogenesis of diabetes mellitus. Known to be a potent stimulator of both hepatic gluconeogenesis and glycogenolysis, glucagon blood levels were found to be absolutely elevated in diabetic keto-acidosis. Morever, even in the absence of acidosis, carbohydrate ingestion in diabetics was not followed by suppression of blood glucagon, as it is normally. Further, somatostatin, an inhibitor of pancreatic glucagon secretion, was later shown[6, 7] to improve carbohydrate tolerance on decreasing insulin dosages in youth-onset diabetes.

But Felig and his associates[8] have marshalled evidence throwing serious doubts on the concept that glucagon has anything more than a relatively minor secondary role in the pathogenesis of diabetes. They showed that glucagon infusions do not disturb carbohydrate tolerance in settings of adequate insulinization, i.e. in normals, non-diabetic obese subjects, and in well-controlled youth-onset diabetics. It was only in settings of insulin lack, such as after dose omission, that glucagon resulted in a rise of blood sugar concentration.

Somatostatin, further was shown to improve oral, but not intravenous, glucose tolerance, even though glucagon levels were nicely suppressed under both circumstances. These results suggested that the glucose-lowering effect of somatostatin may be simply one of inhibition of carbohydrate absorption. This hypothesis is consistent

with the fact that Felig's group has demonstrated[9] a lesser rise in blood levels of orally administered D-Xylose (a nonmetabolizable sugar), with the addition of somatostatin, an effect not overcome even with exogenous glucagon.

Since amino-acid-induced glucagon secretion is unimpaired in diabetes,[29, 30] and since physical activity raises glucagon levels,[10] it is clear that protein ingestion and exercise, **in the presence of insulin deficiency,** may aggravate the diabetic state, via the mediation of this alpha cell product.

Other states associated with hyperglucagonemia, e.g. infections, may accelerate diabetic decompensation **in the absence of adequate insulin reserve.** Whether glucagon has any larger role in the dysmetabolism of diabetes is not clear from the presently available data.

Because it is a subject of unresolved complexity in its own right, and because it does not affect management, to which this book is devoted, we shall say only a few words about the etiology of diabetes. All agree that it tends to run in families, a fact which is consistent with, but does not prove, the widely held belief that it is usually a genetic disorder. However, no simple genetic theory is satisfactory to explain the exact mode of inheritance. In addition, some cases may result, partly or exclusively, from environmental factors, e.g. viral infections involving the pancreas.

From a descriptive point of view, diabetes usually appears in one of two fairly characteristic patterns. In by far the majority of diabetics, the disorder is detected in middle or advanced age, the patient is typically overweight, and exogenous insulin is often neither necessary nor desirable. In contrast to these *maturity-onset diabetes,* those with the *youth-onset type* usually present, in childhood or adolescence, a disease in which obesity is rare and daily insulin injections are absolutely necessary for survival.* The management of this latter type, far more demand-

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* The concordance of these two clinical patterns with age of detection is not quite absolute. For example, Fajans[11] has emphasized the (relatively uncommon) existence of a maturity-onset type of diabetes appearing chronologically in youth and preserving its noninsulin-requiring character for many years. Conversely, some elderly diabetics have an absolute dependency on exogenous insulin and behave chemically similar to the average ten-year-old diabetic. However,

ing both chemically and psychologically, forms the subject of this book.

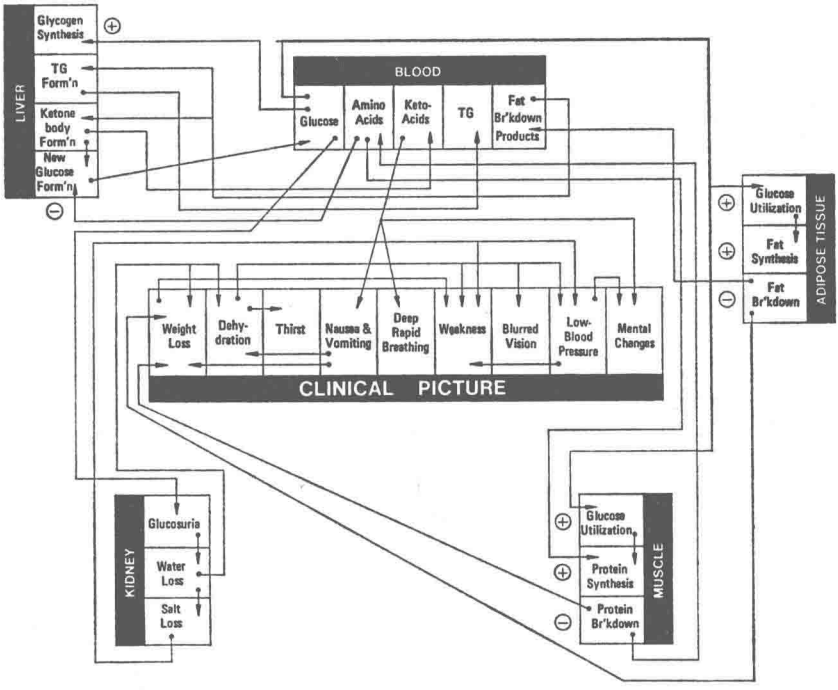

Figure 1. A schematic flow sheet demonstrating the manner of development of the main clinical features of insulin deficiency, based on the hormone's known actions at the tissue level. A stimulatory effect of insulin on a given process is denoted: +, an inhibitory effect: −. See text for details.

What does insulin do? Figure 1 is a somewhat oversimplified summary of its main metabolic actions. The "plus" signs denote stimulatory effects of insulin, the "minus" signs, inhibitory ones. It can be seen that the *immediate* effects of insulin are to preserve the structural integrity of fat and muscle and to maintain the

these are "the exceptions that prove the rule." The clinical homogeneity of the widely-used term, "youth-onset diabetes," is so great that we find it convenient to maintain it, provided that it is borne in mind that most of what is said in this book is equally applicable to all insulin-requiring diabetics, regardless of the age of the appearance of the disease.

blood glucose (blood sugar) concentrations, both by restraining its production by the liver and accelerating its utilization by various tissues. The immediate consequences of insulin lack, therefore, are readily apparent:

1. The dissolution of fat and muscle floods the blood stream with precursors (glycerol and amino acids) for new glucose formation in the liver.
2. Other fat breakdown products arrive at the liver to be converted into acidic substances (keto-acids) whose accumulation upsets the neutrality of the blood (keto-acidosis).
3. The rate of new glucose production from the liver accelerates tremendously because of an increased delivery of precursors, the absence of the normal direct suppression of this process by insulin, and changes in the hepatic milieu resulting from keto-acid formation.
4. Blood glucose concentration rises dramatically because of the unopposed breakdown of liver glycogen, the increase in new glucose formation, and the decline in utilization of glucose that reaches the bloodstream by whatever route.
5. Concentrations of triglyceride (fat) in liver and blood rise because they are formed faster in the liver, partly as a result of the great influx of fat derivatives emanating from adipose tissue; and also because their longevity in the circulation is increased, since clearing of triglyceride from the bloodstream depends on insulin.

The high blood sugar level overwhelms the kidney's usual capacity to prevent appreciable glucose from appearing in the urine. As glucose has the physicochemical property of attracting water to it (osmotic effect), the patient excretes copious volumes of glucose-rich urine. Also pulled along in the torrential flow of urine are various salts (sodium, chloride, potassium), thus depleting bodily stores of deposits. Water and salt loss are further intensified by nausea and vomiting, which result from accumulation of keto-acids.

The secondary consequences of all this determine the clinical picture of *decompensated diabetes.* Depending upon how long the insulin deficit has been developing, the patient shows varying

degrees of weight loss and dehydration. These, plus salt depletion, produce muscle weakness. Further, dehydration results in changes in the water content of the lens of the eye, so causing blurred vision. Acidosis stimulates automatic rapid and deep breathing ("air hunger"), which by expiring volatile acid, represents the body's attempt to restore neutrality. The more nearly complete the state of insulin lack and the longer its existence, the more severe is the acidotic state, and the patient may be comatose and in shock.

It bears reemphasis that the initiator of this cascade of events is *insulin lack—not* ingestion of excessive carbohydrate. In fact, diabetic keto-acidosis often develops in a setting of illness when there is little or nothing ingested on that day. It follows that daily insulin injections must *never* be omitted in insulin-requiring diabetics, even when their appetities may be subpar.

Chronic insulin deficiency results in retardation of normal growth and development in young diabetics. The reasons for this are both the interference with protein and fat synthesis, as denoted in Figure 1, and the dependency of specific serum growth factors, the *somatomedins,* on the presence of insulin.

The incidence of various infections are more common among poorly-controlled diabetics than in the general population, but not in those who are well-controlled. This is thought to be due, in part, to defective white blood corpuscle function in the setting of insulin-lack.

FOR THE PHYSICIAN

The mechanism of impaired host defense in unregulated diabetes has been explored by Bagdade[12, 13] who reports that the specific granulocyte functions of chemotaxis, phagocytosis, adherence to vascular endothelium and microbicidosis are all impaired. In addition, lymphocytic function appears to be defective among these patients. These cellular disturbances are reversed with insulin treatment and are possibly the result of inadequate leukocyte energy production from insufficient insulin-mediated glucose utilization.

Before the availability of insulin, insulin-requiring diabetics died chiefly as a result of overwhelming infections or keto-acidotic coma. Today this is no longer the case. As longevity has progres-

sively increased, mortality is most often due to diseases of blood vessels. These include disease of large blood vessels (macroangiopathy), e.g. heart attacks and strokes, and those of small blood vessels (microangiopathy), i.e. kidney failure.

Besides these *lethal* degenerative complications, diabetics may develop others which can seriously affect the quality of life, e.g. eye disease(cataracts, glaucoma, retinopathy), and nerve degenerations. In general, the longer a patient has had diabetes, the greater the chance that he will have some evidence of one or more of these complications.

These are sobering facts, and they certainly justify the great energies currently being expended both in attempts to develop better methods of prevention and treatment for these conditions, as well as the search for a definitive cure for diabetes. But it must also be said that until we are able to entirely prevent them, the available data, when viewed in quantitative perspective, do not justify the pessimism or anxiety we see so often in patients concerned about degenerative phenomena.

Thus, while diabetes is a leading cause of blindness, and while the physician can detect changes of retinopathy in most diabetics if they live long enough, the vast majority of diabetics do *not* become blind and most have no significant visual impairment from retinopathy. Similarly, although kidney disease is the major cause of death in those whose diabetes first appeared in youth, most patients have no symptomatic evidence of this complication while alive, and longevity continues to increase.

What is the relationship between insulin lack and the development of these long-term complications? Because they were scarcely recognized in the preinsulin era, some had even attributed them to side effects of insulin therapy itself. We now know that this is not the case and that increasing diabetic longevity has simply provided the time necessary for their appearance.

In the past some have denied that their development is related to insulin lack or from resulting metabolic derangements. Even though many centers reported, retrospectively, fewer and/or milder complications among well-controlled, than among poorly-controlled, diabetics, it could not be *proven* that it was the status of control which caused the more benign outcome.