EDITORIAL

EXACERBATION OF DIABETES BY EXCESS INSULIN ACTION

Insulin therapy of diabetes, almost four decades after its introduction, is still beset with grave difficulties. Two particularly disturbing problems are presented by insulin reactions and the unstable ("brittle") form of the disease, which seriously interfere with the pursuit of a normal life. No one can disagree with Marble,[1] who as recently as 1959 succinctly stated that "episodes of hypoglycemia due to insulin constitute one of the major problems in the treatment of diabetes."

No less of a problem is the management of unstable diabetes, a condition characterized by abrupt fluctuations of the glycemic level, which entail wide day-to-day as well as diurnal variations in the degree of glycosuria and are accompanied, as a rule, by intermittent ketosis. In 1955 Colwell[2] estimated that about 10 per cent of insulin-treated diabetics, the majority of them juveniles, fall into this category. But who can draw a sharp line of demarcation between the group of explicitly unstable patients and many others who suffer hypoglycemic reactions of variable frequency and severity? Diabetics suffering the inconveniences and ill effects of hypoglycemic reactions undoubtedly constitute a much higher quota than 10 per cent of insulin-treated patients.

In this communication I wish to call attention to the fact that unstable diabetes, in the case of most adult subjects, is not an idiopathic entity, but a direct consequence of excess insulin action.

This cause and effect relationship is clearly demonstrated in extensive, detailed laboratory data and observations which I have accumulated since 1935 and published last year.[3] These records reveal that patients treated with such doses of insulin that can cause hypoglycemic episodes show a consistent pattern of periodic ebb and tide in the extent of glycosuria, the highest glycosuric tides always occurring in the wake of frank hypoglycemic reactions; but it must be noted that *substantial flare-ups of glycosuria take place even after symptomless, mild degrees of hypoglycemia.*

Anyone who is unaware of the paradoxical fact that *hypoglycemia begets hyperglycemia* (and also ketosis)[4] —i.e., that excess insulin action exacerbates the diabetic syndrome—will be prompted to combat the hypoglycemia-induced glycosuric tide by stepping up the insulin dosage. As a consequence, hypoglycemic episodes increase in frequency and severity, and fluctuations of the blood sugar level become more abrupt and more expansive in both directions; this is then manifested in increasing diurnal variations in the urine sugar, ranging from zero to 5-6 per cent and even higher concentrations. *A vicious cycle leading to higher and higher insulin dosage ensues,* the severity of diabetes progressively increases and can advance to an extremely unstable (unmanageable) state.

This concept implies that severe states of diabetes can be reversed by the application of a regimen in which hypoglycemic episodes—even mild, symptomless degrees of it—are avoided with meticulous care. I have presented experimental proof that this is actually the case. In a paper published in 1951[6] I described an experiment demonstrating that a diabetic man, who had been consistently aglycosuric on dietary therapy alone during the preceding eleven months, developed massive glycosuria and ketosis directly after a not too severe hypoglycemic reaction induced by the intravenous injection of 7 units of insulin in the postabsorptive state. With temporary, cautious insulin therapy he again became aglycosuric without insulin. In another experiment[8] the subject was a man who, after having been an unmanageable diabetic for a number of years on 60 to 180 units of insulin, was restored to a mild state of diabetes by the avoidance of hypoglycemic states, and was readily controlled and perfectly stabilized on 16 units. When, for the experiment, the dosage was raised to 22, then to 24 units per day, it produced hypoglycemic episodes, and the patient promptly reverted to an unstable state, with the characteristic fluctuations of the blood sugar level and glycosuria, accompanied by intermittent ketosis. After this experiment the patient was once more rehabilitated to a mild state of diabetes, and again was easily controlled on only 16 units of insulin.

On the basis of hundreds of case histories in my files and those of my colleagues, it can be stated without qualification that every severe case of diabetes which came our way that had been treated for years with large doses of insulin (30-150 units), responded favorably to application of the precept that *"avoidance of hypoglycemia, even of mild, asymptomatic degrees, is no less important than the control of excessive hyper-*

glycemia and glycosuria."[3] Every one of them was restored "to a status of mild diabetes that can be satisfactorily managed with small doses of insulin or, not infrequently, without insulin." And it may be added that as a result of observing this rule not one of our newly diagnosed cases has drifted into a severe state, even if the initial condition exhibited all of the "classical symptoms" of severe diabetes and required large doses of insulin at the outset. As a matter of fact, the adult patients—with a few exceptions—eventually became aglycosuric without insulin.

The causal connection between excess insulin action and its hyperglycemic-glycosuric aftermath was uncovered in these studies in purely pragmatic procedures, with guidance by facts reaped from a wealth of laboratory tests (mostly quantitative analysis of urine samples collected in fractions around the clock, over extended periods of time). With satisfactory documentation on hand, it was matter of course to inquire into the nature of the physiologic factors and processes underlying the diabetogenic effect of hypoglycemia. We found that what we had accomplished with a purely empirical approach, was nothing more than incorporation in the application of insulin therapy of physiologic laws broadly treated in the literature in the course of the past three and a half decades. Cannon[6] was the first investigator to demonstrate that hypoglycemia—even a slight fall of the blood sugar below the postabsorptive level—stimulates the rate of release of adrenalin into the blood stream. Almost simultaneously, Houssay[7] arrived at the same conclusion by an entirely different experimental approach. Eventually, numerous workers unanimously confirmed these findings, while others subsequently showed that insulin hypoglycemia also accelerates the release of anterior pituitary and adrenal cortical hormones.

These hormones can be designated as "indirect insulin antagonists"; they do not destroy insulin, nor do they inhibit its action, but act in counter-current to insulin action and thereby cancel it. In other words: While insulin enhances assimilation of glucose (transfer into tissue cells), these antagonists simultaneously promote dissimilation. The remarkable constancy of the blood sugar level of healthy persons in the postabsorptive state reflects the sensitivity and promptness of the adrenal-pituitary system in the prevention of hypoglycemic states; it is this normal homeostatic function which is forced to operate on a greatly magnified scale, when hypoglycemia reaches unphysiologically low levels. Under this condition the overly excited glands release excessive amounts of insulin antagonists, which overshoot the goal and thus produce hyperglycemic tides. Consequently the insulin antagonists, instead of serving the homeostatic process, rudely upset and disrupt it.

This is the main pathway through which excess insulin action exacerbates the diabetic syndrome, but there are accessory elements which it brings into play. Hypoglycemic episodes, as is known, entail mental and emotional disturbances, often of severe dimensions. When Graef[8] pointed out that "severe, progressive diabetes is possibly severe and progressive because of challenges to the pituitary and adrenal glands in everyday life," he—if I understand him correctly—had reference to all environmental influences, internal as well as external. This assumption, I feel, is undoubtedly correct; but by the same token, inconveniences and emotional and mental disturbances, attendant to recurrent hypoglycemic reactions, contribute to the "downward progress" of diabetes to a greater extent than occasional incidents occurring in everyday life.

There is still another facet to the problem, and this is that hypoglycemia constitutes a stressor agent, fraught with the danger of alarm and adaptation diseases. As Guest[9] put it, "there is reason to believe that wide and abrupt fluctuations between hyper- and hypoglycemia, and periodic development of ketosis, constitute situations of stress with attendant mutually aggravating metabolic derangements that have far-reaching deleterious consequences."

The deleterious effect of excess insulin action is by no means confined to diabetic persons; it exerts a diabetogenic effect also in cases of organic hyperinsulinism produced by functioning islet cell tumors, and in the state of iatrogenic (artificial) hyperinsulinism, introduced in nondiabetic persons (mental patients or healthy individuals) by insulin injections.[10] The diabetic patient who is subject to hypoglycemic episodes obviously presents a condition in which iatrogenic hyperinsulinism is superimposed on an already deranged state of metabolism and by virtue of this fact is likely to exert its adverse effects with greater potency than in nondiabetic subjects.

From the foregoing it is evident that hypoglycemic episodes, the state of unstable diabetes, and stress and alarm reactions do not present separate problems in the insulin therapy of diabetes; the *agent provocateur* that ushers in all of these phenomena is one and the same factor: iatrogenic hyperinsulinism.

In conclusion I must sound a *serious warning against any abrupt and radical reduction of the insulin dosage.* The changes must be made gradually in a rather laborious procedure, and cannot be successfully carried

out without the judicious use of extensive quantitative laboratory tests. As I pointed out in my detailed article,[3] haphazard changes will in most cases invite grave consequences.

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BOOK REVIEWS

ARTERIAL EMBOLISM IN THE LIMBS. By A. L. Jacobs and C. G. Rob. $8.00, pp. 200, The Williams and Wilkins Company, Baltimore, Maryland, 1959.

This book is impressive as a sincere and objective study of the problem of arterial embolism. The author supports his conclusions by data based on dissections and injections as well as on first-hand examination of patients (eighty-one case histories are given in the Appendix). The conclusions themselves are attractively and provocatively summarized in the last chapter as a series of aphorisms, for example: "Embolism is commonest in the smallest arteries and least common in the largest. This natural anatomical incidence is not evident in hospital series because many of the less serious cases do not come under observation." "Arterial pulsation, though usually weakened, is not uncommonly felt beyond the site of an embolic occlusion in a large limb artery." "Though the number of successes is not great, embolectomy holds first place in the treatment of embolism of the larger limb arteries." Most of these seem useful, although some vascular surgeons might take exception to the following one: "In limbs with adequate collateral circulation, signs of grave ischaemia do not persist for more than two hours after onset." On the whole, this thoughtful book should prove to be extremely helpful for those concerned in the management of sudden vascular occlusions in the extremities.

PANCREATITIS. A CLINICAL-PATHOLOGIC CORRELATION. By Herman T. Blumenthal and J. G. Probstein. $9.50, pp. 379, Charles C Thomas, Springfield, Illinois, 1959.

This useful book may be described as encyclopedic within a small compass. It is remarkable that the authors have been able to condense a great mass of literature so successfully, in addition to analyzing carefully their own series of 163 cases. One consequence of covering the field so completely is that some newer developments, such as the association of pancreatitis with hyperparathyroidism and hyperlipemia, and recent studies on enzymes in the serum, are more or less submerged in the general discussion. This is perhaps of little moment, however, since the newness of such observations does not necessarily endow them with special importance.

The authors classify acute pancreatitis into etiologic types as follows: infectious, vascular, biliary obstructive, pancreatic obstructive, metabolic, toxic and chemical, traumatic, allergic, idiopathic. The last named is still the largest single category (over one third of cases in their series). The most vexatious problems in this respect are well brought out. Among the interesting points in their discussion of etiology and pathogenesis is the suggestion that some of the more recently recognized pancreatic enzymes, such as collagenase and elastase, play an important part in breaking down tissue in the acute disease.

The authors present interesting hypotheses to explain the mechanism of clinical manifestations in some cases. The propensity of acute pancreatitis for mimicking other diseases is indicated. In considering treatment, they emphasize that the management of the acute phase is primarily medical, while the treatment of the complications and sequelae is largely surgical. The importance of watching closely for loss of blood volume and of electrolytes is properly emphasized. The management of disturbed carbohydrate metabolism is considered briefly, with a note of caution about the use of insulin, and consideration of the effect of hypoglycemia on the secretory activity of the exocrine pancreas.

A minor criticism may be leveled at the index, where many page references are listed under a given subject, with no indication as to which one represents the major discussion of the problem. As a consequence, a good deal of thumbing of pages is required to find certain information. In a future edition bold-face type might be used to indicate relative importance.

This volume seems certain to become a standard reference work in a difficult and obscure field.

BOOKS RECEIVED

DIABETES MELLITUS. Third Congress of the International Diabetes Federation, Düsseldorf, July 21-25, 1958. Edited by Prof. Dr. K. Oberdisse and Priv.-Doz. Dr. K. Jahnke, Düsseldorf. German, English and French summaries of each paper are included. $41.65, pp. 799, 225 partly colored illustrations, 178 tables, 1959. Georg Thieme Verlag, Stuttgart. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, New York.