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EDITORIAL

GROWTH HORMONE AND DIABETES MELLITUS

In order to discuss the role of growth hormone in diabetes mellitus it is necessary to propose a definition of this disease. It may be thought of primarily as a genetic disturbance[1-5] whose major biochemical manifestations are hyperglycemia and glycosuria and whose complications, mainly vascular and neurological, are the major structural manifestations. It may be said, moreover, that this primary disturbance *leads* to hyperglycemia and that the tissue lesions may not be complications but an inherent part of the primary disease.

Since the advent of insulin the vascular and neurological lesions have replaced ketoacidosis as the major problem in diabetes. Although good control of hyperglycemia and glycosuria with diet and insulin may influence favorably the development of the ocular angiopathy,[6,7] there remains a high incidence of these lesions with resulting blindness despite such good control.[8]

Growth hormone may be a major factor in the pathophysiology of diabetes mellitus and its effects may be a reflection of the genetic disturbance. Its importance was first realized by the classical experiments of Houssay and those of Young which revealed its diabetogenic effects in experimental animals. The association of acromegaly with diabetes has been for a long time the major argument in support of the hypothesis of the diabetogenic effect of growth hormone in man.

In 1935 Lyall and Innes[9] reported for the first time a case of diabetes with intercurrent pituitary lesion and concomitant improvement of the diabetes. During the following year Chabanier et al.[10] reported on the surgical ablation of a normal pituitary gland in a patient with severe diabetes. Observations of the effects of spontaneous destruction of the pituitary gland on the severity of diabetes then followed. In 1953 the amelioration of diabetic retinopathy in such a case was reported by Poulsen.[11] In 1954 and 1955 the first reports on groups of patients who had undergone surgical hypophysectomy for diabetic retinopathy were reported.[12,13] Since then, this type of therapy has been undertaken by several groups of investigators. It has become apparent that hypophysectomy performed in diabetics causes a marked decrease in the requirements for insulin and that progressive diabetic retinopathy is frequently arrested or improved by this procedure.[14-16]

These observations prompted renewed interest in the study of the role of growth hormone in human diabetes at a time when growth hormone prepared from human[17] and simian pituitaries[18] was found to be metabolically active in man.[19-22]

In a nondiabetic hypophysectomized woman, human growth hormone was found to reverse the increased sensitivity to insulin.[22] In nondiabetic hypophysectomized subjects receiving human growth hormone for six to nine days, small rises were noted in the fasting and postprandial blood sugar levels. However, the same preparation of human growth hormone increased markedly the hyperglycemia and glycosuria and produced ketosis with metabolic acidosis in hypophysectomized diabetic subjects maintained on insulin and on replacement doses of cortisone and thyroid.[22,23] These findings in man corresponded to those in animals.

Methods for the determination of growth hormone levels in blood[24,25] and in urine[26] have been developed recently. Acromegalic patients have been found to have higher levels than normal adults[24-26] but there is no definite evidence that this is so in diabetics.[25] Children have been found to have higher levels than adults[27] but the influence of such levels on the course and problems of juvenile diabetes is unclear. Furthermore, a feedback mechanism between the blood sugar and the growth hormone level has been demonstrated[28] and the response to changes in blood sugar has been shown to differ in different metabolic states.[29] The role of this

mechanism in the development and progression of diabetes and its associated lesions is also unclear.

Large size and islet cell tissue hyperplasia[30] have been observed repeatedly since 1941[31] in newborn or stillborn babies of diabetic women. An analogy may be drawn between these observations and the proliferative changes seen in the islet cell tissues of experimental animals soon after the administration of growth hormone.[32,33] Whether the same mechanism operates in these two situations is not known. Peripheral vascular disease,[34,35] renal disease[36] and other lesions[37] have been reported to precede or be the first clinical manifestation of diabetes. The role of endogenous growth hormone in such cases or even in normal adults has not yet been elucidated. The recent observation of the localization of rabbit antibodies to human growth hormone within the human placenta[38] raises the question of the possible effect of this placental growth hormone on the diabetic state of both mother and fetus. Complete identification and metabolic studies of this agent are still lacking.

It has been reported that growth hormone interferes with the transport of carbohydrate fragments across the cell membrane[39-41] and it may antagonize insulin at that level. The significance of this in relation to the tissue lesions of diabetes is unknown. The peripheral defect in this disease, whether in muscle, fatty or supportive tissue may be of a nature to accentuate this antagonism and by so doing perpetuate and accentuate the extent of the lesions. Another effect of growth hormone of importance in diabetes is its effect on fat metabolism. Its ketogenic effect has already been mentioned and a rise in plasma nonesterified fatty acids has been reported in man[42,43] and monkey[44] following its administration. Total serum lipids as well as the triglycerides and nonesterified fatty acids fractions were observed to be elevated in diabetics even under condition of "good control."[45] This finding may well be a factor in the high incidence of vascular complications in the diabetics. Attempts at lowering plasma lipids by maintaining such patients with diabetic retinopathy on a low fat diet were associated in certain instances with an improvement of the retinopathy.[46] There it does not appear that insulin alone was sufficient to prevent the progress of the retinopathy but that a lowering of blood lipids was occasionally effective. The removal of the source of endogenous growth hormone may benefit the patient by the elimination of an agent which mobilizes the body stores of fat.

Attempts at modifying the chemical structure of growth hormone in order to separate its "protein anabolic effect" from its "diabetogenic" effect have not yet yielded any definitive results. Attempts at blocking the "diabetogenic" activity by means other than insulin and other hypoglycemic agents or by estrogens have not been reported. Meanwhile pituitary ablation remains the only effective method of eliminating growth hormone whether it is carried out by total surgical removal, radioactive yttrium implantation into the gland, stalk section, or heavy particle irradiation. While such procedures have shown promising results in arresting or reversing the course of progressive diabetic retinopathy, the effects on kidney damage, neuropathy, and cardiovascular lesions have not been adequately evaluated. While elimination of the growth hormone probably does not change the basic diabetic defect, it removes a factor which contributes in some unknown fashion to the progression of the vascular lesions.

A view of diabetes which is becoming clearer is that it is a process which starts before birth and its severity probably depends upon the genetic antecedents which bring it about. It should be possible to detect prediabetes at birth and to treat it then, just as this is done for galactosemia or phenylketonuria. It would then be possible to evaluate the role of good control of diabetes with insulin on the progress of the other manifestations of this disease and possibly of growth hormone control in those patients, if any, who would manifest progressive vascular lesions later in life.

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