# EDITORIAL

## HUMAN GROWTH HORMONE

The earliest knowledge of the function of the adenohypophysis was related to its importance in human growth. At the time of Marie's description of acromegaly in 1886 the nature and function of the pituitary was not known. The enlargement of the pituitary in acromegaly and in gigantism drew attention to the organ and led to the first appreciation of its function. An elementary understanding of the gland was evident in Hutchinson's statement in 1900, that "in the pituitary body we appear to have a sort of growth-regulating centre for the entire body, the disturbance of which in early life will produce the phenomena of giantism, and in later life those of acromegaly."[1] Subsequently the pituitary was shown to contain an anabolic hormone which promoted growth, and ways of purifying the growth hormone were devised. The complex pattern of metabolic effects produced by this hormone was studied extensively in animals, but only in the past two years, through the use of human growth hormone, were reproducible effects obtained in man.

The preparation of growth hormone from human pituitaries was undertaken after many failures of material from slaughterhouse animals to prove satisfactory in human studies and following suggestions from animal studies of species differences among growth hormones.[2,3] Pituitaries obtained at autopsy and stored for months in acetone proved to be a satisfactory source of human growth hormone.[4] When prepared by the glacial acetic acid method[5] the human growth hormone preparation was regularly active in man and appeared to be antigenically identical with the hormone present in human blood.[6] Anabolic effects were observed in balance studies by Beck, Pearson, Henneman and their associates[7–9] and similar effects of a preparation made by an alkaline extraction procedure[10] were reported by Bergenstal[11] and by Ikkos.[12] Storage of nitrogen, phosphorus and potassium was usually observed, while effects on calcium and sodium balance were more erratic. Urinary excretion of calcium was frequently increased even when the overall balance was positive. Nitrogen retention was produced with a dose of 1 mg./day in a hypopituitary subject and 2.5 mg./day in an adult subject with normal pituitary function. The initial effect on nitrogen was often large, with storage of 3 or 4 gm. of nitrogen per day. There was usually a fall in blood urea nitrogen concentration within twenty-four hours of a single injection of human growth hormone.[13]

Anabolic doses of human growth hormone in the range of 30 to 150 μg./kilogram/day had little or no effect on blood sugar, glucose tolerance or blood ketones in normal individuals and in nondiabetic hypopituitary subjects[14,15] but a diminished hypoglycemic response to insulin was observed in two of the hypopituitary group.[15] Glucose tolerance was impaired in a nondiabetic pituitary dwarf receiving 600 μg./kilogram/day.[7] Hypophysectomized diabetic patients receiving insulin were more sensitive to diabetogenic effects, exhibiting ketosis and sometimes increased hyperglycemia while receiving approximately 75 to 150 μg./kilogram/day.[15,16]

Growth hormone was found to increase the unesterified fatty acids of plasma[17] and perhaps this effect of growth hormone, by increasing the available substrate for ketone formation, accounts for its ketogenic action. Growth hormone of porcine, bovine, simian and human origin raised fatty acids in fasting dogs, but only human and simian preparations did so in man. The fasting value in man was usually doubled or tripled within four hours by human growth hormone. The effect was suppressed by glucose and food in nondiabetic subjects, but not in the uncontrolled diabetic. The pattern of response of fatty acids to growth hormone suggested that the hormone might normally influence the rate of fat mobilization in the postabsorptive period.[18] Whether fat mobilization is directly facilitated by the hormone or is a response to a need for more calories occasioned by the anabolic effects of the hormone is not known. However, the increased provision of calories from adipose tissue undoubtedly contributes to the anabolic result, and may permit, as in a study of an obese subject,[19] growth hormone to induce a large storage of nitrogen in a subject on a calorically inadequate diet.

The prolonged use of human growth hormone was well tolerated and was effective in stimulating growth. Two milligrams intramuscularly three times a week produced in a pituitary dwarf a growth rate of 2.6 in. per year, and an increase in serum inorganic phosphorus and alkaline phosphatase.[20] There was no change in blood sugar and no allergic reactions in twenty months of treatment.

While apparently not antigenic in man, human growth hormone induced the formation of antibodies in rabbits, permitting Read and Stone to devise an immuno-

logical method for the estimation of the hormone in human blood.[6]

The name growth hormone is likely to suggest that the function of the hormone is limited to the period of growth and to obscure the possibility that this most anabolic of agents may be physiologically important throughout life. Although the opportunity to evaluate growth hormone in human physiology and disease has only recently become possible, it has been seen that man continues to secrete growth hormone in adult life,[6,21] and that the mature and even the aged exhibit metabolic effects from administered human growth hormone.[18] The availability of human growth hormone promises to open up a field of clinical investigation of wide scope and interest.

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# *BOOK REVIEW*

INSULIN CRYSTALS. *By Jørgen Schlichtkrull. d. kr. 30 ($4.35), pp. 140, Ejnar Munksgaard, Publishers, Copenhagen, 1958.*

The studies described in Schlichtkrull's monograph were initiated in 1950 in conjunction with other investigators in the Novo Laboratories in Copenhagen. In the succeeding years this team systematically investigated various aspects of the chemical, biological, and clinical factors influencing the relationship of zinc and insulin, and uncovered much new knowledge about the timing of insulin suspensions. They discovered that long-acting preparations could be prepared without the addition of foreign protein modifying agents, a finding which eventuated in the development of Lente insulin preparations. The present report extends still further these studies of the physicochemical factors involved in crystal suspensions containing no added zinc ions, but which do show a protracted action. When ordinary beef insulin crystals containing two atoms of zinc per unit-cell (or more) were subjected to the influence of temperature under certain conditions, the time action was prolonged. Urea, formamide, and halide in the medium resulted in the formation of sharp-edged single-rhombohedrons having still more prolonged effects. A variety of timings may be produced, but it is not yet known whether these preparations are useful clinically, or whether they have any advantages in therapy.

The monograph is attractively printed and illustrated. The author has succeeded in presenting highly technical data in an understandable manner and he has included background summaries of previous work which are documented by the important bibliographical references. His illustrations of crystal structure are particularly noteworthy. The work represents a significant contribution to knowledge in a field that is not widely followed.