THE YEAR BOOK *of* ENDOCRINOLOGY

(1958-1959 YEAR BOOK *Series)*

EDITED BY

GILBERT S. GORDAN, M.D., Ph.D., F.A.C.P.

Associate Professor of Medicine
Chief of Endocrine Clinics, Department of Medicine
University of California School of Medicine
Associate Physician, University of California Hospitals
Assistant Visiting Physician, San Francisco Hospital
San Francisco, California

THE PRACTICAL MEDICINE YEAR BOOKS

This volume is one of the 15 comprising the Practical Medicine Series of Year Books founded in 1900 by G. P. Head, M.D., and C. J. Head, and published continuously since then. The complete list follows:

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The designation (Series 1958-1959) used on the cover and title page of this volume is to indicate its publication during the "series year" which begins in September 1958.

INTRODUCTION

In the 8 years I have been editing the YEAR BOOK OF ENDOCRINOLOGY I note that all my Introductions to this volume sound a little breathless, as if endocrinology were proceeding along at a breakneck pace. I think the reason is obvious—it is. The year 1958 was no exception. In it we learned simultaneously from Bartter and from Farrell of the factors controlling the secretion of aldosterone, a compound which was unknown when the YEAR BOOK OF ENDOCRINOLOGY began. We have also learned how to tell a genetic female from a genetic male—a feat most of us once thought we could accomplish by simpler technics but which recorded experience shows we could not do at all! We have also lived to see an effective pituitary growth hormone prepared by Raben. This agent not only produces retention of protoplasmic constituents in subjects during short-term balance studies, but actually causes linear growth in patients given long-term courses of treatment as reported by Raben, by Beck and by Henneman. It has even been claimed that bovine growth hormone can be altered chemically so that it may produce similar effects, although the data thus far are based on very short-term studies. We have also learned that the antibodies to thyroglobulin, demonstrable in the blood of patients with lymphadenoidthyroiditis (Hashimoto's disease), are present in the blood of many patients with myxedema, strongly suggesting that "idiopathic" myxedema is often the consequence of thyroidal atrophy induced by an autoimmune mechanism. It has been reported that the presence of these antibodies may be detected by a simple skin test. Sufficient time has now elapsed so that we are beginning to hear of malignancy in patients who have received therapeutic doses of radioiodine for the treatment of hyperthyroidism; both carcinoma of the thyroid and leukemia have been reported. I hasten to add that only a few cases have been detected so far and may be no more than the natural incidence.

Great strides are being made in our knowledge of the disorders of calcium metabolism. Hyperparathyroidism is now being detected in a surprisingly large number of patients.

The use of bone-seeking elements as tracers of skeletal metabolism has begun to add to our knowledge of the metabolically sluggish parathyroid. Of great practical importance is the establishment of cortisone and other adrenal cortical preparations in the treatment of hypercalcemia, particularly that owing to overdose of vitamin D, to sarcoidosis and to malignancies, but apparently not to hyperparathyroidism.

The hypoglycemic sulfonamides—carbutamide and tolbutamide and, more recently, chlorpropamide and metahexamide—and the chemically unrelated diguanides have acted as a shot in the arm to clinical and basic investigation of diabetes mellitus. It is now apparent that these agents can be given in adequate doses over periods of several years with only a very low incidence of toxic effects, and for an impressive number of patients they contribute manfully to the control of diabetes. Many of the untoward reactions reported earlier undoubtedly can be attributed to overdosage or too frequent administration, particularly of the agents with relatively long duration of action, such as carbutamide, chlorpropamide and metahexamide. Of great interest is the demonstration that visible changes in the blood vessels of diabetic patients can occur in a matter of hours and that—at least in the earlier phases—they are completely reversible. In harmony with long clinical experience, they are least marked when diabetes is under the best control.

Research in the field of adrenal cortical physiology and chemistry shows no sign of slowing down. Of considerable theoretical importance is the demonstration by Chart, Sheppard, Allen, Bencze and Gaunt that the amphenone analog, 2-methyl-1,2-bis-(3-pyridyl)-1-propanone (SU-4885) inhibits 11-beta-hydroxylation (Experientia 14:151, 1958). This compound has now been used experimentally in human subjects with a variety of adrenal disorders, primarily as a test of pituitary production of corticotrophin. Because of the toxicity of amphenone, fears of toxicity from this agent have been expressed, and it must be said that the claims thus far from varying groups are divergent and controversial. The well-established usefulness of cortisone in the treatment of congenital virilizing adrenocortical hyperplasia, which grew out of the almost simultaneous work of Bartter and of Wilkins and his group, and which led Jailer to formulate the

now-accepted schema of adrenal steroidogenesis, has culminated in the first report of pregnancy in a female pseudohermaphrodite. In my opinion, the trend toward treating hirsute girls by the similar administration of corticoids has become far too widespread. I have been heartened to note that some of the most careful workers in this field agree that we are seeing too many women treated with adrenal cortical steroids—and, I might add, at great expense—who have not become less hairy and who have suffered adverse effects.

The great revolution in our knowledge of sex differentiation incited by Murray Barr's important observation of the chromatin blob on the nucleolar border of cells of genetic females has now reached a point of such refinement that some persons claim to be able to differentiate between the normal female XX blob and that representing a presumed XXY pattern. Not being competent to discuss such highly technical matters, I have persuaded Dr. Melvin Grumbach, who, with Murray Barr, wrote the definitive article on "Cytologic Tests of Chromosomal Sex in Relation to Sexual Anomalies in Man" (Recent Prog. Hormone Res. 14:255, 1958) to prepare a special article for this YEAR BOOK. I am particularly indebted to Dr. Grumbach, who is one of those rare persons able to combine clinical endocrinology, pediatrics, embryology and cytology into a unified whole. I am also indebted to Dr. Frederic C. Bartter, Chief of the Section on Clinical Endocrinology of the National Heart Institute, for his special article on the control of aldosterone secretion, a subject to which he is one of the prime original contributors.

I cannot close this editorial without a word about the hope raised by the careful preliminary report of Blackburn and Childs of the high order of efficacy of 2-alpha-methyldihydrotestosterone in the treatment of advanced breast cancer (Proc. Staff Meet. Mayo Clin. 34:113, Mar. 4, 1959). This important article appeared too late for inclusion in this year's volume. In a carefully controlled study of previously untreated patients with objectively progressive disease, who were selected on the basis of similar age with respect to the menopause, and of distribution of lesions (visceral, osseous or breast, lymph nodes and skin), these workers compared the antitumor efficacy of testosterone propionate with that of 2-alpha-methyl-dihydrotestosterone. To avoid bias, the

patients were treated by the double-blind technic, in which neither patient nor physician knew which steroid was being given. Using direct measurement of tumor size as a criterion, they observed regression of lesions in 3 of 21 patients treated with testosterone propionate, a figure which is not far from the national average of 20.4%. Of the 27 patients treated with 2-alpha-methyl-dihydrotestosterone, regressions occurred in 12 (45%), 3 of whom had primarily visceral metastases, 8 osseous disease and 1 cutaneous lesions. With the rigid criteria used, these are the most promising results reported thus far from any hormonal treatment of advanced breast cancer. As the authors cautiously observed, however, the series is still small, so these data must be looked on as preliminary, and we shall all await with great interest the results of the larger study now in progress. The dramatic results obtained cannot fail to give hope that this may be the first great breakthrough in hormonal therapy of advanced breast cancer. They are of particular practical and theoretical interest, since this compound has very little androgenic activity, does not inhibit the excretion of gonadotrophin (Blackburn and Albert, J. Clin. Endocrinol., in press) and, in fact, seems to have little or no detectable hormonal activity.

The growth of the medical literature, its increased number of publications and journals, has placed a heavy burden on the Year Book Publishers with which I believe they have coped most efficiently. I particularly wish to thank Mr. William Keville, Managing Editor of the Year Book Publishers, for his efficiency, courtesy, complete cooperation and great help. The handling of this material also calls for considerable secretarial and editorial effort, for which I am greatly indebted to Mrs. Gertrude Leary and to Miss Mary Morrow, but for whose expert editorial talent many more solecisms would find their way into print.

GILBERT S. GORDAN

ADENOHYPOPHYSIS

► Raben's demonstration that his preparation of human pituitary growth hormone from glands removed surgically or at autopsy is an effective anabolic agent as determined by balance study has now been confirmed and extended by the production of linear growth in hypopituitary dwarfs. In the boy treated by Raben (see first article) the growth rate was approximately that seen in preadolescent children. Similar results have been noted in a larger series of patients treated for relatively long periods by Beck and co-workers (see second article). In the largest series reported thus far, Henneman found that linear growth was less than that which occurs normally in prepuberal youngsters and considerably less than that resulting from administration of testosterone compounds. A curious feature is the excretion of calcium during the period of active growth (Ikkos and Luft; Lancet 1:720, Apr. 5, 1958). An interesting observation which may in part provide an assay for the efficacy of growth hormone preparations is a rise in the serum unesterified fatty acid level, presumably reflecting the mobilization of fat from adipose tissue to provide energy for growth. Li has suggested that the larger molecular size of bovine growth hormone might account for its impotence in human subjects. Using chymotrypsin, he has attempted to make an effective preparation from bovine pituitary extracts with smaller average molecular size, and in a preliminary report he, Forsham and co-workers have claimed that nitrogen retention resulted from administration of 10 mg. of this material daily to a short girl with gonadal dysgenesis (Metabolism 7:762, 1958). In a subsequent paper read at the meeting of the Western Society for Clinical Research in Carmel, California (Clin. Res. 7:107, 1959), they reported similar results in 2 of 12 patients so treated. Curiously, there was no change in serum fatty acid concentrations.

Reduction of pituitary function in patients with diabetes or advanced breast cancer has now been produced by high-voltage irradiation of the pituitary, in contrast to earlier failures with standard voltages. That the pituitary infarction produced by stalk section is transient is suggested by the regeneration noted by Daniel and Prichard (Proc. Physiol. Soc., July 11-12, 1958). Abstracts of papers regarding pituitary gonadotrophin will be found in the section on The Reproductive System, including an interesting description of the direct effect of estradiol on pituitary gonadotrophs. Papers dealing with corticotrophin and the pituitary control of adrenal secretion will be found in the section on The Adrenal Cortex.—Ed.

Growth Hormone

Treatment of Pituitary Dwarf with Human Growth Hormone is reported by M. S. Raben[1] (Tufts Univ.). Human growth hormone, prepared by the glacial acetic acid extraction method from pituitaries obtained at autopsy, was continuously effective and well tolerated when administered intramuscularly for 10 months to a boy, aged 17, who was a

(1) J. Clin. Endocrinol. 18:901-903, August, 1958.

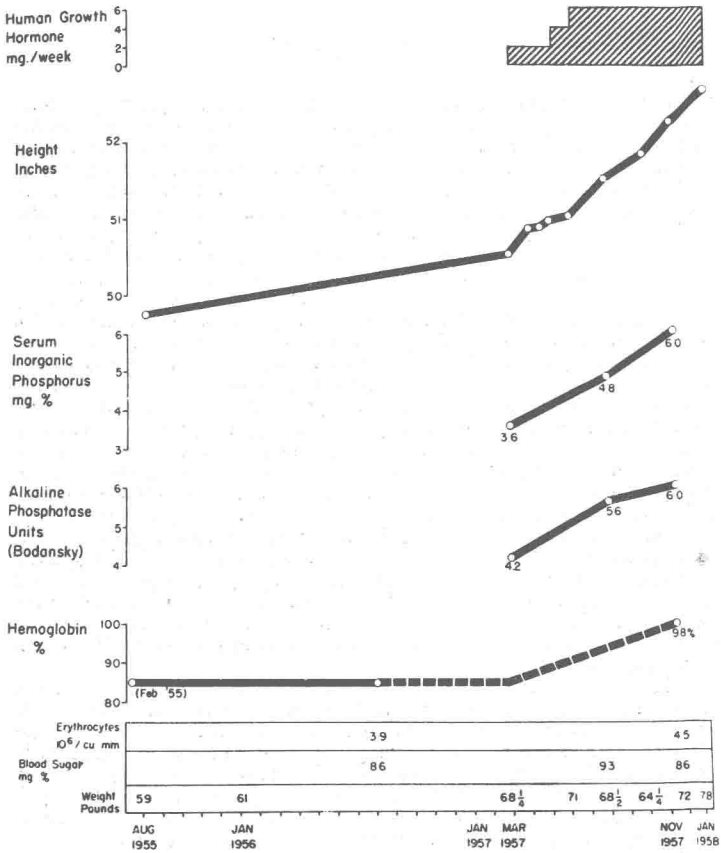

Fig. 1.—Response of pituitary dwarf to treatment with human growth hormone. (Courtesy of Raben, M. S.: J. Clin. Endocrinol. 18:901-903, August, 1958.)

pituitary dwarf. A dose of 1 mg. twice a week produced an initial stimulation of growth but was probably insufficient to sustain an optimal growth rate. A dose of 2 mg. 3 times a week was effective for the last 7 months of treatment and produced a growth rate of 2.6 in. a year, compared with 0.5 in. a year for the 1½ years before treatment (Fig. 1). Total increase in height during the 10 months of therapy was 2.1 in., representing a growth rate slightly greater than that of a normal child the same height.

Concentration of inorganic phosphorus in the serum increased from 3.6 mg. to 6 mg./100 ml. during treatment, and alkaline phosphatase activity rose from 4.2 to 6 Bodansky units. Increase in levels of serum inorganic phosphorus and alkaline phosphatase to levels characteristic for growing children was supportive evidence of the growth-hormone activity. No changes are noted in these levels when animal growth-hormone preparations are used in pituitary dwarfs, even for prolonged periods.

The immature state of the penis and testes was not affected by the treatment, and no pubic or axillary hair appeared. No advance in bone age occurred during therapy, but hemoglobin concentration increased from 86 to 98%, with a possible increase in red blood cell count. No redness, tenderness or induration at the injection site and no generalized allergic reactions were noted. No eosinophils were noted in a differential white blood cell count after 8 months of treatment. Concentration of blood sugar remained normal. The patient seemed to require increased caloric intake to maintain and gain weight during treatment.

No evidence of other pituitary hormone activity was detected during the prolonged use of this preparation, and none was noted when larger doses were used for short periods in balance studies by other workers.

During the therapy, the patient continued to receive, as he had for the 2 preceding years, 5 mg. cortisone orally every 8 hours and 120 mg. USP thyroid daily.

Metabolic Effects of Human and Monkey Growth Hormone in Man. John C. Beck, E. E. McGarry, I. Dyrenfurth and E. H. Venning[2] (McGill Univ.) did metabolic balance studies on 3 patients with dwarfism, 1 with hypophysectomy for metastatic carcinoma of the breast, 1 with postmenopausal osteoporosis and 1 normal control. All received a known diet. The human growth hormone was prepared from pituitaries obtained at autopsy. .

Prompt retention of nitrogen was noted during and after administration of human growth hormone, as seen in Figure 2, where the base or zero line represents the balance of any one element during the control period, which was begun

(2) Ann. Int. Med. 49:1090-1105, November, 1958.

only after the patient had been stabilized on the experimental diet. Nitrogen retention was also produced by administration of monkey growth hormone (Fig. 2). Gain in body weight also occurred with both human and monkey growth hormone. The fall in serum nonprotein nitrogen and blood

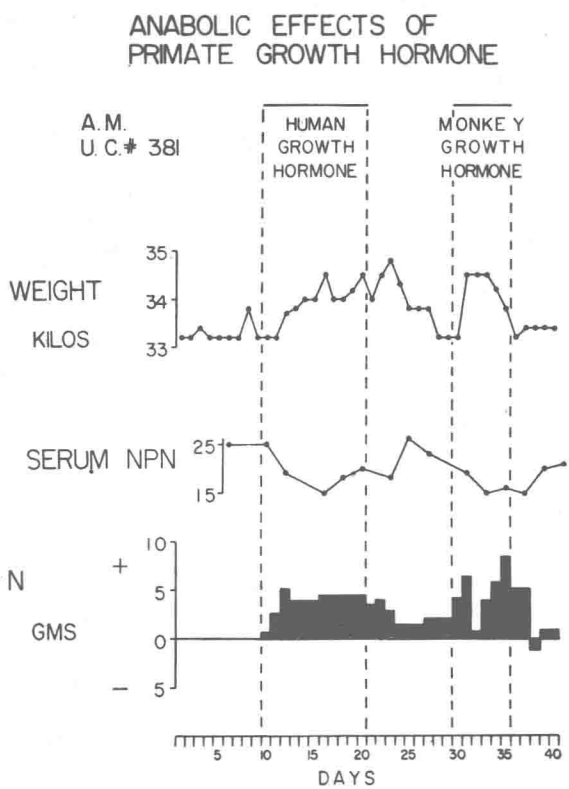

Fig. 2.—Human growth hormone dosage was 10 mg./day for 3 days and 20 mg./day for next 3 days; monkey growth hormone dosage was 40 mg./day for 3 days and 80 mg./day for next 3 days. (Courtesy of Beck, J. C., *et al.*: Ann. Int. Med. 49: 1090-1105, November, 1958.)

urea nitrogen levels, which occurs within 48 hours of the first dose, is further evidence of anabolic activity. Retention of potassium paralleled that of nitrogen. No significant changes in the serum concentration of any electrolyte were noted.

There was marked retention of sodium, but this was not

sustained as long after withdrawal of growth hormone as was retention of the intracellular elements. Neither change in sodium balance nor increase in aldosterone output could be related to contamination with corticotrophin, since no change in either 17-hydroxycorticosteroid or 17-ketosteroid excretion occurred in any of the studies during administration of primate growth hormone.

Administration of human growth hormone resulted in a diabetic type glucose tolerance curve (Fig. 3). No alteration

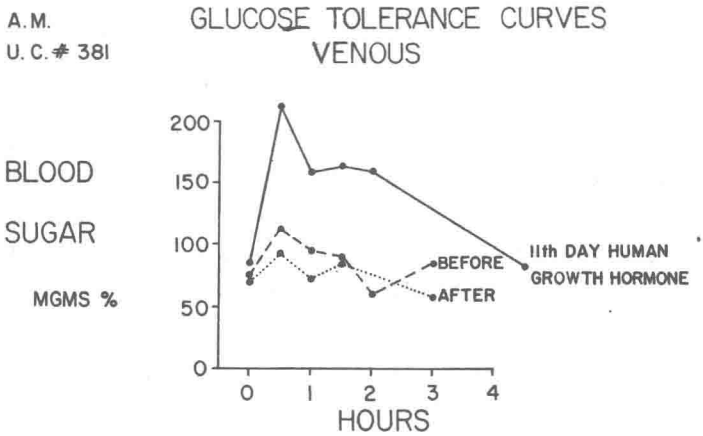

Fig. 3.—Oral glucose tolerance curve during human growth hormone administration in dose similar to that in Figure 2. (Courtesy of Beck, J. C., *et al.*: Ann. Int. Med. 49:1090-1105, November, 1958.)

in glucose tolerance resulted from administration of monkey growth hormone in the one person to whom it was given.

Acromegaly in Girl of 8 Years is described by R. McLaren Todd[3] (Univ. of Liverpool). This condition is exceedingly rare and especially uncommon in childhood.

Girl, 8½, had the abnormal facial appearance of acromegaly. Growth had been rapid from about age 5; at age 7, her height had been 54½ in. (height age of 10½ years) and at age 8½, 60 in. (height age of 12½ years). (The excessive growth is due to excessive production of pituitary growth hormone; this hormone does not cause [illegible]ly skeletal maturation or closure of epiphyses.) The skeletal age was the same as the chronological age. There was no clinical evidence of overactivity of the thyroid, adrenal or sex glands and the clinical findings were supported by these investigations: serum cholesterol, normal;

(3) Arch. Dis. Childhood 33:49-54, February, 1958.

excretion of 17-ketosteroids, only slightly above normal; response to corticotrophin, normal; and blood electrolytes, normal. There was clinical evidence of an expanding intracranial lesion (headache, vomiting and papilledema), which was confirmed by encephalography.

The diagnosis of acromegaly was supported by hematologic and radiologic abnormalities. The glucose tolerance curve was of the diabetic type and the patient showed insulin resistance. Balance studies showed retention of nitrogen (pituitary growth hormone increases utilization of aminoacids for synthesis of tissue proteins, thereby causing nitrogen retention). A high serum phosphorus level (6.8 mg./100 ml.) and the presence of cancellous tufting of some of the terminal phalanges confirmed the diagnosis of acromegaly.

Relief from the intracranial tension was accomplished by a short-circuit operation, which was followed by irradiation of the sella turcica. Follow-up 6 months later showed that the patient's general condition was satisfactory: she had no headaches, the visual fields were normal and the papilledema had completely subsided. The acromegalic features were not more marked.

► [As noted by the author, acromegaly in childhood is extremely uncommon. Usually, pituitary eosinophilism causes gigantism in children and acromegalic features develop only later.—Ed.]

Decreased Insulin Requirement Following Growth Hormone Administration in Diabetic Dogs follows exacerbation of the diabetes induced by the growth hormone. Leo Chaikof and James Campbell[4] (Univ. of Toronto) observed that repeated treatments of metahypophysial-diabetic dogs with growth hormone elicited lessened and varying responses. Permanent diabetes was induced in 4 dogs by injections of growth hormone. After the stable insulin requirements were determined, growth hormone was again given subcutaneously for 4-6 days. After this treatment, the insulin requirements declined in 3 dogs to levels less than the initial requirement and persisted at low levels for several weeks. After repeated treatments with growth hormone, the decline in insulin need was irregular and inconstant. The experiments also showed a heightened resistance to insulin evident during growth hormone treatment, so that (as a consequence of increased demand for insulin by extrapancreatic tissues) about 4 times the usual doses of insulin were required to inhibit diabetogenic action. Histologic examination of the pancreas during the phase of reduced insulin requirement in the interval between growth hormone administration did not show regeneration of the islet cells. Depancreatized dogs re-

(4) Endocrinology 61:618-626, December, 1957.