1957–1958
SERIES

Year Book
OF
ENDOCRINOLOGY

GORDAN

THE YEAR BOOK *of* ENDOCRINOLOGY

(1957-1958 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
Consultant Endocrinologist, Langley Porter Clinic
of the State Department of Mental Hygiene
San Francisco, California

THE YEAR BOOK PUBLISHERS

INCORPORATED

200 EAST ILLINOIS STREET CHICAGO 11

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:

Medicine: *Infections,* edited by PAUL B. BEESON, M.D.; *The Chest,* by CARL MUSCHENHEIM, M.D.; *The Blood and Blood-Forming Organs,* by WILLIAM B. CASTLE, M.D.; *The Heart and Blood Vessels and Kidney,* by TINSLEY R. HARRISON, M.D.; *The Digestive System,* by FRANZ J. INGELFINGER, M.D.; *Metabolism,* by PHILIP K. BONDY, M.D.

General Surgery edited by MICHAEL E. DEBAKEY, M.D., with a section on *Anesthesia,* by STUART C. CULLEN, M.D.

Drug Therapy edited by HARRY BECKMAN, M.D.

Obstetrics & Gynecology edited by J. P. GREENHILL, M.D.

Pediatrics edited by SYDNEY S. GELLIS, M.D.

Radiology: *Diagnosis,* edited by JOHN FLOYD HOLT, M.D., and FRED JENNER HODGES, M.D.; *Therapy,* edited by HAROLD W. JACOX, M.D., and MORTON M. KLIGERMAN, M.D.

Ophthalmology edited by DERRICK VAIL, M.D.

Ear, Nose & Throat and Maxillofacial Surgery: *The Ear, Nose & Throat,* edited by JOHN R. LINDSAY, M.D.; *Maxillofacial Surgery,* by DEAN M. LIERLE, M.D., and WILLIAM C. HUFFMAN, M.D.

Neurology, Psychiatry & Neurosurgery: *Neurology,* edited by ROLAND P. MACKAY, M.D.; *Psychiatry,* by S. BERNARD WORTIS, M.D.; *Neurosurgery,* by OSCAR SUGAR, M.D.

Dermatology & Syphilology edited by RUDOLF L. BAER, M.D., and VICTOR H. WITTEN, M.D.

Urology edited by WILLIAM W. SCOTT, M.D.

Orthopedics and Traumatic Surgery edited by EDWARD L. COMPERE, M.D., with a section on *Plastic Surgery,* by NEAL OWENS, M.D.

Endocrinology edited by GILBERT S. GORDAN, M.D.

Pathology and Clinical Pathology edited by WILLIAM B. WARTMAN, M.D.

Cancer edited by RANDOLPH LEE CLARK, JR., M.D., and RUSSELL W. CUMLEY, Ph.D.

Dentistry

TABLE OF CONTENTS

The designation (Series 1957-1958) used on the cover and title page of this volume is to indicate its publication during the "series year" which begins in September 1957.

THE YEAR BOOK *of* ENDOCRINOLOGY

(1957-1958 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
Consultant Endocrinologist, Langley Porter Clinic
of the State Department of Mental Hygiene
San Francisco, California

THE YEAR BOOK PUBLISHERS

INCORPORATED

200 EAST ILLINOIS STREET CHICAGO 11

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:

Medicine: *Infections,* edited by PAUL B. BEESON, M.D.; *The Chest,* by CARL MUSCHENHEIM, M.D.; *The Blood and Blood-Forming Organs,* by WILLIAM B. CASTLE, M.D.; *The Heart and Blood Vessels and Kidney,* by TINSLEY R. HARRISON, M.D.; *The Digestive System,* by FRANZ J. INGELFINGER, M.D.; *Metabolism,* by PHILIP K. BONDY, M.D.

General Surgery edited by MICHAEL E. DEBAKEY, M.D., with a section on *Anesthesia,* by STUART C. CULLEN, M.D.

Drug Therapy edited by HARRY BECKMAN, M.D.

Obstetrics & Gynecology edited by J. P. GREENHILL, M.D.

Pediatrics edited by SYDNEY S. GELLIS, M.D.

Radiology: *Diagnosis,* edited by JOHN FLOYD HOLT, M.D., and FRED JENNER HODGES, M.D.; *Therapy,* edited by HAROLD W. JACOX, M.D., and MORTON M. KLIGERMAN, M.D.

Ophthalmology edited by DERRICK VAIL, M.D.

Ear, Nose & Throat and Maxillofacial Surgery: *The Ear, Nose & Throat,* edited by JOHN R. LINDSAY, M.D.; *Maxillofacial Surgery,* by DEAN M. LIERLE, M.D., and WILLIAM C. HUFFMAN, M.D.

Neurology, Psychiatry & Neurosurgery: *Neurology,* edited by ROLAND P. MACKAY, M.D.; *Psychiatry,* by S. BERNARD WORTIS, M.D.; *Neurosurgery,* by OSCAR SUGAR, M.D.

Dermatology & Syphilology edited by RUDOLF L. BAER, M.D., and VICTOR H. WITTEN, M.D.

Urology edited by WILLIAM W. SCOTT, M.D.

Orthopedics and Traumatic Surgery edited by EDWARD L. COMPERE, M.D., with a section on *Plastic Surgery,* by NEAL OWENS, M.D.

Endocrinology edited by GILBERT S. GORDAN, M.D.

Pathology and Clinical Pathology edited by WILLIAM B. WARTMAN, M.D.

Cancer edited by RANDOLPH LEE CLARK, JR., M.D., and RUSSELL W. CUMLEY, Ph.D.

Dentistry

TABLE OF CONTENTS

The designation (Series 1957-1958) used on the cover and title page of this volume is to indicate its publication during the "series year" which begins in September 1957.

INTRODUCTION

So much is going on in clinical endocrinology that the reader will be spared a homily from the editor bewailing the impossibility of keeping up with the literature, the questionable merit of the all-too-numerous publications, the difficulties of evaluating the technical means by which modern information is obtained, the pressures on the physician that divert him from his primary task, the problems of our scientific leadership and the important corollary of the support of clinical applied and basic research, to say nothing of the dilution of our daily mail by government-subsidized advertising matter we could do better without. Important as these matters are, we can concern ourselves more constructively just now with the revolutionary strides being made in our knowledge of the chemistry and physiology of the endocrines and with the clinical applications of this new information. Let me hasten to remark that it is the intention of this volume to depict the endocrine literature, albeit in miniature. The articles selected for abstracting and presentation have been chosen because, in the opinion of your editor, they represent what is being reported. This is not a textbook of endocrinology, and this year's literature does not necessarily cover every pertinent field, for which the interested reader is referred to one of the numerous excellent texts published in the past few years. Parenthetically, let me add that a particular effort is made to search out those articles which are not generally available in the journals received by most American physicians. Thanks to the excellent structure and complete co-operation of the Year Book Publishers, pertinent articles in all languages can be and are considered for inclusion here.

One of the long-unexplained problems of clinical endocrinology has been why people with hypopituitarism do not respond to anterior pituitary growth hormone. It now appears that the lack of response to this material is attributable to species difference, since the preparations then in use were

derived from ox or sheep pituitary glands. In the current year, extracts rich in growth factor have been prepared from human pituitary glands, and these preparations have been shown to be fully effective in man. Renewed interest in clinical diabetes insipidus and the actions of the antidiuretic hormone has resulted in a re-examination of some of the clinical phenomena involved. Both the group at the Mayo Clinic and at Johns Hopkins Hospital have described the clinical occurrence of the "normal interphase," in which experimental diabetes is temporarily relieved, presumably because of transient secretion of antidiuretic hormone by the cells of the medial eminence and the posterior lobe.

In the case of the thyroid gland, some of the most interesting developments relate to the various types of thyroiditis. One of these concerns the occurrence of subacute thyroiditis during an epidemic of mumps in Israel. The isolation of the virus from the thyroid gland of afflicted patients is, I believe, the first instance in which a viral cause of this disorder has been established. Subacute thyroiditis apparently occurs much more commonly than was thought, frequently being mistaken for the common cold. Chronic thyroiditis (Hashimoto's disease), the diagnosis of which could previously be established only by biopsy, has been shown to be associated with rather characteristic abnormalities of the serum proteins, so that now the diagnosis can be made by laboratory means without recourse to surgical operation. The presence of antibodies to thyroglobulin suggests an autoimmune mechanism, which may account for the destruction of the gland and resulting myxedema. Since similar antibodies are found in the serum of some patients with myxedema, it is possible that some cases of idiopathic myxedema are the end result of an unrecognized chronic thyroiditis. The alternative explanation that thyroid failure may cause the alterations in the serum proteins seems less likely in view of the high incidence of positive reactions in thyroiditis and the relatively low incidence in myxedema. These studies have been interpreted to indicate that thyroiditis may be diagnosable by laboratory means and treatable by administration of thyroid substance, taking one more thyroid disorder away from the surgeons.

In carbohydrate metabolism, the biggest news is the identification of the enzymatic defect in galactosemia and the use of a specific enzymatic test in the diagnosis of this disorder. On the endocrine side, the two most active fields are insulin antagonism and the actions of hypoglycemic agents. Naturally, the long-term effects of the hypoglycemic compounds are still not known, but studies on the large numbers of patients who are receiving carbutamide in Europe and tolbutamide in the United States should soon result in definitive data. In addition to the hypoglycemic sulfonamides, two other groups of compounds have now received sufficient clinical trial to be identified accurately as hypoglycemic in human diabetes: the diguanides and indole acetic acid. While opinion as to their mechanism of action is not uniform, these compounds appear to cause the release of insulin from the pancreas and to interfere with its subsequent destruction.

Specific methods for the separation and identification of the individual adrenal cortical steroids of body fluids have furnished more precise information about the function of the adrenal cortex in health and disease than is known about the workings of any other endocrine gland. The thyroidologists, however, show promise of catching up very quickly. Aldosterone, a rather unique adrenal cortical steroid in that it is only partially—if at all—under adenohypophysial control, continues to receive a great deal of attention. Certainly much remains to be learned about its biologic actions, the factors controlling its release and its place in the pathophysiology of adrenal disease and disorders of fluid balance. Aldosterone-producing tumors, first described by Conn in October 1954, are now being reported regularly. Recently, the opposite condition, aldosterone deficiency, has been characterized by Hudson, Chobanian and Relman of Boston. In their case, hyperkalemia was associated with Stokes-Adams attacks.

To me, one of the most satisfactory developments in adrenal cortical physiology is the report by Jailer and his group that the adrenal cortical hyperplasia of Cushing's disease is associated with the presence in the blood of an adrenal growth factor. This is the first direct confirmation of the hypothesis of Harvey Cushing, who first described this disease in 1932, that the adrenals are made overactive by stimulation

from another source, presumably the pituitary gland. Amphenone, which has been shown to act on the adrenal cortex as propylthiouricil acts on the thyroid gland, i.e., by interfering with the formation or release of its hormones, secondarily causing hyperplasia of the gland, has now been used successfully in patients with adrenal cortical tumors to relieve some of their distressing hormonal symptoms.

The many isolated facts resulting from Murray Barr's brilliant demonstration that chromatin sex patterns can be detected in suitable cells (most practically obtained by buccal or vaginal smear) were marshaled into orderly array in an outstanding presentation by Grumbach and Barr at the Laurentian Hormone Conference in September 1957. It is now clear that the lack of sexual development in young "girls" with what was once thought to be "ovarian agenesis" is, in most cases, the result of prenatal damage to a testis, and that some infertile men with gynecomastia and atrophic testes (Klinefelter's syndrome) have the chromatin pattern of females. Indeed, milder forms of the latter disorder have been reported to account for as many as 3% of all sterile men!

The influence of sex hormone on the cause and development of cancer of the breast and prostate has come in for new scrutiny. Mustacchi and Shimkin, of the United States Public Health Service, have found that the incidence of cancer is no greater in acromegaly and no less in hypopituitarism than in the general population. The Public Health Service has set up a major co-operative program including 27 participating institutions, providing adequate statistical control of selection of patients, choice of experimental therapy and objective evaluation of results, to quantitate and compare the antitumor efficacy of various endocrine treatments for advanced breast cancer. This program makes it possible to learn quickly the true value of any new "cancer cure."

The new synthetic androgen, fluoxymesterone, has been reported by B. J. Kennedy of the University of Minnesota to be more effective than testosterone propionate in the treatment of advanced breast cancer. Data from other sources confirm that fluoxymesterone is at least no less effective, and the fact that this unusual derivative of methyltestosterone does not produce much growth of facial hair, deepening of the voice

or annoying increase of libido certainly makes it superior to other androgens as far as distressing virilization is concerned. While both adrenalectomy and hypophysectomy can produce regressions in some cases of breast cancer, the drastic nature of these operations and the fact that a minority of patients benefit—and then only transiently—reserve these procedures for patients who no longer respond to x-rays, estrogens or androgens. Because the evaluation of the antitumor efficacy of the many endocrine manipulations introduced in the past 15 years requires eluding many pitfalls, I have prevailed on Dr. George Escher of the Sloan-Kettering Institute to prepare a special article on this subject. His extensive experience with the problem makes it possible for him authoritatively to communicate to the practicing physician the exact therapeutic place of these endocrine procedures in the practical therapy of advanced breast cancer.

I wish to thank the Year Book Publishers for their many considerations and efficient handling of the ever-increasing volume of the medical literature, Mrs. Gertrude Leary for secretarial devotion beyond the call of duty and Miss Mary Morrow for expert editorial help.

GILBERT S. GORDAN

GENERAL ENDOCRINOLOGY

Differential Diagnosis of Hirsutism. J. Marsalek, M. Talas, D. Novosad and L. Bartosová[1] (Palacky Univ.) studied 23 patients with hirsutism with regard to estrogens, pregnanediol, follicule-stimulating hormone (FSH), 17-ketosteroids and their fractions, the Thorn test, blood cholesterol, sodium and potassium levels and conditions of the sebum and of the menstrual cycle. In hirsutism due to hyperplasia of the adrenal cortex, characteristic diagnostic features are: permanently increased output of 17-ketosteroids in the urine, as evidenced by chromatography—higher fractions III and IV (total amount more than 50%); increased pregnanediol production and reduced FSH production, lowered cholesterol level in the blood, significant reduction of eosinophils in the Thorn test and reduced sebum. The ovaries are of normal size.

An irregular cycle with enlarged ovaries and anovulation are indicative of the Stein-Leventhal syndrome. Output of 17-ketosteroids is normal, and by chromatography the total amount of fractions IV and V is higher than 50%. Familial hirsutism is the commonest form of this disorder. It is characterized by normal 17-ketosteroid excretion and normal or changing menstrual cycle. Only the sebum excretion was found increased.

► [Hirsutism is a problem which the endocrinologist frequently has to grapple with. Occasionally, hirsutism is symptomatic of one of the serious endocrine disorders, e.g., adrenocortical tumor or hyperplasia, ovarian dysfunction or acromegaly. More often, no satisfactory diagnosis can be made, and the patient is turned away with a reassuring pat on the back, advice is given regarding cosmetic care and a note is made on her chart that she has simple hirsutism, heterosexual hypertrichosis or possibly familial or racial hirsutism.

One feature difficult to interpret is that urinary excretion of 17-ketosteroids by hirsute women is slightly greater than the norm, i.e., 16-25 mg. daily. Recently, several investigators have suggested that the combination of hirsutism and increased 17-ketosteroid excretion reflects adrenocortical hyperfunction and that suppression of adrenal overactivity by administration of corticoids helps the patient. Such treatment effectively reduces the 17-ketosteroid excretion—both in these cases and in normal subjects—and

(1) Arch. Gynäk. 188:443-456, May, 1957.

in some patients who are not ovulating, basal body temperatures become diphasic. The evidence that increased adrenal function is the malefactor, however, is far from complete. Most young women with this condition are fertile, come from racial stock noted for hirsutism, in particular peoples of the Mediterranean basin or central Europe, and are not greatly bothered by a hair growth which is normal for their familial or ethnic pattern. As Segaloff pointed out in discussion of the interesting report by Perloff and his group (A.M.A. Arch. Int. Med. 100:981, 1957), the urine of these women does not contain the chromogen excreted in congenital adrenocortical virilizing hyperplasia. Anatomic hyperplasia of the adrenals has not been reported in this condition. Evidence that hirsutism is controlled by administration of corticoids has not been convincing so far. Another possible interpretation of the findings is that our concept of the normal amount of female facial hair and urinary 17-ketosteroid excretion should be revised upward. I have been impressed by the fact that at least a fourth of the women in mental hospitals have facial hirsutism, presumably because they do not take care of their appearance. Cleghorn of the Allen Memorial Institute in Montreal has wittily offered as the best explanation that razor blades are not permitted in mental hospitals (*Hormones, Brain Function and Behavior* [New York: Academic Press, 1957], p. 24).

I am indebted to S. M. Garn of the Fels Research Institute at Antioch College, Yellow Springs, O., for the information that areolar hair and hypogastric hair occur in about 20% of women, varying with race and age, and was interested to learn that women from the hairier groups of mankind are far furrier in this respect than men from the more glabrous populations (Ann. New York Acad. Sc. 53:498, 1951; cf. also P. N. Shah; Am. J. Obst. & Gynec. 73:1255, 1957).—Ed.]

Role of Cholesterol in Steroidogenesis in Man was studied by George V. LeRoy[2] (Univ. of Chicago). Using cholesterol labeled with radiocarbon or tritium as a tracer, it was shown in vivo that it is a precursor for the adrenal corticoids whose principal metabolites are tetrahydrocortisone, tetrahydrohydrocortisone and 11-ketoetiocholanolone, as well as for steroid hormones whose principal metabolites are androsterone and etiocholanolone. The intact human endocrine system appears to be capable of performing the principal biosynthetic reactions responsible for steroidogenesis from cholesterol that have been shown in vitro using perfused organs, tissue slices and breis.

The key reactions are: (1) removal of the side-chain of cholesterol to give C^{21}, C^{19} and C^{18} steroids (2) hydroxylation by the adrenal cortex at C^{11}, C^{17} and C^{21} of the tetracyclic nucleus; and (3) rearrangement of the A-ring (by the placenta) to yield estrone, a C^{18} aromatic steroid.

It also was found that 0.5-1% of the plasma-free cholesterol that is utilized daily goes into the biosynthesis of cor-

(2) Tr. A. Am. Physicians 70:202-215, 1957.

ticoids. In pregnancy, about 0.0001% of the daily cholesterol turnover goes into the production of estrone.

Clinical Manifestation of Adiposogenital Dystrophy in Adult Men: Results of Follow-up Study of Fat, Feminine Boys. Svend G. Johnsen[3] (Univ. of Copenhagen) presents result of a long-range study of what happens to boys with pronounced obesity, feminine distribution of fat, small external genitals and no signs of intracranial lesions. There were 184 patients, including 13 classified as having simple obesity, 38 uncertain and 17 seen as adults only. The other 116 adults had been classified during childhood as having adiposogenital dystrophy. Initial examination and classification were made 10-15 years before follow-up in adulthood. Among the patient group, as compared with normal men, 27% showed penile underdevelopment and 39% had reduced androgen excretion. About the same number showed abnormalities in secondary sex characteristics. Fertility was reduced in 43% of the patients studied, with more abnormal head forms found in the sperm of the patient group. Many patients also showed impaired muscular strength.

Hypogonadism in adults was well correlated with diagnosis of adiposogenital dystrophy in childhood, whereas boys who had only simple obesity without special features and had normal genitals attained normal sexual development. Body growth and skeletal proportions were normal, even in severe hypogonadism, however. In severe hypogonadism in adults there was complete lack of puberal development, though in many there was only slight impairment of spermatogenesis or testicular androgen production.

The treatment of choice is chorionic gonadotrophin injection. Patients thus treated near puberty subsequently showed comparatively better testicular androgen production than spermatogenic function, indicating function of the Leydig cells had been selectively stimulated by treatment. Fat, feminine and hypogenital boys are not variants of ordinary obesity, but should be regarded as true endocrinologic problems, and their developmental defect should be corrected as far as possible by chorionic gonadotrophin injections.

(3) Acta endocrinol. (supp. 31) 24:191-197, 1957.