THE YEAR BOOK *of*
ENDOCRINOLOGY

(1960-1961 YEAR BOOK *Series)*

EDITED BY

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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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INTRODUCTION

The First International Congress of Endocrinology met in Copenhagen July 18-23, 1960, only a week after the Fourth International Goitre Conference in London. Both meetings were marked by superb preparation, the convening of the most distinguished and productive people in the fields, important announcements and the exposure of areas of major differences in interpretation of some of the terms commonly used by all. For example, at the International Goitre Conference, it quickly became apparent that the word "cretin" is used differently by people in countries where endemic cretinism had once flourished from the way it is used by the Anglo-Americans, who had forgotten the work of McCarrison and of Osler. It was because of such differences in language, which reflect a difference in thinking, that I persuaded one of the foremost experts on cretinism, Dr. Aurelio Costa, of Turin, Italy, to prepare the special article "What Is a Cretin?" which appears in this volume. It was also at one of these Congresses that Vasily Baránov, Member of the Academy of Medical Sciences of the USSR, agreed that he and his colleagues would bring us up to date on recent advances in Soviet endocrinology. Their special article also appears in this volume.

Of the hundreds of contributions made at these Congresses, only a few can be singled out here for mention. Perhaps the most important single announcement was that of Howard Rasmussen of the Rockefeller Institute, who reported the isolation, amino acid constitution and biologic actions of parathyroid hormone. Genest, of Montreal, made the very important announcement that angiotensin II stimulates the production of aldosterone. This observation has already been confirmed by the work of at least four other laboratories. In this connection, Bartter, of the National Heart Institute, described a remarkable case of hyperaldosteronism apparently resulting from hyperplasia of the juxtaglomerular apparatus.

Further important discussions of the clinical manifestations of hyperaldosteronism and the role of aldosterone in malignant hypertension, as well as a lively discussion on the

controls of aldosterone secretion, were presented at the even better than customary Laurentian Hormone Conference, September 4-9, 1960. This Conference was also highlighted by Sawyer's superb presentation of new knowledge of neurohypophysial physiology and pharmacology, Diczfalusy's masterful study of estrogen metabolism in the human fetus and newborn and Nowakowski's clarification of the genetic aspects of male hypogonadism. All in all, it seems that 1960 was another good year for endocrinology.

Mechanisms of hormone action are now being elucidated. The important work of Rachmiel Levine and his group at Michael Reese Hospital in Chicago, that insulin facilitates the transport of hexoses across cell membranes, has now been widely confirmed and accepted. It is also generally accepted now that insulin facilitates the transfer of amino acids across the cell membrane independently of its effect on hexose transport. Oscar Hechter, of the Worcester Foundation, Shrewsbury, Massachusetts, has shown that ACTH does for the adrenal cortex exactly what insulin does for muscle cells. The concept of the enzymatic mechanisms of estrogen action so brilliantly set forth by Claude Villee and his group (see last year's YEAR BOOK) also seems well founded. Pesch, Segal and Topper, at the National Institutes of Health, have shown that progesterone, by stimulation of the 4-epimerase reaction, can repair the metabolic defects of congenital galactosemia. The actions and assay of human growth hormone, discussed in detail in last year's YEAR BOOK, were widely confirmed and amplified in 1960. The problems of insulin assay, particularly at normal or subnormal levels, and of insulin transport are also receiving a good deal of attention. The possibility of an autoimmune cause for diabetes mellitus has also been considered. Autoimmunity seems more certainly implicated in chronic lymphocytic thyroiditis and its late sequela, myxedema. Nowadays, the mere diagnosis of hypothyroidism is insufficient. The physician must also say whether it results from autoimmune mechanisms, five (or perhaps six) specific enzymatic defects in thyroid hormone synthesis, iodine deficiency or excess, antithyroid substances in food or drugs, thyroidectomy or lack of thyrotrophin. The presence, in the blood of patients with Graves' disease, of a thyroid-activator, first announced by Adams and Purves, has now been confirmed. This mate-

rial has certain characteristics which distinguish it from the ordinary pituitary gonadotrophin, and there is suggestive evidence that this substance may be produced in some site other than the pituitary, although no alternative source has been established.

Attempts to lower serum lipid levels by thyroid hormone analogues have been successful, although complete dissociation from thyroid metabolic activity has not been established. The perplexing problem of parathyroid, pituitary and pancreatic islet adenomatosis and its association with peptic ulcer has been much written about. Zollinger's contention that the Zollinger-Ellison syndrome is not a part of the syndrome of endocrine adenomatosis seems well founded, in view of the fact that in his syndrome 50% of the islet cell tumors are malignant. One of the most gratifying developments in endocrine diagnosis is the demonstration that pheochromocytomas or paragangliomas can be localized preoperatively by the urinary catecholamine pattern. Moving on to the adrenal cortex, the most striking news is the role of aldosterone in malignant hypertension. It is now clear that the kidney itself elaborates a humor which stimulates aldosterone to act on renal tubular transport of salt. This implies a sort of "Operation Bootstrap" by which the kidney can enlist the adrenal cortex to aid it in conserving sodium. Why the high aldosterone secretion rates in cirrhosis and congestive failure are not similarly associated with hypertension is not yet understood.

The ever-increasing reports of pituitary tumors in patients who have undergone adrenalectomy for Cushing's disease both contribute to our knowledge of the pathogenesis of this condition and cast doubt upon adrenalectomy as the best method of treatment. Variants of the classic pattern of virilizing adrenocortical hyperplasia now being reported contribute considerably to our knowledge of the enzymatic methods of adrenal cortical steroid hydroxylation. The efficacy of o,p' DDD, introduced by the late Delbert Bergenstal for the control of metastasizing adrenocortical tumors, has now been firmly established. Since the adrenal cortex, kidney and gonad arise from a common embryonic source, it is not surprising, that anomalies of one are sometimes associated with anomalies of another of these organs. Renal anomalies are being reported with increasing fre-

quency in gonadal dysgenesis and in Klinefelter's syndrome.

The most fundamental change in our knowledge of disorders of sex differentiation stems from the now classic work of Murray Barr of London, Ontario, and of C. E. Ford and his group at Harwell, England. Chromatin counts of desquamated cells, and now careful counts of the chromosomes themselves, have turned up the most surprising anomalies. We had barely become accustomed to the idea that the normal chromosome number is 46, while that in most cases of gonadal dysgenesis is 45 and that in chromatin-positive Klinefelter's syndrome 47, when we are overwhelmed with the news of counts up to 69 chromosomes per cell! Investigation of disorders of sex differentiation has been greatly stimulated by these discoveries. It will be noted that an unprecedented number of new cases of true hermaphrodism are described in this volume. Gonadal neoplasms in patients with disorders of sex differentiation, particularly testicular feminization (male pseudohermaphrodism), are being recognized as a serious problem calling for prophylactic gonadectomy. Gonadal hormones for the treatment of neoplastic diseases are being improved. Published data indicate that existing compounds produce regressions in 20-40% of the cases of advanced breast cancer. Published data also confirm Blackburn and Childs' report that 2-α-methyldihydrotestosterone propionate is at least as effective as testosterone propionate, possibly more so, and distinctly less virilizing. Fluoxymesterone has not lived up to its earlier promise of being more effective than testosterone propionate, although it is only slightly less so and has the advantage of working when taken by mouth. Segaloff and his group have announced that δ-1-testololactone induces regressions in 30% of cases of advanced breast cancer. The amazing feature of this report is that δ-1-testololactone is devoid of hormonal activity. These data require confirmation in larger series. Segaloff and Steelman, and Albert and his group at the Mayo Clinic, and others have succeeded in separating the various urinary and pituitary gonadotrophins. An immune assay for gonadotrophin has also been described.

Not all the news in 1960 was good. It is with great personal regret that I record the deaths of Axel Westman, Karl Paschkis and Joseph W. Jailer. All of them were prolific and precise contributors to our knowledge of endocrinology.

both clinical and experimental, fine teachers and fine gentlemen.

I am happy at this point to acknowledge my indebtedness to the Year Book Medical Publishers for continued cooperation, courtesy and consideration and to Miss Frances Wetherhold and Mrs. Gertrude Leary for expert editorial and secretarial aid. I am indebted to Drs. I. S. Edelman, Wallace V. Epstein, Francis Greenspan and Richard Havel for critical review of parts of the manuscript.

GILBERT S. GORDAN

ENDOCRINOLOGY IN SOVIET PERIODICALS, 1950–60

V. G. BARANOV, M.D., Member of the Academy of Medical Sciences of the USSR, L. L. LIEBERMAN, M.D., and A. M. RASKIN, M.D.

This review of Soviet scientific periodicals includes only some of the published works on endocrinology. The presentation is concise and incomplete because of the authors' desire to include as many publications of Soviet scientists as possible. Many of them are not well known to American readers. Being limited as to space, we could not include monographs.

The Thyroid Gland

V. I. Levenson (1) reported that autoradiographs made 30 and 60 minutes after intraperitoneal injection of I^{131} into rats showed activity in the form of rings over the epithelium and the marginal zone of intrafollicular colloid. In frozen sections which lacked colloid, a small amount of PBI^{131} was found in the epithelium. Radiochromatography of thyroid tissue after hydrolysis revealed that the activity of iodothyronines increased for 1 to 24 hours, whereas that of iodotyrosines decreased. Levenson postulated that the formation of iodinated proteins starts in epithelial cells and goes on in the colloid.

V. B. Zolotarevski and V. I. Levenson (2) showed the presence of ribonucleic acid in both epithelium and colloid of rats. Methylthiouracil increased, and desiccated thyroid decreased, the nucleic acid content of epithelium.

Ya. Kh. Turakulov (3) gave 100-200 mc. I^{131} to 48 patients with goiter 24 hours before operation and fractionated iodinated substances from the removed goiters. The total amount of iodine and its protein fraction were decreased in the nodular tissue of endemic goiters and in the colloid of cystic goiters. The proteolytic activity of nodules and the colloid also decreased. These changes varied in different nodules in multinodular goiters. Radiochromatography of butanol extracts of homogenated and hydrolyzed goiters revealed that in hypo- and euthyroid nodules the amount of iodides, mono-

iodotyrosine and diiodotyrosine increased at the expense of thyroxin.

Ya. Kh. Turakulov, V. M. Sorokin and R. K. Islambekov (4) determined plasma PBI and plasma and urine iodine fractions in 32 patients with thyrotoxicosis treated with I^{131}. Iodinated tyrosines and a considerable amount of triiodothyronine appeared in urine and plasma several days after administration of a therapeutic dose of I^{131}. The authors believe that iodinated tyrosines and much greater than normal amounts of triiodothyronine appear in blood as a result of disturbances in hormone formation in the thyroid caused by I^{131}. They think that these data support their earlier hypothesis that thyroxin synthesis proceeds from free mono- and diiodotyrosine and not from condensation of fully iodinated tyrosines in the molecule of thyroglobulin.

R. K. Islambekov (5) gave desiccated thyroid to rabbits for 70 days. One month after the last dose, morphologic changes in the thyroid were similar to those seen in Graves' disease. The I^{131} uptake curve in these animals rose sharply during the first hours and then fell gradually toward the end of the 24-hour period.

M. F. Merkulov (6) studied the distribution of S^{35} compounds in the thyroid gland of rats after intravenous injection of labeled thiourea in doses of 10 mg./kg. Sulfate accounted for 95% of the S^{35}; the other 5% was found in the form of protein. Radioautography 5 minutes to 72 hours after injection showed that protein-bound sulfuric compounds and labeled sulfate accumulated mainly in the intrafollicular colloid.

Yu. N. Eremin (7) studied the histologic picture and I^{131} uptake in rats fed different diets. In animals receiving less than 1.2 μg. iodine daily, the weight of the thyroid glands increased. In this group of animals a diet that was 54% fat reduced thyroid function and caused growth of connective tissue and edema and atrophy of the parenchyma of the glands. When fat constituted 5% of the diet, changes were less pronounced. The minimal changes were in animals whose diet was 27% fat.

Yu. I. Plotnikova (8) showed that a diet that contained 49 μg. iodine and was 3.5% protein lowered thyroid function and in some rats led to atrophy of the follicles. When the diet contained the same amount of protein but only 0.78 μg.

iodine, parenchymatous microfollicular goiter with nondifferentiated tissue developed and thyroid function decreased. When 32% of the diet was protein, goiter of a similar type developed, but the tissue was differentiated and thyroid function increased.

E. A. Loskutova and N. F. Nikolaenko (9) found that application to rats of strong interrupted sound and light stimuli decreased thyroid I^{131} uptake. The weight of thyroid glands and the height of the follicular epithelium did not change in rats of middle and old age and increased in immature animals. The stimuli intensified the influence of methylthiouracil on the weight of thyroid glands, height of the follicular epithelium and I^{131} uptake. The authors suggest that nervous factors which stimulate thyrotrophin production at the same time inhibit the function of thyroid, perhaps through nervous influences bypassing the hypophysis.

Yu. B. Skebel'skaia (10) proved that in rats ACTH (inactivated by the method of Li, Simpson and Evans) decreased the I^{131} uptake. Rats whose adrenocorticotrophic function was blocked by large doses of desoxycorticosterone responded to súrgical trauma by decreased I^{131} uptake. The author proposed that in stress the anterior hypophysis secretes, in addition to ACTH, a substance without adrenocorticotrophic properties but capable of suppressing the ability of the thyroid to accumulate iodine. This substance is contained as an admixture in commercial ACTH preparations. Caffein lessens the inhibitory influence of ACTH and stress on I^{131} uptake. The author's explanation is that excitation in the central nervous system by caffein causes the hypophysis to secrete increased amounts of thyrotrophin.

A. A. Voitkevich (11) investigated the influence of ACTH and cortisone on thyroid structure. After the administration of either substance, the thyroids of puppies revealed morphologic signs of increased secretory activity of varying degrees in different parts of the gland. Voitkevich observed intense transformation of single cells of thyroid epithelium and of the whole follicles into light islets of large parafollicular cells. Cortisone and especially ACTH promoted the differentiation and new formation of follicles in the thyroid.

L. L. Lieberman (12) showed that ventilation increased proportionally with elevation of the basal metabolic rate. Spirograms revealed arrhythmias in 26 of 43 thyrotoxic