THE YEAR BOOK *of*
ENDOCRINOLOGY

(1959-1960 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

Since the first YEAR BOOK devoted entirely to endocrinology appeared in 1950, many striking changes have occurred. Refined technics have made it possible to measure accurately microgram amounts of then-unknown substances. Single hormones have developed into families of molecules: witness the thyronines and tyrosines, the ACTH-MSH (melanocyte stimulating hormone)-adrenal growth factor complex, and the adrenal steroids. It may be salutary to remind ourselves that 10 years ago there was room for controversy as to whether the actions of the adrenal cortex could be explained by a single steroid. The burgeoning sciences of genetics and immunology are also strongly influencing endocrinology. Many endocrine disorders are familial, e.g., goitrous hypothyroidism, some of the disorders of sex differentiation, pheochromocytoma, congenital virilizing adrenocortical hyperplasia, hyperparathyroidism and endocrine adenomatosis, to mention just a few. The recognition of autoimmune antibodies in the blood of patients with chronic thyroiditis and myxedema has stimulated both immunology and thyroidology. Parallel discoveries are undoubtedly just around the corner for the other glands. Immune mechanisms have been used successfully to measure microamounts of pituitary hormones in blood and, while technically not free from pitfalls, may be expected to have similar usefulness for measurement of other hormones. Preliminary data for insulin are already available. Just beginning to make sense are the enzymatic actions of steroid hormones. In years gone by, many of us mixed up steroids and enzyme systems and reported crude effects, including an action of estrogen on dehydrogenases, but the amounts used and the crudeness of the methods permitted no extension of these observations to the living animal. The fine technics of Claude Villee were the first to clarify mechanisms by which estrogens might provide energy through their action on isocitric dehydrogenase to explain their well-known actions in vivo. These studies were further extended by Talalay, whose work suggested that estrogens might in fact act as coenzymes in a hydrogen transfer sys-

tem, though more recently Villee, whose report is abstracted in the chapter on The Reproductive System, has actually separated the estrogen-sensitive, soluble pyridine nucleotide transhydrogenase from the estradiol dehydrogenases in human placenta. It is apparent that we are much further along in understanding the actions of steroids than we were in 1950. A second example of a steroid-dependent enzyme system has been demonstrated by Lewis Engel. He reported (Conference on the Biologic Effects of Steroids, Vergennes, Vt., Sept. 27-Oct. 2, 1959) that corticosterone and hydrocortisone, in amounts so small as to approach those occurring naturally, in the presence of diphosphopyridine nucleotide stimulates glutamic dehydrogenase. Testosterone by itself is ineffective in this system but when added to corticosterone blocks the stimulating action. It is tempting to speculate that this may be the first demonstration of an enzymatic mechanism that would explain the anabolic effect of testosterone. The system is apparently specific for active corticosteroids, since the inert isomers are ineffective. The enzymology of thyroid hormone synthesis has also been clarified; still lacking is the enzyme which performs the important function of coupling the two tyrosine rings to produce thyroxin. The enzyme defects in thyroid hormone synthesis, like the enzyme defects of adrenocortical steroid synthesis, are found to have genetic implications, since they are familial.

Pinpointing of exact mechanisms is not limited to enzymology, genetics and immunology. The neuroanatomists and neurophysiologists have localized to millimeter areas the hypothalamic sites controlling the several pituitary hormone secretions. This is a long step toward demonstrating the mechanisms that coordinate the actions of the body's two great integrators—the nervous and endocrine systems. But the hypothalamus has no monopoly on endocrine control. The brilliant work of Gordon Farrell has localized to the pineal gland the elaboration of a lipid-soluble neurohumor that directly controls the release of aldosterone from the adrenal cortex.

It is no longer presumptuous to ask whether neoplasia of endocrine-sensitive organs may result from prolonged stimulus to these organs. The combination of chromophobe adenoma of the pituitary and hypogonadism was ascribed in the

past to crowding out of gonadotrophin by the adenoma. Now the question is being asked: Can the pituitary respond by the formation of an adenoma to long-standing gonadal deficiency? Furth has produced adenomas of the pituitary in mice by radioiodine-induced hypothyroidism. These tumors elaborate large amounts of thyrotrophin, which, incidentally, appears to be free of exophthalmos-producing factor. Evidence is lacking that chromophobe adenomas in hypogonadal people elaborate gonadotrophin. A similar situation is found, however, in parathyroid adenomas, which have been found rarely in patients with long-standing steatorrhea. Since steatorrhea can produce secondary hyperplasia of the parathyroid, considerable controversy has resulted from the suggestion that parathyroid adenomas in patients with steatorrhea may be more than coincidental.

The exact amino acid sequences have been worked out for a number of protein and peptide hormones. The beautiful work of Sanger was appropriately recognized by the award of the Nobel Prize (his lecture, delivered December 10, 1958, is abstracted in the chapter on Carbohydrate Metabolism). ACTH, melanocyte-stimulating hormone and the posterior pituitary hormones have also been characterized. Chemical modification of thyroxin has led to a number of thyroid analogs with divergent actions. In some, the action on the heart is increased, e.g., triiodothyronine, triac and tetrac, while in others it is minimized, e.g., triprop and dextrothyroxin. Minimization of myocardial action has led to the interesting observation that by giving thyroxin analogs, one can lower the serum cholesterol level without accelerating the heart rate. Similarly, androsterone, which has always been considered a weak metabolite of testosterone and, from the recent brilliant work of Seymour Lieberman, also of dehydroepiandrosterone, can in suitable circumstances lower the serum cholesterol level.

For 15 years it has been known that the synthetic goitrogens stimulate hyperplasia of the thyroid gland. In suitable strains of rodents, these agents can induce not only hyperplasia but tumors which infiltrate, metastasize and can be transplanted. Some of the goitrogenic compounds are given for other purposes, e.g., sulfonamides for infection. One, aminotriazole, is used as a weed killer. The Great Cranberry

Scare of 1959 resulted from the detection of aminotriazole in the berries. That it was found at all is a tribute to modern methods for the chemical detection of minute amounts of materials. Public Law 85-929, September 26, 1958 (85th Congress, H.R. 13254), intended to prevent adulteration of foods, prohibits the release of foods containing additives that are "found to induce cancer when ingested by man or animal." Certainly, none of us wishes carcinogens in our food. Goitrogens, however, are compounds that, when given in extremely large amounts for extremely long times to specifically susceptible strains of rodents produce cancers of the thyroid but, according to adequate actuarial information, do not do so in man. Furthermore, the amounts that could reasonably be ingested in cranberries are obviously insignificant. Greater amounts of naturally occurring goitrogens are ingested by people who eat turnips or soybeans (see Thyroid Gland). A similar situation is found in the use of stilbestrol to caponize cockerels or to fatten cattle. Again, detection of minute amounts of estrogen in the meat of caponettes or stilbestrol-treated beef is a tribute to modern chemical technics. Estrogens also occur naturally in foods, and in this case published information suffices to show that stilbestrol is *not* a carcinogen in man. In fact, the series published by Henneman and Wallach (J.A.M.A. 171:1637-1642, Nov. 21, 1959) and of Mustacchi and Gordan (A. Segaloff [ed.] *Breast Cancer* [St. Louis: C. V. Mosby Company, 1958], pp. 163-169) suggest that in human subjects stilbestrol may *prevent* cancer! Meanwhile, how many hundreds of thousands of women properly taking stilbestrol for good medical reasons have been scared out of their wits by headlines? Careful screening of insecticides by workers at the Food and Drug Administration has shown that the insecticide DDD causes atrophy of the adrenal cortex. The *o,p'* derivative has been found to be the most effective and least toxic, and the late Delbert Bergenstal of the National Cancer Institute found that it caused regressions of widespread adrenal cancer.

The studies of Daughaday and of Slaunwhite and Sandberg have clarified the important matter of the binding of cortisol (hydrocortisone) to serum proteins and its transport in the blood. The cortisol-binding protein to which it adheres six thousand times more strongly than to albumin has been

named transcortin. Kenneth Savard, the expert steroid chemist at the University of Miami, has suggested that a protein carrying cortisol might be called "cor-tote" and, if it binds so tightly, "cor-set." Cortisol binding is increased in pregnancy and after administration of estrogens and certain derivatives of 19-nortestosterone. High levels in the plasma, therefore, probably do not indicate increased adrenocortical function but rather increased binding protein, just as in the case of thyroid hormone binding and transport.

Perhaps the most important development in our knowledge of adrenocortical disease in the past few years is the tardy recognition that Cushing's disease (bilateral adrenocortical hyperfunction) is often associated with pituitary tumors. These have been recognized most commonly in patients whose Cushing's disease has been treated by bilateral adrenalectomy. Practically, this rediscovery leads us to wonder whether adrenalectomy is really the best treatment for Cushing's disease, not only because the pituitary tumors are apparently stimulated to grow by this operation but also because adrenalectomy produces Addison's disease and a lifetime demand for exogenous corticosteroids. Theoretically, this observation is a major confirmation of the pituitary origin of Cushing's disease and brings us full cycle to Harvey Cushing's interpretation in 1932. Except in rare cases in which the disease is so fulminating that the surgeon's hand is forced, it would appear that the therapy of Cushing's disease should be directed to the pituitary rather than the adrenal. This has long been my personal preference (Gordan and Lisser, *Endocrinology in Clinical Practice* [Chicago: Year Book Publishers, Inc., 1953], p. 158). A recent personal communication from Louis Soffer reports satisfactory control of Cushing's disease by pituitary irradiation, unilateral adrenalectomy, or a combination of both measures in 75% of his patients. A reservation in this matter is the diagnostic problem of ascertaining that the disease is due to bilateral adrenocortical hyperplasia and not to tumor, though I personally believe that this can usually be done by adequate clinical, chemical and roentgen studies. Another reservation is based on the demonstration by Swedish workers that transplantation of adrenal tissue in the thigh muscles at the time of bilateral adrenalectomy supplies adequate adrenal function.

Also from Sweden is the demonstration of one of the major disadvantages of induced Addison's disease. In the 1957-1958 epidemic of Asian influenza, 5 of the 10 deaths in the city of Malmö occurred in patients with adrenal insufficiency.

Murray Barr's epoch-making discovery of the chromatin blob on the nuclear border of cells from females, first applied to the elucidation of disorders of sex differentiation by Polani and his co-workers in 1954, is now used routinely. Until technics become simplified, it is not likely to be supplanted by the more elegant and definitive chromosome counts stemming from the beautiful work of C. E. Ford. Chromosome counts have important clinical implications since it now appears that the chromosomal pattern in chromatin-negative gonadal dysgenesis is XO rather than XY and in chromatin-positive Klinefelter's syndrome is XXY rather than XX. Mongolism is also associated with an abnormal chromosome which is not one of the sex chromosomes.

Finally, the careful clinical screening of androgen derivatives by the Cooperative Breast Group of the Cancer Chemotherapy National Service Center headed by Albert Segaloff has led to important preliminary data. Blackburn and Childs have presented carefully derived and conservatively interpreted data suggesting that 2-alpha-methyldihydrotestosterone, a weak androgen, may be equal to or better than testosterone propionate in the treatment of advanced breast cancer. Segaloff has found that delta-l-testololactone produces regressions similar in number to those obtained by testosterone propionate. What is particularly significant here is that delta-l-testololactone has no apparent endocrine activity. It is not androgenic; it does not inhibit gonadotrophin output. The other promising compound, 2-alpha-methyldihydrotestosterone, does not inhibit gonadotrophin secretion, either. Thus, the efficacy of androgen derivatives in the treatment of advanced breast cancer appears to be separable from their androgenicity and their ability to inhibit gonadotrophin secretion. These are, therefore, simply chemotherapeutic agents which suppress cancer by unknown means. The concept of hormone dependency of human breast cancer has been dealt a serious blow by these observations.

As in the past, I take pleasure in thanking the Year Book Publishers for a relationship which has been thoroughly

comfortable and rewarding to me. To them goes the credit for culling the great mass of medical journals and seeing that articles of endocrine significance reach me. To them also goes the credit for the superb job of publication to which we have become accustomed. I wish also to acknowledge my indebtedness to Miss Frances Wetherhold and Miss Dawnna Renfro for expert editorial and secretarial aid and to Drs. I. S. Edelman, Wallace V. Epstein and Francis Greenspan for critical review of parts of the manuscript.

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► While the exact nature of the hypothalamic neurohumors involved in pituitary secretion has not been established, it appears that neurohypophysial hormones may have similar effects. Since the neurohypophysis is anatomically an outpouching of the hypothalamus, this similarity is not surprising. As will be seen in the chapter The Adrenal Cortex, the neurohumor serotonin has a stimulatory action on that organ, which, incidentally, is also directly responsive to neurohypophysial hormones. Another neuroendocrine tissue, the adrenal medulla, like the hypothalamus and posterior pituitary gland, is responsive to reserpine (see the chapter The Adrenal Medulla).—Ed.

Further Study of an ACTH-Releasing Protein from Hypophysial Portal Vessel Plasma is presented by John C. Porter and H. W. Rumsfeld, Jr.[1] (Southwestern Med. School). Blood that accumulated in the sella area of dogs after removal of the pituitary was aspirated. The source of the blood was in part from the hypophysial portal vessels. The plasma was fractionated by the method of Cohn and hydrocortisone-treated intact rats were used to estimate ACTH-releasing activity.

The ACTH-releasing activity of portal vessel plasma is found in the protein fraction III_0. This fraction contains three major proteins with isoelectric points of pH 4.4, 5.1 and 6.6. Starch column electrophoresis showed that intermediate peak 2, or a component of this peak, was associated with the active substance. Moving boundary electrophoresis demonstrated a single component with a stipulated mobility midway between peaks 2 and 3.

The activity of fraction III_0 was destroyed by incubation with trypsin and pepsin and by reflux with 0.1N NaOH but was stable to reflux in 0.1N HCl. After dialysis against distilled water for 24 hours, ACTH-releasing activity was present in the dialysate.

The study indicates that the constituent in portal plasma responsible for ACTH release in the corticoid-treated rat can be dissociated from plasma proteins. The protein component described may carry a neurohumoral agent which increases rate of release of ACTH.

Neurohypophysial Hormones and Release of Gonadotrophins. Experiments have indicated that the hypothalamus

(1) Endocrinology 64:948-954, June, 1959.