CLINICAL ENDOCRINOLOGY

BY

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PREFACE

THIS book is written for the general physician and for those aspiring to become clinical endocrinologists. Stress has therefore been laid on the clinical features of endocrine diseases and diagnostic procedures and treatment have been described in some detail. To remind the reader of the debt we owe to the pioneers of the subject the historical aspects of each disease have been briefly described. As in other branches of medicine, a knowledge of physiology is, in the author's opinion, essential for the proper understanding of disordered function and for rational therapeutics, and therefore a brief account has been given of the actions of the various hormones. The anatomy of the endocrine glands has been purposely omitted because, although it is of advantage to be cognisant of the situation of these organs, this knowledge is acquired in one's preliminary studies and detailed information is more suitably obtained in textbooks of anatomy. The author has not been bold enough to include diabetes mellitus, for the reason that it is a separate branch of endocrinology and the province of physicians who devote themselves almost entirely to its study.

During the last two decades enormous strides have been made in our knowledge of endocrinology, largely through the work of the chemists and physiologists. There was a time within the memory of the author when endocrinology was the Cinderella of medicine, but now it encroaches on almost every branch and through the original investigations at the Mayo Clinic it has been shown to play an important part in diseases in which hitherto an endocrine factor had never been conceived. The result has been that almost over-night rheumatologists, ophthalmologists, dermatologists and a host of others have taken up the study of this complex subject. A vast literature has grown up, so that to keep pace with the publications relating even to only one gland is a task of some magnitude. As far as possible those authors who made the original observations have been quoted in this book, but, to avoid being cumbersome, a large number of investigators who have contributed to the subject have had to pass unmentioned, their place being taken by those who have written monographs or reviews.

The author expresses his thanks to Messrs. Butterworth & Co., Ltd., for kindly granting him permission to incorporate certain sections of his contribution to their publication " Medical Treatment; Principles and Their Application," edited by Dr. Geoffrey Evans. He also thanks Dr. Oliver Garrod for his suggestions and criticism of the chapter on Diabetes Insipidus and Mr. C. W. S. Taylor, B.Sc., A.R.I.C., of the Ciba Laboratories, Ltd., for obtaining for him certain references in respect of the chemistry of the steroid hormones. The author should record his indebtedness to that valuable book by Sir

Humphry Rolleston, " The Endocrine Organs in Health and Disease," which is a mine of historical information.

The bulk of the illustrations are photographs of the author's own cases and for others he is indebted to Dr. William Evans, Mr. M. A. Falconer, F.R.C.S., Dr. A. Shapiro and Dr. D. A. G. Galton and to his colleagues and erstwhile colleagues at St. Bartholomew's Hospital, namely, Sir Francis Fraser, Sir Thomas Dunhill, Mr. Geoffrey Keynes, F.R.C.S., Dr. C. F. Harris, Mr. Rupert Corbett, F.R.C.S., Mr. John Hosford, F.R.C.S., Mr. C. Naunton Morgan, F.R.C.S., Dr. E. F. Scowen, Dr. A. W. Franklin, Dr. I. G. Williams and Dr. V. C. Medvei. Thanks are due to Messrs. Butterworth & Co., Ltd., for permission to publish Figures 2 and 3, which appear in the author's article on Acromegaly in the *British Encyclopædia of Medical Practice*, 2nd Edition and Figure 21 from *Surgical Progress* 1952, to the F. A. Davis Company for Figure 37 from the author's article in *Cyclopedia of Medicine*, to the Editor of the *British Journal of Cancer* for permission to publish Figures 42 and 43, to the Editors of the *Proceedings of the Royal Society of Medicine* for Figures 10 and 25, to the Clarendon Press for Figures 11, 12 and 36, to Messrs. John Wright & Sons for Figure 45, and to the Photographic Department of the Luton and Dunstable Hospital for Plate II. Finally, it is a pleasure to record the author's indebtedness to Mr. N. K. Harrison, A.R.P.S., and his staff of the Photographic Department, St. Bartholomew's Hospital, for their long-continued and helpful co-operation.

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CHAPTER I

THE PITUITARY HORMONES[1]

THE ANTERIOR LOBE

THE effects of hypophysectomy and the administration of specific extracts of the anterior lobe of the pituitary gland have demonstrated that the anterior lobe controls by means of its secretions the function of nearly all the other endocrine glands. There are at present six different hormones that are known to be elaborated, namely, the growth hormone, the two gonadotrophic hormones (the follicle stimulating hormone and the luteinizing or interstitial cell stimulating hormone), the thyrotrophic hormone, the adrenocorticotrophic hormone and the lactogenic hormone. The secretion of certain hormones of the anterior lobe itself, however, appears to be kept in check by the hormones of those glands which are stimulated by its specific secretions. Evidence for this statement is found in the excessive excretion in the urine of the follicle stimulating gonadotrophin that occurs after castration and in its disappearance from the urine as a result of the administration of suitable doses of œstrogen. Similarly, thyroidectomy causes an increased production of thyrotrophic hormone which is diminished or abolished by the administration of thyroid hormone. There normally exists a delicate hormonal balance between the anterior lobe of the pituitary gland and the peripheral glands, so that excessive pituitary secretion and secondary hyperactivity of the peripheral glands are prevented.

THE GROWTH HORMONE

HISTORICAL NOTE

That the pituitary gland secreted a hormone concerned with growth was long suspected as a result of clinical observations; gigantism was connected with hyperactivity of the gland and dwarfism was observed to be sometimes associated with its destruction. In the experimental field Aschner (1909) demonstrated that removal of the pituitary gland from puppies caused arrest of growth and of development. This work was subsequently confirmed in the rat by Smith (1926) and by many other investigators. The proof of the existence of a growth hormone was supplied by Evans and Long (1921), who reported the experimental

[1] For references see page 557.

production of gigantism in rats by daily injections of extract of the anterior lobe of the pituitary gland over a prolonged period. The growth hormone (termed by H. M. Evans "somatotropin") was isolated in pure form by Li and Evans (1944). It is a protein, readily destroyed by pepsin and trypsin, with a molecular weight of 44,250 (Li, Evans and Simpson, 1945).

ACTIONS

Growth. The growth hormone causes gain in body weight through its direct action on the tissues and not through the mediation of other endocrine glands. Li and Evans (1948) injected pure growth hormone into adult female rats six days a week for 435 days and observed that growth continued during the whole period with no sign of lack of responsiveness. The average gain in weight was 289 g., compared with 57 g. in the control animals; the average body length of the experimental rats was 45·5 cm., of the control animals 40·9 cm. The weights of the liver, kidneys, heart, stomach and intestine of the injected rats per 100 g. of body weight remained practically the same as in the control animals.

The site of action of growth hormone in promoting growth of bone appears to be localized mainly in the proliferating zone of the epiphyseal cartilages (Freud, Levie and Kroon, 1939). After hypophysectomy the dimensions of the epiphyseal plate are reduced and a calcium barrier appears between the epiphysis and the diaphysis, preventing longitudinal growth. The administration of growth hormone leads to the rapid disappearance of this "closing membrane" and restores the dimensions of the cartilaginous plate by stimulating firstly chondrogenesis and later osteogenesis (Kibrick, Becks, Marx and Evans, 1941).

The growth promoting action of growth hormone is enhanced by the administration of thyroid hormone. Evans, Simpson and Pencharz (1939) observed that excessive growth produced by anterior pituitary extracts is not dependent on the presence of the thyroid gland, but is greater when the thyroid gland is present; that the promotion of the growth of thyroidectomized or thyroidectomized-hypophysectomized animals in excess of normal secured by anterior pituitary extracts is maximal only if the thyroid hormone is administered at the same time; and that thyroid hormone, which promotes the growth of thyroidectomized animals, does not have this effect when it is administered to thyroidectomized-hypophysectomized animals.

Metabolism. Growth hormone has been shown to cause nitrogen retention, a reduction in the level of the blood amino acids, an increase in the protein content and a decrease in the fat content of the carcass, an increase of the plasma alkaline phosphatase and an increase of the plasma inorganic phosphorus (Li and Evans, 1948). The hormone thus promotes the anabolism of protein. Nitrogen retention leads to

water retention and the water content of animals treated with growth hormone is significantly higher than in the control animals. This fluid retention accounts for the obese appearance of the animals treated with growth hormone. Young (1945) suggested that depletion of the fat stores was due to increased combustion of fat to supply the necessary energy for the building up of protein into muscle.

Evans, Meyer, Simpson and Reichert (1932) produced a diabetic state in dogs by the daily injection of a preparation of pituitary growth hormone for 8–9 months and the condition persisted for some weeks after the treatment was stopped. Young (1937) induced permanent diabetes in two dogs by the daily injection of anterior pituitary extract; the disorder differed from that caused by pancreatectomy in that the animals were able to survive without the administration of insulin. The islets of Langerhans showed disappearance of the cytoplasmic granules of the beta cells or extensive hyalinization of the cellular tissue (Richardson and Young, 1938). The factor responsible for these changes was known as the diabetogenic hormone. Young (1940), who had observed that diabetogenic preparations of the anterior lobe usually possessed growth promoting activity, suspected that the growth hormone and the diabetogenic principle might be identical, and later pure growth hormone was found to be diabetogenic in the cat and in the dog (Cotes, Reid and Young, 1949; Campbell, Davidson, Snair and Lei, 1950).

STANDARDIZATION

There are three methods for the standardization of growth hormone that may be employed.

(1) *Body growth of normal female rats.* The preparation to be assayed is injected intraperitoneally or subcutaneously into groups of at least 10 normal female rats, 5 to 6 months of age and weighing 220 to 280 g., for 20 days (17 injections). A unit is contained in that daily dose which causes a total increase of weight of 40 g. during this period (Evans, Uyei, Bartz and Simpson, 1938).

(2) *Body growth of hypophysectomized female rats.* Nine intraperitoneal injections of the preparation are given in 10 days to groups of 10 completely hypophysectomized female rats, 28 to 30 days of age at operation, starting 10 to 14 days after the operation. A unit is the daily dose which causes an average gain in weight of 10 g. (Evans, Uyei, Bartz and Simpson, 1938).

(3) *Tibia of hypophysectomized rats.* The preparation is injected intraperitoneally daily for 4 days into hypophysectomized female rats, 26 to 28 days of age at operation, starting 12 to 13 days after the operation. The animal is killed 24 hours after the last injection, the right tibia is split, stained with silver nitrate and sodium thiosulphate and the uncalcified portion of the epiphysis is measured. The initial

effects of growth hormone consist mainly of chondrogenesis and the resulting increase in the width of the cartilage is, within certain limits of dosage, proportional to the quantity of growth hormone injected (Evans, Simpson, Marx and Kibrick, 1943).

THE GONADOTROPHIC HORMONES

HISTORICAL NOTE

For many years before the demonstration in 1926 that the anterior lobe of the pituitary gland secreted a hormone essential for the normal development and function of the gonads this relationship was strongly suggested by clinical and laboratory observations. Experimentally it had been shown that hypophysectomy caused atrophy of the reproductive system (Crowe, Cushing and Homans, 1910; Aschner, 1912) and that the injection of anterior lobe extracts into normal female rats produced excessive luteinization of the ovaries (Evans and Long, 1922). The work of Smith (1926, 1927), of Zondek and Aschheim (1926) and later of other investigators demonstrated conclusively that the anterior lobe maintained and controlled the activity of the ovaries and testes. The administration of gonadotrophic extracts to immature rats or mice induced precocious sexual maturity, ovulation and the formation of corpora lutea.

Fluhmann (1929) and Zondek (1930) observed that women at the menopause or after castration contained in their blood and urine a gonadotrophic hormone the effect of which was predominantly follicle stimulating. Fevold, Hisaw and Leonard (1931) first separated pituitary gonadotrophic extracts into two fractions—one which caused maturation of the follicles of the ovaries and the other which brought about luteinization after the follicles had been stimulated to activity by the follicle stimulating fraction. These discoveries led to the conception that there were two gonadotrophic hormones—the follicle stimulating hormone and the luteinizing hormone. It was later shown that the follicle stimulating factor stimulated spermatogenesis in the male animal, but had little or no effect on the testicular interstitial tissue (Smith, Engle and Tyndale, 1934). Stimulation of the interstitial tissue was found to be brought about by the luteinizing substance and therefore the term interstitial cell stimulating hormone was applied to this hormone rather than luteinizing hormone because lutein tissue does not occur in the male organism.

The interstitial cell stimulating hormone was isolated in pure form from the anterior lobes of sheep and swine by Li, Simpson and Evans (1940) and by Shedlovsky and his colleagues (1940) independently. The hormone behaves as a homogeneous protein. The follicle stimulating hormone has not yet been isolated, but almost pure preparations