CLINICAL ENDOCRINOLOGY

For Practitioners and Students

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FOREWORD

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THERE has long been a need for a simple practical and authoritative book of the fascinating but complex subject of endocrinology which, from day to day, presents a bewildering array of new contributions to knowledge by the clinician, the experimental physiologist, the pathologist and those who work in many branches of chemistry. The transference of this new knowledge to everyday medical practice is no easy matter. There are, among many other problems, the difficulties of recognizing mild degrees of endocrine dysfunction and sub-clinical states, of assessing which gland is predominantly at fault in an organism which is governed by the complementary action of many glands, of discounting or appraising the significance of concomitant disease, and of prescribing appropriate treatment. The approach of the physician to the problems of endocrinology is therefore fundamentally different from that of the experimental physiologist, for the latter works in a relatively pure field and is largely concerned with factual observation. In the subject itself the student of today may find himself out of date tomorrow, even by the time he comes to take his higher examinations, whilst the established physician and the practitioner have neither time nor opportunity to study the specialized journals which deal with the subject. Indeed, the whole profession needs constantly to review its knowledge of facts which have become established.

In these circumstances, the very practical contribution of Dr. Martin and Dr. Hynes should be warmly welcomed as presenting a difficult subject in most readable form and in the best traditions of the Cambridge Medical School, with a logical approach to the many problems so that no dogmatic statement is made unless it is supported by physiological or pathological evidence.

LIONEL WHITBY.

Cambridge.

PREFACE TO THE SECOND EDITION

In the six years which have elapsed since publication of the first edition, endocrinology has continued to progress at an ever-increasing pace. Major advances, such as the introduction of cortisone, ACTH, and radioactive iodine into the clinical sphere, have taken place and amply confirmed the close relationship which exists between the research worker and clinician.

We have again endeavoured to present to practitioners and students a practical account of endocrine disease from the viewpoint of the general physician, together with the essential details of physiological and pathological background. The various advances made in many endocrine diseases and the shifting emphasis on their different aspects or components, has entailed considerable rewriting of most chapters. But we have retained, so far as possible, the general layout and sectional headings of the first edition. New illustrations have been added and the lists of references, which enable wider reading by post-graduate students, have been completely revised and brought up-to-date. In order to keep within the bounds of our subject, and to avoid embarking upon a textbook of general medicine, we have not given accounts of the numerous non-endocrine diseases for which cortisone or ACTH can be used in treatment.

Our thanks are due to the many friends and colleagues who assisted us in various ways with the first edition, and who have done so again.

In addition, we are indebted to Dr. Leslie Cole for Fig. 29, Dr. Raymond Greene for Figs. 8 and 9, Dr. James Bull for Figs. 1 and 12, and Dr. Paul Fourman for Fig. 6. Dr. M. Rosemary Miller has given us invaluable help with revision of the manuscript and, as before, we are most grateful for the unfailing help and courtesy of the Publishers.

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PREFACE

THE rapid advance and increasing complexity of endocrinology have created difficulties both for the practitioner using hormone therapy and for the student working for higher degrees. Text-books of physiology and general medicine can give only restricted accounts of endocrine disorders, and the papers and monographs of endocrinologists are too often marred by the over-enthusiasm of the pioneer. Our aim in this book has been to give a balanced account of endocrine disease, to refrain from any speculation, however intriguing, without a firm physiological or pathological basis, and to indicate the limitations of hormone therapy as clearly as its potentialities. We have written from the view-point of the general physician, who recognizes a clinical syndrome, then wishes to understand its physiological and pathological background, and is finally more concerned with efficient treatment than with the academic pleasure of diagnosis.

Endocrinological diagnosis and treatment are alike dependent on a proper understanding of endocrine inter-relationships and the mutual balance of hormones. No part of this book, therefore, can stand alone, but we have attempted to cover each subject in its appropriate section, and to indicate by cross-reference where a more detailed account of its different aspects will be found. The index has also been designed to this end.

Many reputable commercial firms give their proprietary hormone products names which unfortunately disguise their composition and nature. We have listed many such names, both British and American, in various tables, but there must be many omissions which in no way reflect unfavourably on those products not included.

It is impossible to write of endocrinology without encroaching on other specialities such as surgery, gynæcology, and neurology. We trust that we have emphasized in the text the cases in which we, like our readers, would enlist the help and advice of colleagues with specialized knowledge in these fields.

We have borne in mind the needs of practitioners and post-graduate students who may wish for more detailed knowledge of some particular disease than is contained in this book. We have therefore included bibliographies of easily-accessible reviews and key-papers in the English language, which will serve as a guide for wider reading. We have also referred to a number of papers of outstanding historical importance in the development of endocrinology, as well as to others which describe recent work.

We have deliberately excluded diabetes mellitus. The proper treatment of such an important and complex disease would have doubled the size of this book, and even then we could not have rivalled the excellence of the standard monographs on the subject.

Our thanks are due to many friends and colleagues who have assisted us in various ways. Sir Lionel Whitby and Dr. Leslie Cole gave us access to some of the cases depicted. Sir Gordon Gordon-Taylor and the Directors of the Bland Sutton Institute and X-Ray Department, Middlesex Hospital, kindly allowed us to reproduce Figs. 28 and 29. Figs. 21, 22 and 30 are used by kind permission of the Hospital for Sick Children, Great Ormond Street. Dr. F. R. Berridge has advised us on radiological matters, Mr. H. E. Tunnicliffe on the physiological sections, and Mr. S. J. Hopkins on pharmacy. We are greatly indebted to Mr. H. P. Hudson for the photographic work and to Mr. B. W. Gurner for the drawings. Finally, we are glad to acknowledge the unfailing help and advice of the Publishers.

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CONTENTS

CHAPTER		PAGE
I.	The Pituitary	1
II.	Fröhlich's Syndrome and Obesity	45
III.	The Pineal Body	53
IV.	The Thyroid Gland	55
V.	The Parathyroid Glands	116
VI.	The Thymus	133
VII.	The Adrenal Glands	136
VIII.	The Testes	177
IX.	The Ovary	198
X.	The Breast	228
XI.	Hormone Implantation	236

CHAPTER 1

THE PITUITARY

THE pituitary was so named by Vesalius (1514–1564), who believed that it transferred mucus (Lat. *pituita*) from the brain through the cribriform plate of the ethmoid into the nose. This view persisted until the eighteenth century and the pituitary aroused no especial interest until Pierre Marie described two cases of acromegaly in 1886 and, in 1888, stressed the associated pituitary enlargement. Thereafter knowledge of the gland steadily accumulated, and increasing realization of its importance led Langdon-Brown (1935) to describe it as "the leader of the endocrine orchestra". Since then, the isolation and investigation of its hormones has continued and still further demonstrated the astonishing scope and complexity of pituitary functions.

ANATOMY

The average pituitary is 10 mm. long, 13 mm. broad, 6 mm. in depth and weighs 0·6 g. It is larger in adult women than in men for the anterior lobe is bigger and may enlarge with successive pregnancies. The gland lies in the sella turcica covered by an extension of the dura—the diaphragma sellæ—through which its stalk passes just behind the optic chiasma. The anatomy of the pituitary is best understood from its embryological development. One part, the *pars nervosa*, is formed as an outgrowth from the floor of the third ventricle. A second outgrowth from the primitive stomodæum, Rathke's pouch, grows upwards and backwards towards the pars nervosa and envelops it from before backwards. The anterior wall of the pouch grows upwards and invests the tuber cinereum as the *pars tuberalis*, whilst the posterior wall of the pouch forms the *pars intermedia* adjacent to the pars nervosa. The vestigial lumen of Rathke's pouch makes the anatomical division between the anterior and posterior lobes, but physiologists prefer a functional separation into a *glandular* division or *Adenohypophysis*, and a *neural* division or *Neurohypophysis* derived from the two embryological components.

Adenohypophysis

The adenohypophysis or glandular division consists of the pars anterior or distalis, the pars tuberalis and the pars intermedia.

Pars anterior. The pars anterior forms the greater part of the pituitary gland, lying in front and to the sides of the pars nervosa.

Histologically it consists of cords of cells surrounding numerous blood sinusoids. Two specific types of cells are recognized:—

Chromophobe cells which are agranular and may be precursors or resting forms of the secreting chromophil cells. They probably secrete no hormones for chromophobe adenomata produce endocrine effects only by destruction of the active pituitary cells.

Chromophil cells are granular and are described as *acidophil* or *basophil* according to whether they stain with acid or basic dyes. The granules may represent the secretion of the cells for these revert to the chromophobe state if all their secretion is discharged. The acidophil cells comprise about one-third, and the basophil cells about one-sixth of the specific pituitary cells. Adenomata of these cells are associated with the various forms of hyperpituitarism (*vide infra*).

Pars tuberalis. The pars tuberalis is rarely found in man and consists histologically of vesicles lined by strands of basophil cells.

Pars intermedia. In man the pars intermedia consists only of a thin layer of palely basophilic cells. It often contains colloid cysts.

Neurohypophysis

The neural division or neurohypophysis consists of the pars nervosa or *infundibular process*, the pituitary stalk or *infundibular stem*, and the *median eminence* of the tuber cinereum. The median eminence and infundibular stem are together termed the *neural stalk*.

The neural stalk contains very numerous non-myelinated nerve fibres arising from the supra-optic, paraventricular and other hypothalamic nuclei which pass in the supraoptico-hypophysial tract to the neurohypophysis. It has been estimated that there are 100,000 fibres in the supraoptico-hypophysial tract alone. The only specialized cells in the neurohypophysis are *pituicytes* which are modified neuroglia of unknown significance. Hyaline (Herring) bodies are also present which were formerly thought to be cellular secretions from the pars intermedia, which migrated up the pituitary stalk to the hypothalamic centres or passed into the cerebrospinal fluid of the third ventricle. But, according to Harris (1951), the active substance in posterior pituitary extracts is formed in the tissues of the neurohypophysis, is liberated under direct control of the hypothalamo-hypophysial tract, and is passed directly into the bloodstream. The cells which form the active substances are unknown.

Blood Supply

The *adenohypophysis* or anterior pituitary has a blood supply from branches of the internal carotid and posterior communicating arteries which form a rich vascular plexus in the pars tuberalis. From this, large capillary loops enter the tissues of the median eminence and come into close contact with the nerve fibres of the

hypothalamo-hypophysial tract. The blood from the capillary loops then drains into large *portal trunks* which pass down the pituitary stalk and redistribute the blood into the capillaries and sinusoids of the anterior pituitary.

The significance of these vascular arrangements, whereby the blood is in close contact with the hypothalamic nerve endings above and the anterior pituitary below, is the constitution of a neuro-vascular link. Harris (1951) suggests that the hypothalamus thereby influences the secretion of the adenohypophysis by means of some chemotransmitter, liberated by the hypothalamic nerve endings into the capillary loops and carried, by the portal tracts, to the anterior pituitary or pars distalis.

The *neurohypophysis* has a separate blood supply derived from the inferior hypophysial arteries.

Nerve Supply

The *adenohypophysis* or glandular division is said to be supplied by branches from the cervical sympathetic chain, by parasympathetic fibres of the greater superficial petrosal branch of the facial nerve, and the hypothalamo-hypophysial tract. But section of these nervous pathways is compatible with normal function and few nerve fibres are found in the anterior lobe. On the other hand, the *neurohypophysis* or neural division is richly innervated by the supraoptico-hypophysial tract whose section is followed by atrophy of the part and the onset of diabetes insipidus.

THE PHYSIOLOGY OF THE ANTERIOR PITUITARY

Although there are only two varieties of functioning cell in the anterior pituitary it influences, directly or indirectly, growth, sexual development, carbohydrate and fat metabolism, thyroid and adreno-cortical functions, and the secretion of milk. Six distinct hormones are produced which have been isolated in pure, or nearly pure, states and which have well defined actions.

The fact that a principle with a definite pharmacological action can be extracted from an endocrine gland does not necessarily prove that a hormone with a similar action is secreted in the intact animal or man. The chemical isolation of the pituitary hormones requires drastic chemical processes which may well break down natural hormones and yield compounds with quite different actions. The only direct proof that a chemically produced fraction has the same action as a natural hormone, is the isolation of a similar principle from the blood. This has been achieved for the lactogenic principle and the two gonadotrophic hormones, and the others correct various defects induced by hypophysectomy so that they too probably correspond to natural hormones. It is also difficult to accept that two types of cell secrete six different hormones, while very little is

known as to how they enter the bloodstream. They may reach it as six different substances, or as different fractions of a large molecule which are selectively taken up by the appropriate receptive tissues.

The six anterior pituitary hormones are:—

(i) Growth hormone or somatotrophin, (ii) and (iii) the two gonadotrophic hormones—the follicle-stimulating or FSH and the luteinizing hormone or LH, (iv) lactogenic hormone, (v) thyrotrophin or thyroid-stimulating hormone or TSH, and (vi) adrenocorticotrophin or ACTH.

The control of the secretion of these hormones is not yet precisely known but both nervous and humoral mechanisms are involved in it.

By a series of beautiful experiments Harris (1951) demonstrated that the normal stimulus to anterior pituitary activity is derived from the hypothalamus. The portal system of vascular trunks (p. 3) appears to form a link between the hypothalamic nerve endings in the median eminence above and the adenohypophysis below. Harris suggests that the hypothalamus, which receives stimuli from the rest of the body, influences anterior pituitary secretions by liberating, at the hypothalamic nerve endings, chemotransmitters which are carried in the blood of the portal trunks to the anterior pituitary. A particularly striking experiment showed that pituitary grafts in hypophysectomized rats could attain normal function if placed adjacent to the tuber cinereum in the subarachnoid space, and thus gain revascularization from the portal trunks. If the grafts were placed at a distance away from the portal trunks, revascularization from other vessels was not followed by active function. There is, as yet, little evidence as to the means whereby the chemotransmission of stimuli between the hypothalamus and the adenohypophysis is effected. Nor is it known whether a specific transmitter-substance is needed for stimulation of secretion of each of the six anterior pituitary hormones.

Growth Hormone

It has become evident that the growth hormone (somatotrophin) exerts widespread metabolic effects in the body and that its name denotes but one of many functions.

The ultimate isolation of the hormone, finally achieved by Li, Evans and Simpson (1945), had been foreshadowed by the knowledge that hypophysectomy in young animals caused virtual cessation of skeletal and visceral growth and, conversely, that gigantism could be produced in young rats by intraperitoneal injection of crude anterior pituitary extract.

Growth effect. Growth hormone will restore bone growth in a young animal after hypophysectomy by causing disappearance of the calcium barrier, or "closing membrane", which arises between the epiphyses and diaphyses of a long bone after pituitary extirpation.

Active chondrogenesis and osteogenesis are restored and the bone resumes longitudinal growth. In intact young animals the administration of growth hormone results in accelerated growth, and giant forms with visceral hypertrophy may be produced. Growth hormone is ineffective without the synergistic aid of other hormones; thus a thyroidectomized animal will not respond to it unless thyroid hormone is also supplied. Insulin is also necessary for the full action of growth hormone, but Salter and Best (1953) have recently shown that protamine zinc insulin and a high carbohydrate diet will induce some growth in hypophysectomized rats thus deprived of growth hormone.

Metabolic effects. These are widespread and at present incompletely understood. It is, however, clear that growth hormone causes depression of the breakdown of protein and carbohydrate, and an increase in the oxidation of fat. It also causes a diminished sensitivity to insulin but, at the same time, probably stimulates growth of both α and β pancreatic islet cells and enhances the insulin content of the gland. Prolonged administration in susceptible animals leads to diabetes from exhaustion atrophy of the insulin-secreting islet cells. These effects were formerly known as the diabetogenic effect of the anterior pituitary, but have since been linked with the growth hormone. According to Young (1945), the action of growth hormone depends, at least in part, on the ability of the pancreas to secrete extra insulin. If it can do so, then growth results but, if not, diabetes is produced.

Gonadotrophic Hormones

Deficiency of the anterior lobe of the pituitary in man, and hypophysectomy in animals, may be followed by atrophy of the gonads and loss of sexual function. Two pituitary hormones have been separated, one controlling the production of gametocytes, and the other the secretion of sex hormones. They exert analogous effects in both sexes but are usually named in accordance with their actions on the ovaries. They are the *follicle-stimulating hormone* (FSH) and the *luteinizing hormone* (LH).

The follicle-stimulating hormone initiates the activity of the gonads at puberty and maintains the production of ova and spermatozoa during the reproductive period of life. In the female it stimulates ripening of the Graafian follicles and the production of œstradiol, thus bringing an animal on heat.

The luteinizing hormone controls the second half of the ovarian cycle. Under its influence the follicles develop into corpora lutea after ovulation; the secretion of œstrogens is inhibited, and the uterus undergoes the changes of pregnancy or pseudopregnancy.

In the male, LH stimulates the interstitial cells of the testes to secrete testosterone. Although the pituitary of either sex secretes

both gonadotrophic hormones their relative amounts differ. In the male, enough LH is produced to maintain the interstitial cells of the testis but, in the female, a higher output is needed for the formation of corpora lutea which produce progesterone (p. 203).

The secretion of the gonadotrophic hormones is under nervous control. Thus the rabbit does not ovulate until stimulated by coitus; the necessary reflexes passing to the hypothalamus and thence by the neurovascular link to the anterior pituitary. In other animals the breeding season begins when days lengthen naturally or when winter nights are shortened by artificial lighting. Since the reflex commences in the retina, blind animals cannot breed.

Gonadal influence on the pituitary. Castration or spaying is followed by hyperplasia of the basophil cells of the anterior pituitary which secrete the gonadotrophins. Some of the cells become so distended with collagenous material that they resemble signet rings (*castration cells*). The output of gonadotrophins is greatly increased as the pituitary vainly attempts to stimulate the lost gonads and restore the normal output of sex hormones. Conversely, the prolonged administration of œstrogens or androgens may inhibit the secretion of gonadotrophins and thus produce gonadal atrophy. The high œstrogen level of pregnancy reduces the pituitary output of gonadotrophin (p. 210) and ovulation consequently ceases. The pituitary maintains the proper level of sex hormones in the blood of normal animals. A fall in the sex hormone level causes an increased pituitary output of gonadotrophins which stimulates the gonads to greater activity; a rise in the sex hormone concentration causes the reverse effects.

Non-pituitary Gonadotrophins

Many effects of pituitary gonadotrophins are imitated by hormones secreted by the placenta in pregnant women and horses. The human placental hormone, *chorionic gonadotrophin*, is excreted in the urine, but the *equine gonadotrophin* of pregnant mares can only be obtained in useful quantities from the serum.

Chorionic gonadotrophin. Human chorionic gonadotrophin can be detected in the urine as early as the sixteenth day after fertilization. The amount increases rapidly to a maximum in the eighth week of pregnancy and then falls, but the hormone persists in the urine until separation of the placenta during labour or abortion. Chorionic gonadotrophin has a similar action to pituitary LH. Injections of it into *males* stimulate the interstitial cells of the testis to secrete a greatly increased amount of testosterone. The sexual organs undergo hypertrophy as a result and attain adult size in immature animals, but spermatogenesis is not initiated. Chorionic gonadotrophin may be used therapeutically for undescended testes in boys (p. 189). In *women* injections of chorionic gonadotrophin

stimulate further maturation of the Graafian follicles after ovulation, with the formation of corpora lutea. The normal function of the hormone is probably to maintain the corpus luteum during pregnancy (p. 210). The *Aschheim-Zondek* and *Friedman* pregnancy tests depend upon the presence of chorionic gonadotrophin in pregnancy urine. Injections of the urine into immature female mice or into continent female rabbits (which do not normally ovulate except after coitus) cause ovulation and the appearance of corpora lutea.

The effect of chorionic gonadotrophin is greatly augmented if gonadotrophic extracts of the pituitary are included in the injection. Commercial preparations of the combined hormones are available (Table II, p. 36). Large amounts of chorionic gonadotrophins are present in the urine of patients with chorionepithelioma or hydatidiform mole. A similar hormone is excreted in the urine of patients with teratomata or other malignant tumours of the testis. The assay of the hormone aids the diagnosis, and control of treatment (p. 192).

Equine gonadotrophins. Pregnant ponies secrete more equine gonadotrophin than other horses; the maximum concentration in their serum at about the tenth week of pregnancy is 200–400 I.U. per ml.

Injections of equine gonadotrophin combine the effects of FSH and LH pituitary hormones and can therefore maintain the gonads of hypophysectomized animals. Equine gonadotrophin is not excreted in the urine so that a therapeutic injection probably exerts a more prolonged effect than chorionic gonadotrophin. Repeated injections of either chorionic or equine gonadotrophin become gradually less effective in animals owing to antihormone production (p. 11), and a similar phenomenon may limit their use in man.

Assay. Gonadotrophins are assayed by comparing their effects with that of an international standard preparation of the same hormone. The international unit (I.U.) of *chorionic gonadotrophin* is defined as having the same activity as 0·1 mg. of the standard preparation, as judged by the cornification of the vaginal epithelium of the immature rat. The international unit of *equine gonadotrophin* has the same activity as 0·25 mg. of the corresponding standard preparation.

The Lactogenic Hormone

The influence of the pituitary upon lactation is clinically evident. Thus complete failure of lactation is a feature of post-partum Simmonds's disease (p. 32) whereas, in acromegaly, lactation may be prolonged in women for as long as five years after parturition, and male giants have secreted milk under the stimulus of hyperpituitarism. Lactation in animals ceases if the pituitary is extirpated.

Prolactin, the pituitary hormone controlling lactation, has been isolated in the chemically pure state. Injections of it have little

or no effect on the resting breast, but they initiate the secretion of milk in mammary glands already "prepared" by œstrogens and progesterone (p. 229). Prolactin acts directly upon the breast alveoli, and injection into one duct will only produce an effect in the associated alveoli of it. The secretion of prolactin is stimulated by suckling by means of a reflex passing *via* the hypothalamus to the anterior pituitary. Prolactin is also closely concerned with other hormones in the process of lactation; it also has some gonadotrophic action in that it stimulates the corpus luteum to produce progesterone. Growth hormone is probably concerned in formation of the constituents of milk, and normal thyroid function is necessary for the maintenance of lactation.

Assay. This is based upon the fact that prolactin stimulates the growth of the crop-gland in pigeons. The test-material is injected intramuscularly or intracutaneously over the gland and the effect is compared with that of a standard preparation. An *international unit* is the specific activity of 0·1 mg. of the standard preparation and is practically equal to the original Riddle unit.

The Thyrotrophic Hormone

Hypophysectomy in animals and Simmonds's disease in man is followed by atrophy of the thyroid. The thyrotrophic or thyroid-stimulating hormone (TSH) raises the basal metabolic rate and causes hyperplasia of the thyroid epithelium in man and animals. But injections have no effect in cases of spontaneous myxœdema as the thyroid gland is atrophic and cannot respond. Injection into animals cause thyroid hyperplasia, increased basal metabolism, and exophthalmos. These quasi-thyrotoxic manifestations diminish as antihormones develop (p. 11) although exophthalmos may persist. The eye changes appear not to be mediated by the thyroid for, in guinea-pigs, exophthalmos can be more readily produced by injections of TSH if the animal is thyroidectomized (Friedgood, 1941). The hormone acts directly upon the thyroid gland and may do so *in vitro* on slices of thyroid tissue which undergo epithelial hyperplasia. The secretion of TSH is inversely controlled by the level of thyroid hormone circulating in the blood; hypothyroidism stimulates the secretion and hyperthyroidism depresses it.

Assay. There is no standard method for the assay of TSH. All those in common use depend upon the production of epithelial hyperplasia in, or increase in weight of, the thyroid gland after injection into guinea-pigs.

The Adrenocorticotrophic Hormone

The close relationship existing between the anterior pituitary and the adrenal cortex is shown by Cushing's disease (p. 25) associated with a basophil adenoma of the pituitary, and by Cushing's syndrome