Clinical Endocrinology for Surgeons

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PREFACE

Clinical Endocrinology has made astonishing progress in the past two decades, and surgeons are becoming involved increasingly in all its aspects. It is one of the many fields of medicine in which physicians and surgeons are drawing close together and making their own contributions to the joint management of individual patients. This unity of the medical and surgical aspects of endocrinology has not received proper acknowledgement in the standard textbooks. Those on surgery discuss the endocrine glands at length, but do not treat them as parts of an integrated system or supply the surgeon with an adequate account of the medical features. Medical and endocrinological works, on the other hand, tend to dismiss the surgical aspects or to deal with them in a cursory fashion. We have attempted to provide here a systematic account of clinical endocrinology in which the essential unity of the endocrine system is emphasized and in which both medical and surgical aspects are treated together.

We hope that the book will be of use to young surgeons who are studying for higher degrees and diplomas, to established surgeons who encounter unfamiliar problems in endocrinology and to physicians who wish to know more about the surgical aspects of their clinical problems.

We make no apology for introducing much elementary chemistry, physiology and pathology, for patients cannot be investigated and treated in a rational manner unless these aspects of the subject are understood, at least in principle.

The amount of space which we have devoted to each subject depends not only on its clinical importance but also on the adequacy with which it is treated elsewhere and on the urgency with which practical guidance may be required. Thus, diseases of the thyroid, which concern the surgeon very frequently, are discussed at considerable length, while anomalies of sexual development, which are rare, are also described in some detail because knowledge of the subject has developed rapidly in recent years and has not yet been synthesized and incorporated in the surgical literature. Again, the general account of diabetes mellitus is very brief, but the treatment of diabetes (and particularly of diabetic coma) in relation to surgical operations is described in detail, for a competent physician may not always be available in an emergency. Short descriptions of most surgical operations on the endocrine glands are provided, but detailed accounts of operative technique must be sought elsewhere.

The book is divided into three parts. Part I deals with the anterior pituitary and its target glands and contains two chapters which are intended to help the understanding of the great interdependence of these parts of the endocrine system. Chapter 2 on the steroid hormones serves as an introduction to the adrenal cortex and the gonads, while Chapter 6 on steroid hormone therapy provides a link between these glands, on the one hand, and general surgery, on the other. Part II deals with the other major endocrine glands which are not, so far as is known, dependent on the anterior pituitary or on any other gland. Part III is unusual in that it provides a discussion of the endocrine aspects of many problems in general surgery. It presupposes a working knowledge of the material in the first two parts of the book.

The " further reading and references " listed at the end of each chapter represents the papers and books which we have found most helpful in our own practice and in the preparation of this book and gives the sources of the numerical and other data which we have quoted. The lists are selective rather than comprehensive.

Wherever possible we have referred to our own experience and to that of our colleagues, who have been very generous in providing us with analyses of their material and in criticizing our early typescript. To a large extent, therefore, the book represents the work and views of the Belfast medical school as a whole, although we accept responsibility for all that we have written.

We are particularly grateful to three colleagues who have helped with the actual writing of the book. Dr. Mary McGeown wrote Chapter 10 and graciously accepted our editing to bring the arrangement into line with that of the rest of the text. Dr. M. T. Harrison (now lecturer in medicine in the University of Glasgow) and Dr. E. B. Dowdle (now senior lecturer in the Department of Medicine in the University of Capetown) wrote the first drafts of parts of Chapters 15 and 17 respectively and allowed us to expand them.

Many others have helped in different ways, and we are very grateful to all of them. Professor J. H. Biggart allowed us to draw on the pathological material in his department, and members of his staff (whose help is acknowledged below and in the text) analysed some of it for us. Mr. D. W. Neill and Dr. R. Chenneour gave much valuable advice about clinical biochemistry and allowed us to quote data from their laboratories. The elegant diagrams and illustrations of our artist, Mr. G. A. Smith, form an important part of the book. Mr. R. Wood and his assistants provided prints of these and most of the clinical photographs, and were most cooperative and patient. Mr. J. H. Restrick, Mr. G. McIlhagger, Mr. W. Black and their staff gave advice on pharmaceutical matters. Miss J. Webster and her staff helped us greatly with the bibliography. We have received skilful secretarial assistance throughout the preparation of the book from Mrs. H. N. Read and Miss M. M. Scott. The latter has undertaken the major share with devotion and untiring care. Mr. K. F. Kyle kindly assisted us in reading the proofs. Several colleagues and authors have generously loaned us clinical photographs or allowed us to reproduce figures. They are all acknowledged in the text.

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We are especially grateful to Professor H. W. Rodgers and Dr. J. A. Weaver, both of whom cheerfully shouldered disproportionate shares of the routine work of the departments of surgery and metabolism respectively in order to free us for writing. We thank Mr. H. C. Edwards for suggesting, nearly six years ago, that we should write this book and hope that he will not be unduly disappointed in the result.

CONTENTS

INTRODUCTION

One of the most remarkable things about the animal body is the way in which it maintains its integrity in a hostile world. It does so by means of a highly delicate and complex organization which is controlled mainly through the nervous and endocrine systems. The integrative action of the nervous system was recognized long ago by Sherrington. That of the endocrine system has become apparent only recently.

Endocrinology is a young branch of biological science and has, until recently, been concerned with classification rather than measurement and with biological rather than biochemical description. Now, however, it is approaching maturity and narrow hypotheses are giving place to broad conceptions. Most of the secretions of the endocrine glands have been identified, many can be estimated by chemical methods and some of them have been synthesized. The chemical processes involved in their biological effects are still, however, largely unknown. Formerly the individual endocrine glands and their disorders were considered in water-tight compartments. Today they are seen to be closely integrated and to influence most of the metabolic processes of the body in health and disease. The endocrine glands are involved not only in the diseases which we commonly regard as endocrine in nature but also in such common events as the response of the body to infection and trauma and the development of cancers of the breast and prostate. A few years ago the role of the surgeon in clinical endocrinology was that of performing a few standard operations, such as thyroidectomy, for the relief of endocrine disorders. Today the scope of such procedures is much greater, and surgeons are learning that endocrinological problems may arise when least expected in any of their patients.

ANATOMY OF THE ENDOCRINE SYSTEM

The endocrine system has three main divisions. The first consists of the anterior pituitary (the adenohypophysis) and the glands which it controls by means of its trophic hormones. These are the adrenal cortex, the gonads and the thyroid. The second comprises a group of glands which secrete in response to various stimuli, but which are not, apparently, under the direct control of the anterior pituitary or of any other gland. These are the posterior lobe of the pituitary (the neurohypophysis) and the adrenal medulla, both of which are in part under the direct control of the nervous system, the parathyroids and the islet cells of the pancreas. The third division is not usually considered to be part of the endocrine system proper.

It includes a number of organs which secrete hormones but which also have other specialized functions. Parts of the alimentary tract, for instance, elaborate hormones which help to control alimentary function, and most of the tissues of the body produce histamine.

Most endocrine glands, the adrenal cortex and the thyroid, for instance, are composed of secretory cellular epithelium, but two, the neurohypophysis and the adrenal medulla, are made up of neural tissue. Within the glands hormones are synthesized, stored and finally released. Facilities for storage are not great, however, except in the thyroid gland.

PHYSIOLOGY OF THE ENDOCRINE SYSTEM

The endocrine glands produce their effects by elaborating "internal secretions" (the term used by Claude Bernard) or "hormones" (so named by Starling from a Greek word meaning "to stimulate"), which are released into the circulation. Some glands, such as the thyroid, secrete one hormone only (or hormones with similar actions), while others, notably the adrenal cortex, secrete several with quite distinct functions:

Hormones vary greatly in the complexity of their chemical structures. Some, such as insulin and the trophic hormones of the anterior pituitary, have complex protein or polypeptide molecules, others, such as the steroids, are of intermediate complexity and some, such as adrenaline and thyroxine, are relatively simple.

The secretions of most, if not all, the endocrine glands are controlled by delicate "feed back" mechanisms whereby the production of a hormone is stimulated when its action is required and inhibited when the effect has been achieved. These mechanisms are of two main types. (1) The secretion of the trophic hormones of the anterior pituitary is governed by the hormones produced by their target glands. For example, a low concentration of cortisol in the blood stimulates the secretion of ACTH, while a high concentration inhibits it. (2) The secretions of the other glands are governed directly by the physical or chemical processes which they regulate. Thus, the secretion of antidiuretic hormone is controlled by the osmotic pressure of the blood, and the secretion of insulin is regulated by the blood glucose level. The first form of control has important clinical implications. It may be interfered with deliberately when, for instance, testicular function is depressed by the administration of oestrogen for the control of prostatic cancer, or inadvertently when adrenal failure is induced by the administration and subsequent withdrawal of cortisone.

Some hormones, such as adrenaline, circulate in the blood in a free state, while others, such as thyroxine, are bound to specific plasma proteins. Some again, such as cortisol, are partly bound and partly free. The hormones permeate most of the tissues of the body but influence only those which are capable of responding to them. The glands and organs which are influenced by hormones are called target glands and target organs or end-organs. The ability of the end-organ to respond to its specific stimulus and not to any other hormone is an essential feature of the endocrine system. Some hormones, such as the trophic hormones of the anterior pituitary, act only on one target gland or end-organ. Others have both specialized functions and more general actions. The sex hormones, for instance, influence specialized tissues such as the sex organs, but also have important actions on metabolic processes. Still others, such as growth hormone, thyroxine, insulin and cortisol, exert important effects on all the tissues of the body without subserving any specialized local functions.

Many hormones enhance or antagonize the effects of others, and much of the stability of the body is due to the physiological balancing of their synergistic or opposing actions. Thus, insulin, growth hormone, thyroxine, adrenaline, cortisol and glucagon all influence the metabolism of carbohydrate in different ways. In disease the effect of hormonal antagonism is seen in the development of diabetes mellitus as a complication of acromegaly or Cushing's syndrome and in the deterioration of diabetes if it is complicated by thyrotoxicosis. Conversely, destruction of the pituitary by disease, or its removal by hypophysectomy, leads to amelioration of the diabetic state.

The actions of some hormones, adrenaline, for instance, are immediately obvious, while others, such as insulin and vasopressin, exert their effects within minutes or hours. Some, thyroxine, for example, require some days before they produce measurable effects, and others, such as the sex hormones, influence processes which are measured in weeks. Growth hormone and the sex hormones exert a controlling influence over the growth and development of the body over a period of many years.

The fates of hormones after they have exerted their physiological effects differ considerably. Some are metabolized completely in the liver or other tissues, while others are partly metabolized and partly excreted in the urine, often in conjugated forms, together with their breakdown products.

For years the importance assigned to the anterior pituitary—"the leader of the endocrine orchestra"—has obscured the close relationship between the endocrine and the nervous systems. It is appreciated now that the hypothalamus, which is itself influenced by the higher nervous centres, exerts a close control over the anterior pituitary and therefore an indirect control over its target glands. The neurohypophysis and adrenal medulla are, as we have seen, under the direct control of the nervous system. Two glands only—the parathyroid and the islet cells of the pancreas—are not apparently under nervous control. Conversely, many hormones influence the functions of the nervous system. The feed-back control systems of the target glands of the anterior pituitary are operated partly by the actions of hormones on the hypothalamus. Thyroxine, cortisol and insulin influence profoundly the function of the nervous system as a whole.

DISORDERS OF THE ENDOCRINE GLANDS

Diseases of the endocrine system often cause dysfunction of one or more of its parts. Hormones may be secreted in excess, causing syndromes of glandular hyperfunction, or in deficient amounts, causing syndromes of hypofunction. The overactivity or underactivity of one gland may affect adversely the function of another gland. For instance, hyperfunctioning lesions of the adrenal cortex may cause amenorrhoea through its influence on the anterior pituitary, or diabetes mellitus because of the antagonism between cortisol and insulin. Long-standing thyroid failure may be followed by atrophy of the adrenal cortex and relative adrenal insufficiency.

Whereas most diseases of the endocrine glands result from too much or too little hormone production, some disorders may be due to a disorder in the metabolism or breakdown of a hormone. The gynaecomastia and hypogonadism found in hepatic cirrhosis is an example of this mechanism. Finally, endocrine glands are sometimes affected by disorders, such as tumours, which have no recognizable effect on their endocrine activity.

Hyperfunction of a gland is usually associated with hypertrophy, hyperplasia or neoplasia. The tumours may be benign adenomas or malignant carcinomas. It is uncertain whether these lesions constitute varying degrees of a continuous process or whether they are essentially different. Lesions in glands which are under the control of trophic hormones may reflect primary changes and activity in the anterior pituitary or even higher in the hypothalamus. Sometimes there is hyperfunction without any recognizable histological lesion. Occasionally signs of hyperfunction are present (hirsutism, for example) without there being any direct evidence of increased secretion of a gland. It is assumed, without much direct evidence, that in such cases there is an increased sensitivity of the target organ to a normal level of circulating hormone.

Hypofunction is usually caused by destruction of a gland by some pathological process such as haemorrhage, infarction or neoplasia, or by its surgical removal. More recently genetically determined enzyme deficiencies, resulting in defective hormone synthesis, have been recognized as causes of glandular failure. Such defects may cause goitres or congenital virilizing adrenal hyperplasia. Sometimes a gland is congenitally absent or hypoplastic and sometimes hypofunction is physiological. The gonads, for instance, function naturally only during the reproductive period. Diminished secretion by the anterior pituitary causes secondary hypofunction of the glands which depend on it. Occasionally glandular hypofunction may be apparent without there being any evidence of diminished secretion by the gland. Such a condition is believed to be due to end-organ insensitivity, as occurs in pseudohypoparathyroidism and possibly primordial dwarfism.

Abnormal function of the endocrine glands can be recognized clinically and by various radiographic and laboratory methods. The concentration of many hormones in body fluids can be determined by precise chemical methods, and new methods are being developed constantly. Doubtless effective methods will be developed eventually for them all. These are of great potential value, but much work remains to be done before the information which they yield can always be interpreted correctly.

ENDOCRINE THERAPY

Many endocrine disorders can be treated effectively. Hyperfunction can be abolished by surgical removal of tumours of overactive glands, or by the administration of hormones or other chemical substances which modify or depress their secretions. The effects of hypofunction can often be overcome by substitution therapy or by the injection of trophic hormones.

There are other diseases of the body, such as carcinoma of the breast or prostate, which are not primarily disorders of the endocrine glands, but in which hormones play an important role. These can be influenced profoundly by the administration of hormones or by the ablation of endocrine glands.

Hormones may be used therapeutically and for diagnostic purposes in a bewildering number of ways. The following list summarizes the most important applications.

1. The stimulation of a poorly functioning gland (e.g. the use of chorionic gonadotrophin for hypogonadism).
2. Replacement therapy for deficient endogenous hormone production (e.g. thyroxine in hypothyroidism).
3. Inhibition of the production of a hormone from another gland (e.g. cortisone inhibition of pituitary ACTH in the adrenogenital syndrome or stilboestrol inhibition of pituitary gonadotrophin in cancer of the prostate).
4. Diagnostic purposes (e.g. the use of ACTH in distinguishing between primary and secondary adrenocortical failure, or thyroxine in a therapeutic trial in suspected hypothyroidism).
5. Antagonism of the harmful effects of another hormone (e.g. the use of testosterone to counteract the catabolic effects of cortisone, or of glucagon in the treatment of insulin hypoglycaemia).

6. Specific pharmacological effect of the hormone (e.g. the use of cortisone in inflammatory and allergic diseases).

The following chapters deal systematically with all the aspects of clinical endocrinology which have been discussed briefly in this introduction.

FURTHER READING

General Articles

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PART I

THE ANTERIOR PITUITARY AND ITS TARGET GLANDS

CHAPTER 1
THE ANTERIOR PITUITARY

The pituitary gland has two main divisions, an anterior or glandular part (the adenohypophysis) and a posterior or neural part (the neurohypophysis). Both are connected directly to the hypothalamus (although in different ways) and are controlled by it. The anterior pituitary is of central importance in the endocrine system as a whole, for its trophic hormones control the functions of the adrenal cortices, the gonads and the thyroid gland, and its secretions also exert other widespread effects. The posterior pituitary has quite different functions and will be considered in Chapter 8.

The pituitary lies below the hypothalamus in the sella turcica or pituitary fossa of the sphenoidal bone. Its two divisions differ in development and structure as well as in function. The anterior pituitary arises from Rathke's pouch, an epithelial outgrowth from the oral cavity, and retains its epithelial structure. The posterior part is formed from a diverticulum in the floor of the third ventricle and is composed of nervous tissue. The two parts combine and, in the adult, are joined to the hypothalamus by the infundibulum or pituitary stalk. The anterior pituitary has two main divisions, the anterior lobe proper and the intermediate lobe. An extension of the anterior lobe (the tuberal part) passes upwards and envelops the stalk.

The stalk has two components, one vascular, connected with the adenohypophysis, the other neural, joined to the neurohypophysis. The vascular part, or hypophyseal portal system, arises as a plexus of capillaries within the median eminence of the hypothalamus. These coalesce into larger vessels which pass down the stalk and then divide again to form large sinusoids around the secretory cells of the gland.

HISTOLOGY OF ANTERIOR LOBE

Histologically the anterior lobe consists mainly of solid cords of secretory epithelial cells, surrounded by connective tissue and sinusoids. Three main morphological types can be distinguished with conventional stains, but with more refined methods such as the iron-periodic-acid Schiff (Iron-PAS) stain further subdivisions are possible. The cell types, their staining reactions, their approximate relative numbers and their probable functions are shown in Table I.1. The proportions vary with sex, age and the state of health. The different staining reactions probably represent not only different types of cell but also different phases of activity of the same cells. Some at least of the chromophobes, for instance, are probably chromophil cells in a resting phase.

TABLE I.1. *Cell types of anterior lobe of pituitary*

Conventional stains			Iron-PAS stain *			
Cell type	Colour of granules	Relative proportion (approx. %)†	Cell type	Colour of granules	Relative proportion (approx. %)*	Possible secretion
Chromophobe	Nil	50	Chromophobe	Nil	20	Resting phase
Chromophil						
Acidophil	Pink	40	α	Orange	50	GH ? Prolactin
Basophil	Blue	10	β	Red	14	ACTH TSH
			γ	Light blue	8	? actively secreting form of β and δ cells
			δ	Blue	8	FSH LH (ICSH)

* Rasmussen (1938). † Ezrin et al. (1958 and 1959).

Ectopic anterior pituitary tissue is found regularly in man, as an embryological vestige, along the original course of Rathke's pouch, that is in the posterior wall of the pharynx and in the sphenoid bone. This "accessory pituitary" consists mainly of chromophobe cells, but chromophils are sometimes found. It has no direct connection with the hypothalamus and is unlikely to be functional.

FUNCTIONS OF ANTERIOR PITUITARY

The anterior pituitary secretes six principal hormones:

I. Acting mainly on body tissues in general—
 1. Growth hormone (GH)

II. Acting mainly on target-glands—
 2. Adrenocorticotrophin (ACTH)
 Gonadotrophins—
 3. Follicle stimulating hormone (FSH) (Testis and Ovary)
 4. {Interstitial cell stimulating hormone (ICSH) (Testis)
 Luteinizing hormone (LH) (Ovary)
 5. Thyroid stimulating hormone (TSH)

III. Acting on specific body tissues and glands—
 6. Prolactin (Breast and Ovary)

There is also evidence that it may secrete two other hormones:

IV. Acting on specific body tissues—
   7. Haemopoietin (Haemopoietic tissue)
   8. Exophthalmos producing substance (EPS) (Orbital tissues)

The sites at which the hormones are produced are not yet certain, but it is likely that each type of cell will be found to have a specific secretion. A tentative scheme, based on the available evidence, is shown in Table 1.1.

CONTROL OF HORMONAL SECRETION

The hypothalamus controls the function of the anterior pituitary, probably by means of "neurohumours" which are secreted by the hypothalamic nuclei and carried in the blood, via the hypophyseal portal system, to the gland. The neurohumours have not yet been isolated, but are probably polypeptides. The hypothalamus itself is controlled by nervous influences from the higher centres of the brain, which may stimulate or depress it. The hormones of the target glands of the anterior pituitary also inhibit, by means of a sensitive mechanism, the secretion of trophic hormones when adequate stimulation of the glands has been achieved, but it is not certain whether their inhibitory effects are exerted on the hypothalamus or on the pituitary. Thus, a humoral stimulus from the hypothalamus causes the anterior pituitary to secrete TSH, and this in turn stimulates the production of thyroxine by the thyroid. When sufficient thyroxine has been secreted its concentration in the blood inhibits the hypothalamus (or the anterior pituitary) and the release of TSH. Conversely, when the concentration of thyroxine in the blood is low the hypothalamus is stimulated and TSH is liberated. There are similar "feed-back" relationships between the other trophic hormones and the products of their target glands.

ANTERIOR PITUITARY HORMONES

The anterior pituitary hormones are all proteins or polypeptides, and the structures of some, but not all, are known in detail. The physiological activity seems to reside in certain groupings of amino acids rather than in the whole molecules. These groupings may well be the same in all species, although the complete proteins from different animals vary considerably.

1. *Growth hormone* (*GH*, *somatotrophin*)

GH acts in various ways to promote the growth of the body. It stimulates the growth of the epiphyses, causing an increase in length of the cartilage bones. The closure of the epiphyses is controlled by other influences, some of them hormonal, and GH has no effect on the length of bones once the epiphyses have closed. GH causes all other tissues and organs of the body, including the other endocrine glands, to enlarge along with the bones. There is evidence that it stimulates the growth of some hormone-dependent tumours of the breast. The secretion of GH may be partially inhibited by the sex hormones.

GH influences several metabolic processes in the body. It promotes the anabolism of protein and the retention of nitrogen, potassium and phosphorus. These actions clearly facilitate growth. In addition, it mobilizes fat from the peripheral depots, promotes gluconeogenesis in the liver, inhibits the utilization of carbohydrate and causes the retention of sodium and water. GH antagonizes the actions of insulin on the tissues but is ineffective when insulin is totally absent.

GH is, to some extent, species-specific, and preparations from animals other than monkeys are ineffective in man. It is not yet generally available for therapeutic use.

2. *Adrenocorticotrophic hormone* (*corticotrophin, ACTH*)

ACTH promotes the growth of the adrenal cortices and stimulates the production of their hormones. It is a polypeptide, containing 39 amino acids, but shorter sequences have been shown to possess ACTH activity. Recently a polypeptide of 23 amino acids, with ACTH activity, has been synthesized.

ACTH has some unimportant actions other than those on the adrenal. These include slight melanocyte-stimulating activity and general effects on metabolism. Commercial preparations vary considerably in their activity. Refractoriness to potent batches may develop after a time when they are given subcutaneously or intramuscularly. This may be the result of local destruction in the tissues, for it does not occur when ACTH is injected intravenously. ACTH will be discussed more fully in Chapter 3.

3 *and* 4. *Gonadotrophins*

The gonadotrophins, which govern the growth and function of the ovaries and testes, are the same in both sexes. Their molecules are complex glycoproteins. It is usual and convenient to describe two principal gonadotrophins, but there is evidence that there may be only one human pituitary gonadotrophin (HPG) with two types of action. The first (follicle stimulating hormone, FSH) acts mainly on the ovarian follicle in the female and on the germinal epithelium in the male. The second has different names in the two sexes. It acts mainly on the corpus luteum in the female (luteinizing hormone, LH) and on the Leydig or interstitial cells in the male (interstitial cell stimulating hormone, ICSH). Prolactin is a subsidiary gonadotrophin in the female.

In the female the secretion of gonadotrophins starts shortly before puberty and continues into old age. Their secretion varies with the phases of the menstrual cycle and with pregnancy and lactation. In general, FSH and LH bear a reciprocal relationship to each other, so that when the secretion of one waxes that of the other wanes. After the menopause, when