INTRODUCTION TO CLINICAL ENDOCRINOLOGY

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PREFACE

I HAVE attempted to present clinical endocrinology in terms of applied physiology. For this reason the book contains more information on hormones than on endocrine glands and only scant mention of pathological processes not accompanied by disorders of function. In aiming at coherence and simplicity I have sacrificed full discussion of alternative views and omitted references to the literature; thereby failing to pay tribute to those whose discoveries have illuminated endocrinology. All these points are well covered in full textbooks of endocrinology, to which this work is an introduction. However, I have included a short reading list for those who wish to make a more comprehensive study of the subject.

The absence of illustrations is due partly to economic considerations and partly to my deliberate choice. Photographs show with dramatic clarity the grotesque end point of disease yet seldom portray fully the early clinical signs. This may give a visual bias against early diagnosis. Personally, I believe that the student will learn more from the careful examination of one patient than from an album of photographs.

It is a pleasure to record my gratitude to Dr. Russell Fraser and Dr. John Ellis for accepting the onerous task of correcting the manuscript, and for their most helpful criticism. I am indebted to Mrs. E. Scott for the low calcium diet printed in the appendix, and to Mrs. M. Stone for her help with the typescript. I would also liked to thank my publishers for their constant help, which has made my path smooth. Finally I am deeply grateful to my wife for her untiring work in all stages of the preparation of this book.

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CHAPTER I

GENERAL PRINCIPLES

CLINICAL endocrinology is not concerned solely with fat boys and bearded women; nor is it an esoteric cult based on the application of bizarre eponyms to apparently unrelated physical signs. As the endocrine system plays a large part both in health and in many types of disease the proper approach to the subject lies through a knowledge of physiology and general medicine which must be broadened to include certain aspects of gynaecology, neurology and paediatrics.

Until the beginning of the twentieth century the central nervous system was considered to be the sole co-ordinating mechanism of the body; the concept of chemical integration of the organism grew with the development of chemical physiology. The idea of a chemical messenger secreted by a cell to influence the working of some distant part of the body was crystallized by Bayliss and Starling (1902) when they introduced the word hormone (Greek: ὁρμάω — I stimulate). The synthesis and secretion of hormones is the primary function of the endocrine glands.

The endocrine glands are so called because their secretions are discharged directly into the blood stream. All these glands secrete their hormones into the systemic circulation, except for the pancreas, whose islets of Langerhans secrete into the portal system. A gland may be composed of cellular elements, like the thyroid, or of neural tissue, like the adrenal medulla. Within the gland the hormones are synthesized, stored and finally secreted. Some storage of hormone occurs in all glands but the thyroid is the only one with special storage space in the centre of each secretory unit. It is important to remember this property of storage, because it represents the difference between the rate of hormonal synthesis and secretion. Hence a high concentration of hormone in the gland does not indicate activity so much as inhibition of secretion with continued synthesis. Conversely, the immediate response to stimulation is a discharge of stored hormone prior to an increase in the rate of synthesis with the result that hormone concentration in the gland drops sharply.

Hormones are physiological substances, some being proteins or polypeptides, others steroid in nature. They provide a humoral mechanism for the regulation of biological processes, playing an important role in growth, maturation, reproduction and the maintenance of a constant

internal environment. In their mode of action they resemble chemical catalysts, exerting their influence not by the initiation of physiological mechanisms, but by regulating the rate at which the mechanism operates.

The exact nature of hormonal action is dependent on the characteristics of the hormone and the organ, or organs, on which it acts. Any tissue which is the site of action for a hormone is termed an end-organ. Some hormones act on one end-organ only, others have a general effect, as well as specific action on certain organs. In the first category are the trophic hormones of the anterior pituitary, each of which stimulates its specific endocrine gland and has no other action. They exert an indirect action on the body as a whole through the gland they stimulate. The second category is illustrated best by the sex hormones. For instance, testosterone produces marked growth of the seminal vesicle. This growth entails protein anabolism. At the same time the hormone stimulates the anabolism of protein throughout the body. Similarly oestrogens cause a marked retention of water in the uterus, and some retention of water in other tissues. Moreover the general effects of these two hormones are roughly similar, both causing retention of water and calcium, yet their effects on the sexual end-organs are directly opposed. This illustrates the concept that few hormones are completely specific by virtue of their intrinsic properties, but that specificity is conferred by the responsiveness of end-organs. This also applies to the hormones which have a wide effect on metabolism, such as thyroxine, growth hormone, and hydrocortisone. Thyroxine influences the metabolic rate, water balance, and vascular system of the body, its variety of actions depending on the reactivity of specific physiological mechanisms rather than specific organs.

The interaction of hormone and end-organs is of fundamental importance in clinical study, as disorders of function may arise from changes in the level of circulating hormone or the sensitivity of the end-organ to hormone action. The effect of hormone deficiency on an organ is imitated by a failure of that organ to respond to normal hormonal stimulation. For instance eunuchs have no beard because the testes are not functioning. But the healthy Red Indian male never grows a beard by virtue of his genetic constitution, yet his virility is unquestionable. Another example is provided by the difference in the clinical picture of thyrotoxicosis according to the age of the patient. In the elderly the disease commonly presents with cardiac manifestations, which do not occur in the young. The hormonal stimulus is the same in all age groups but the elderly heart reacts rapidly to a small increase in circulating hormone. Thus genetic, biochemical and age factors influence the interaction of one hormone and its end-organ.

In clinical medicine one observes the final result of this interaction. It is obvious that physical signs are not a direct indication of the rate of hormone secretion.

Now the various physiological factors governing hormone action have been described, the interdependence of the endocrine glands must be considered. The amount of hormone produced by any one gland is subject to controlling influences which finally integrate the whole system. These influences are of three main kinds. Firstly, the regulation of hormone secretion by the concentration of certain chemicals in the blood stream. Secondly, the control of activity by the anterior pituitary. Thirdly, the controlling influence of the hypothalamus correlating the endocrine and nervous systems.

The simplest type of regulating mechanism, analogous to the thermostatic control of a water heater, is shown by the parathyroid glands which appear to have no other governing process than the concentration of calcium in the blood stream. A more complex mechanism governs the posterior pituitary, in which hormone secretion is directly related to the osmotic pressure of the blood, but is also subject to nervous control through the hypothalamus, which may over-ride the primary homeostatic mechanism.

The anterior pituitary exerts an overall effect by the secretion of a number of trophic hormones, which govern the action of the glands they stimulate. Thyrotrophic hormone (T.S.H.) regulates the activity of the thyroid, and adrenocorticotrophin (A.C.T.H.) the activity of the adrenal cortex. There is a reciprocal relationship between the amount of trophic hormone released by the pituitary and the level of circulating hormone from the stimulated gland. In essence this 'feed-back' mechanism is similar to the homeostatic control of the glands already described. The action of a hormone in suppressing the pituitary appears to be limited to inhibition of its specific trophic hormone, hence administration of thyroxine will only suppress the output of thyrotrophic hormone. There are important clinical implications in this pituitary-target gland relationship. On the one hand, the administration, in non-endocrine disease, of large doses of cortisone suppresses the secretion of adrenocorticotrophic hormone, with consequent adrenal inactivity. Hence, abrupt cessation of treatment will leave the patient in a state of adrenal hypofunction, with all its attendant dangers. On the other hand, the mechanisms can be used deliberately as in the administration of oestrogen for the treatment of carcinoma of the prostate. The oestrogen inhibits the output of gonadotrophin, with resultant testicular atrophy. It acts, via the pituitary, as a medical castration. There is also a diagnostic use, particu-

larly in hypogonadism. If the disturbance is due to destruction of the gonad the low level of circulating sex hormone will give rise to an excessive secretion of gonadotrophins. However, gonadal atrophy, from failure of pituitary stimulus, will be associated with a very low level of gonadotrophin secretion. Assay of the excreted gonadotrophin enables the clinician to decide which type of hypogonadism is present.

The last link in endocrine integration lies between the hypothalamus and the pituitary. As this provides a connection between the higher cerebral centres, the autonomic system and the endocrine system, the link is of the greatest importance. Unfortunately its details remain obscure, and even its nature is in doubt. It is most probable that the hypothalamus has a regulating effect on the anterior lobe of the pituitary by some humoral mechanism; there is certainly no evidence for a neural connection. The regulating effect can be illustrated by the effect of the hypothalamus on sexual maturation. Experiments have shown that the pituitary synthesizes gonadotrophins some time before the onset of puberty. The release ot these hormones which set off puberal sex growth is due to a stimulus from the hypothalamus. It is not surprising that lesions of the hypothalamic area in humans are often associated with precocious or delayed puberty. There is also experimental evidence for hypothalamic regulation of the secretion of thyrotrophic and adrenocorticotrophic hormones. In the case of thyrotrophin the hypothalmus appears to alter the quantitative aspects of the pituitary-thyroid 'feed-back' mechanism. The level of circulating thyroid hormone required to suppress the pituitary activity is changed. If the pituitary-thyroid regulation is akin to the thermostat, then the hypothalamus acts like the control which adjusts the temperature at which the thermostat will operate.

Much has been said on the production and action of hormones, without a mention of their eventual fate. This is not because the subject is unimportant but rather because so little precise information is available. The blood level of a hormone is the balance between secretion and destruction, so that variation in the speed of destruction may influence profoundly the amount of available hormone. However, even the sites of destruction are not fully known. Whether or not a hormone is destroyed by the tissue on which it acts is still undecided. But it is clear that the liver inactivates many of the steroid hormones, and diseases of the liver may be associated with endocrine dysfunction, due to failue of hormone inactivation.

It is now possible to summarize these generalizations in terms of clinical endocrine disorders. All such conditions arise from some disturbance of the normal endocrine equilibrium. Primary endocrine disease can be

conceived as a failure at any point in the basic pattern of hormone production, destruction, and end-organ response. Hypothyroidism is due to failure of secretion by the thyroid either because it has been destroyed (primary myxoedema), or because its pituitary control has failed (pituitary hypothyroidism), or from selective failure of hormone synthesis (certain types of goitrous cretin). If, however, production of a hormone is normal, failure of destruction results in an excess of circulating hormone, as in cirrhosis of the liver which may be associated with gynaecomastia from excess oestrogen. Lastly the varying response of the end-organ to a given amount of hormone may determine the clinical picture. A rare, but interesting, example of this is pseudo-hypoparathyroidism, in which the body is completely unresponsive to its own or injected parathyroid hormone. The resultant tetany with low serum calcium is exactly similar to that occurring after removal of the parathyroids.

The situation is more complicated when a single pathological process causes more than one endocrine disturbance, as is seen commonly with lesions of the anterior pituitary. An acidophil adenoma producing an excess growth hormone will press on the rest of the gland so that secretion of other hormones is reduced. The interplay of various hormones may also lead to more than one disorder, thus evidence of adrenal hypofunction is common in myxoedema because the adrenal is affected by the lack of thyroid hormone. Correct diagnosis depends on a careful appraisal of such interactions, with the avoidance of such terms as 'pluriglandular disorder' which is merely a substitute for thought.

It is too easy to assume that primary endocrine disease is the cause of certain syndromes. Dwarfism will result from destruction of the pituitary in a child, but it does not follow that all dwarfs lack a pituitary. But this does not minimise the role of the endocrine system in various types of disease. The malnutrition of coeliac disease is associated with infantilism because pituitary function is depressed. Similarly lesions of bone arising in long standing renal failure are linked with parathyroid hyperplasia. It is important to keep endocrinology in the field of general medicine, and to realize how many diseases have an endocrine aspect, and how diseases of the glands masquerade as more general conditions.

CHAPTER II

THE HYPOTHALAMUS AND POSTERIOR PITUITARY

Anatomy and Physiology

There is every justification for a composite description of the hypothalamus and posterior pituitary for, although the two lobes of the pituitary are contiguous, they differ in origin, structure and function, while the posterior lobe is linked to the hypothalamus by form and function.

In embryo the posterior pituitary arises as a diverticulum passing downwards from the third ventricle. When fully formed the lobe consists of neural tissue which continues up the pituitary stalk to the hypothalamus forming one functional unit, the supra-optico-hypophyseal tract. The hypothalamus itself forms the basal portion of the diencephalon, lying in relation to the floor and lower part of the walls of the third ventricle. Anatomically speaking it comprises the optic chiasma, pituitary, tuber cinereum and corpora mamillaria. In physiological terms the latter two structures are usually called the hypothalamus.

The hypothalamus provides a connecting link between the cerebral cortex, whose stimuli it receives, and various homeostatic mechanisms, on which it exerts a regulatory effect. Its effects are mediated by neural pathways, particularly through the autonomic system, by the neuro-secretory mechanisms of the posterior pituitary, and by an influence on the anterior pituitary. There are no neural connections between the hypothalamus and the anterior pituitary, but there is a portal system of blood vessels which links the two structures. It is probable that this allows for some humoral mechanism by which the anterior pituitary is influenced by the hypothalamus.

Certain metabolic functions under the control of the hypothalamus are of considerable importance in endocrinology. Correlation of experimental work and human autopsy material has given some indication as to the anatomical localization of the controlling centres, but much of the physiology remains obscure. However the endocrine and metabolic aspects of hypothalamic function may be classified as follows:

(1) Regulation of energy balance

control of { sleep
body temperature
appetite.

(2) Regulation of sexual function.
(3) Influence on carbohydrate metabolism.
(4) Control of water balance.

The normal rhythm of sleep is controlled by centres in the lateral hypothalamus. Lesions of this area result in narcolepsy and other disturbances of sleep.

The maintenance of a normal body temperature despite varying environmental temperatures depends on centres in the tuber cinereum. Both heat production and heat loss are under their influence. Breakdown of this mechanism is followed by great variations from the normal body temperature. Acute lesions are often associated with hyperthermia, the body temperature rising to 106° or more.

The paraventricular nuclei exert a marked effect on the appetite for food. Destruction of these nuclei in experimental animals is followed immediately by a dramatic increase in appetite. The food intake in one day may be equal to the body weight. It follows that marked obesity is a common clinical feature of hypothalamic disease. Little is known of the normal control of appetite, but there are good grounds for assuming that the paraventricular nuclei play an important role.

The areas concerned with sex function are ill defined, and there does not seem to be any exact localization. The mamillary bodies appear to exert a controlling influence on the secretion of pituitary gonadotrophins. The anterior pituitary manufactures gonadotrophins prior to puberty, but the release of these hormones is dependent upon a stimulus from the hypothalamus which initiates puberty. Likewise the maintenance of a normal menstrual cycle is dependent on a complicated interplay of gonadotrophins, whose release is controlled by the hypothalamus. Consequently lesions in the area of the corpora mamillaria are associated with abnormalities in the age at which sexual development occurs; on the one hand, precocious puberty, and, on the other, delayed development or sexual infantilism. In adults gonadal atrophy can occur, but the most obvious sign is amenorrhoea.

Alteration in the body's sensitivity to insulin, due to the effect of the autonomic nervous system, may give rise to hypo- or hyper-glycaemia. Clinically this effect is usually transitory, in association with acute lesions. In very rare instances an insulin resistant hyperglycaemia becomes permanent.

The supra-optico-hypophyseal tract secretes two hormones, both recently identified and synthesized. The two hormones are very similar

in structure, both being polypeptides. The first, oxytocin, causes contraction of the uterus, although its role in human physiology is uncertain. The second, vasopressin, causes vasoconstriction and inhibits water diuresis. It is unfortunate that the name vasopressin is used because its normal physiological role is in the control of water balance rather than blood vessel tone. Antidiuretic hormone (A.D.H.) is a better name, as it represents the physiological action of the hormone. Secretion of A.D.H. is determined by impulses from the cerebral cortex, and by osmoreceptors in the hypothalamus. Hence variations in emotional state are associated with changes in the output of A.D.H. Strong emotions, such as fear, result in marked diminution of urine output. However, body water balance is controlled largely by the osmoreceptors. Intravenous infusion of hypertonic saline in the normal subject results in a decrease in urinary output. Loss of body water causes a rise in the osmotic pressure of the blood, which leads to an increased output of A.D.H. so that water loss via the kidney is diminished. Conversely a decrease in osmotic pressure inhibits A.D.H. secretion so that excess water is passed out through the kidneys. Diuresis after the ingestion of a large quantity of water is dependent on this mechanism. It has also been found that injection or inhalation of nicotine stimulates the secretion of A.D.H., providing a valuable test of hypothalamic function.

A.D.H. regulates water balance solely by acting on the distal tubules of the kidney. It is in this part of the kidney that water resorption occurs and the quantity resorbed is governed by the amount of circulating A.D.H. There is no evidence that A.D.H. has any other renal effect in the human; its action is related entirely to the conservation of water and has no direct effect on the excretion of electrolytes. Of course, an increase in urine volume by virtue of diminished water resorption will be accompanied by a fall in the urinary concentration of chloride and specific gravity, but chloride excretion itself is not dependent on A.D.H.

There is one important factor that influences water resorption by the kidney in relation to A.D.H. For many years it has been known that injury to the posterior pituitary, with failure of A.D.H. secretion, is followed by polyuria only when the anterior pituitary is intact. Recent work has shown that it is the maintenance of normal adrenal function that allows polyuria when A.D.H. is absent. This experimental work is confirmed by clinical experience, for a slow growing tumour which initially destroys the supra-optico-hypophyseal tract will cause polyuria, but, at a later stage, when the anterior pituitary is destroyed, the polyuria diminishes. Moreover polyuria will return if A.C.T.H. or cortisone is

administered to the patient. If the hypothalamic area is intact but the adrenal ceases to function, as in Addison's disease, diuresis does not follow an ingested water load. The capacity to secrete a water load is restored by the administration of cortisone. This complicated and ill-understood piece of physiology does have clinical importance and will be referred to again in relation to diseases of the anterior pituitary and adrenal.

Diabetes Insipidus

The disorder of function is a failure of renal water resorption due to an ineffective circulating level of A.D.H. Lesions of the supra-optico-hypophyseal tract cause the disease by diminishing or destroying the secretory capacity of this tissue. In rare instances the syndrome is produced by insensitivity of the renal tubules to the action of A.D.H. in the absence of other evidence of renal failure.

Aetiology

The disease is more common in males and is predominantly an affliction of childhood or early adult life. Clearly the lesion may often be such as to give rise to a general clinical picture of which diabetes insipidus is only a small part, and therefore the diagnosis of diabetes insipidus must always be followed by a systematic appraisal of the patient for other disorders of function. The very varied aetiology of the lesion is as follows:

(1) *Idiopathic*

A localized ,presumably degenerative, lesion of the supra-optico-hypophyseal tract occurring in children or young adults, with no other disturbance of function. This is a rare form of the disease, and the diagnosis must be regarded with suspicion. All too often the development of other clinical disturbances some time after the onset of diabetes insipidus makes it obvious that the aetiology is not idiopathic.

Several family histories have been recorded in which many members of succeeding generations are afflicted. In some families the disease is resistant to injected A.D.H. and may be presumed to be due to renal tubule insensitivity and not to hypothalamic dysfunction.

(2) *Infection*

Many forms of chronic meningitis or arachnoiditis may cause the disease, with associated neurological disturbances.

(3) *Xanthomatosis*

In children the Hand-Schuller-Christian syndrome is associated with diabetes insipidus in over 50 per cent of cases. In adults generalized

xanthomatosis, often with pulmonary involvement, may give rise to the disease.

(4) *Trauma*

Fractures of the skull base or operations in the region of the hypothalamus commonly give rise to a transient form of the disease. In some cases the condition becomes permanent.

(5) *Tumours*

Many types of tumour, both primary and secondary give rise to the disease, and commonly affect other aspects of hypothalamic function. The growths may be situated around the third ventricle or in the posterior fossa.

Clinical Course

The prime symptoms are gross polyuria and thirst. The urine is free of abnormal constituents but has a constantly low specific gravity (about 1002). The polyuria is constant, the volume passed at night being equal to that of the day. As the capacity of the bladder increases very large quantities are voided each time it is emptied. The thirst is persistent and agonizing; patients will drink from puddles or even their own urine in an effort to assuage it. As the disease progresses, dehydration gradually appears, the weight falls, the skin becomes dry and inelastic, and the lips parched and cracked. Intense thirst kills an appetite for food, and destroys sleep. Loss of water from the body causes constipation, and it also causes some salt loss, with resultant muscle weakness and cramps. It is a miserable condition in which the patient's life is confined between the water jug and the lavatory.

The natural history of the disease is dependent more on the general effects of the causative lesion than on the disturbance of water balance. Normal hydration can be maintained indefinitely with pitressin therapy. Occasionally idiopathic diabetes insipidus ends with spontaneous cure. If a tumour gives rise to the condition it may destroy the anterior pituitary with amelioration of the polyuria.

Diagnosis

Thirst and polyuria are prime symptoms of diabetes mellitus, which is distinguished immediately by the presence of glycosuria. The same symptoms may be marked in certain cases of renal failure, but here the presence of albuminuria and uraemia makes the diagnosis clear. Polyuria in such cases is due to failure of the renal tubules to respond to A.D.H. This can be demonstrated by the continued diuresis despite the injection

of posterior pituitary extracts. A rare syndrome in early childhood is nephrogenic diabetes insipidus, which is a specific failure of tubular response to A.D.H. in the presence of otherwise normal renal function. These 'water-babies' show no evidence of a hypothalamic lesion and do not respond to injected posterior pituitary extract.

Psychogenic polydipsia provides the major difficulty in diagnosis. As an hysterical phenomenon, intense thirst will be followed by polyuria, if the water intake is excessive. Thirst is the primary symptom, as compared to the primary polyuria of diabetes insipidus. The clinical differentiation of the two conditions may be very difficult if there is no evidence of organic disease and no other stigma of hysteria. Three forms of test are of diagnostic use.

The most reliable procedure employs a water load, with stimulation of the supra-optico-hypophyseal tract by nicotine (inhaled or ingested). Provided fainting, which alters renal blood flow, is avoided, the test gives a valid index of hormone secretion which can be compared to the effect of intravenous A.D.H. on water diuresis. By this means diabetes insipidus can not only be diagnosed by the failure of nicotine to inhibit diuresis, but the sensitivity of the kidney to A.D.H. is determined as well. However, it must be noted that the test requires careful attention to technical detail before good results are obtained.

Another test is based on the stimulation of the osmoreceptors by hypertonic solutions. Water diuresis is promoted by the ingestion of water, and then hypertonic saline is infused intravenously. The diuresis will cease in the normal, and continue in diabetes insipidus. The objection to this routine lies in the salt load which the kidney has to handle. The result may not indicate excretion of water, as an osmotic diuresis may arise.

The simplest procedure is the withholding of water for as long as the patient can tolerate it. In diabetes insipidus polyuria continues with no rise in the specific gravity of the urine and loss of body weight; the volume of urine passed by the hysteric will diminish markedly with a considerable rise in specific gravity, and there is no loss of weight. Unfortunately the test often fails because the hysteric will not suffer water deprivation even when sedated. Moreover the kidney, adapted to producing large quantities of urine, will not suddenly conserve water when the patient's intake is stopped. So the test is useful in excluding diabetes insipidus when the urine output drops and the specific gravity increases; but if this does not occur, then the patient still may or may not have diabetes insipidus.