CLINICAL ENDOCRINE PATHOLOGY

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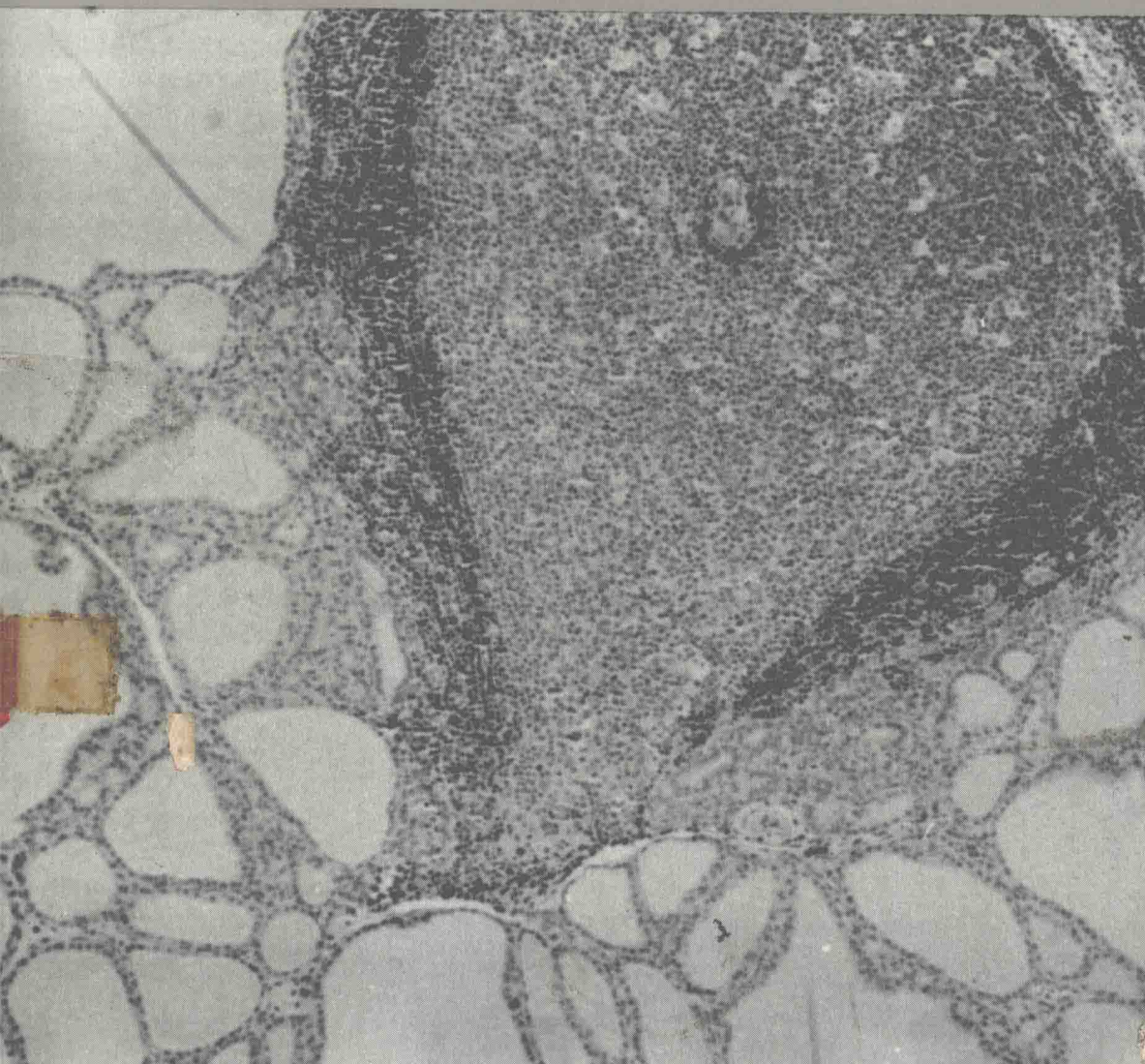

Clinical Endocrine Pathology

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Preface

This book was written because there seemed to be a need for a work correlating the functional and anatomical changes in endocrine diseases and discussing their bearing on laboratory diagnosis. There are of course several excellent books on endocrinology at undergraduate and postgraduate levels, and in the present work the clinical descriptions have been omitted or cut to a minimum, except where some special point needs discussion. There are also many accounts readily available of current biochemical procedures used in diagnosis. However, the anatomical bases of these disorders, and the mechanisms of their production, are often treated in a rather summary fashion. It is true that histology, even when aided by electron microscopy and histochemistry, is often rather inadequate for assessing the hormones a gland is actually secreting in a given situation, but this failure has sometimes led to an undue neglect of the structural bases, and it is hoped that this book will go some way to fill up the gap. Although technical details in performing the diagnostic laboratory tests are not dealt with, the principles underlying them are explained and the book is therefore intended as a companion to the standard works on clinical endocrinology and clinical biochemistry.

The diseases due to disturbances of the gastrointestinal hormones do not overlap greatly with the more conventional endocrine disorders and are not dealt with separately. It has, however, been necessary to mention some of them in the chapters dealing with the multiple endocrine tumours and other disorders.

An explanation of the principles used in selecting the references is perhaps called for. Those results which are fully established, or subjects where a good bibliography is very readily available in the larger textbooks, have not received many references. On the other hand, the more controversial subjects, or those where the references are more scattered in the specialist journals, are rather more fully documented. It is hoped that this weighting of the bibliography does not give undue emphasis to the more obscure points; it is intended merely as a time-saving expedient for the reader who wishes to pursue a topic further.

We are much indebted to our Publishers, Blackwell Scientific Publications, for their forbearance and patience during our delays in preparing the book. We also wish to thank Mrs Vellenoweth for her expert help in typing the manuscript.

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Liverpool, 1977

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Introduction

Many of the diseases that form the subject of this book are associated with the production of too much hormone, too little hormone or, occasionally, with the secretion of an abnormal hormone. The causes of these aberrations of secretion, their biochemical consequences and the principles of the methods by which they can be diagnosed will be described, but before dealing with the details it is convenient to give some generalisations about the control of hormone secretion.

The non-peptide hormones secreted by the adrenals, the thyroid and the gonads are synthesised in life by a series of steps, each of which is controlled by a specific enzyme. These synthetic pathways are known reasonably well, and much information has been gained from the study of congenital disorders due to deficiency of one or other of these enzymes, or from the study of drugs which block one particular step. On the other hand, in the case of the cells secreting protein or peptide hormones, almost nothing is known about the synthetic paths beyond that which is common to the biosynthesis of all proteins, and the intracellular defects responsible for abnormalities of protein hormone production are not understood. In some cases the hormone is stored in the cell as part of a larger molecule such as 'big ACTH', 'big growth hormone' or 'proparathormone'. Under certain conditions, especially in secreting tumours, a considerable fraction of the secretion enters the blood in the 'big' form. In other disorders, often familial, a molecular variant of the hormone is secreted, and since there may be some dissociation between the biological and the immunological determinants in such molecules, there may be discrepancies between the levels of radioimmunoassayable 'hormone' and the biological activity.

CONTROL MECHANISMS

The mechanisms by which the secretory activity of the endocrine glands are controlled are of great importance in pathology, and the glands fall into two classes: those controlled by the nervous system and those directly controlled by the blood levels of hormones or other chemicals.

There are several sites where the nervous system controls the secretion of an endocrine gland; thus the adrenal medulla receives preganglionic fibres, the renin-secreting juxtaglomerular apparatus in the kidney receives postganglionic fibres and the pineal body has a postganglionic supply from the superior cervical ganglion. By far the most important of the neuro-endocrine links, however, is that between the hypothalamus and the pituitary.

The influence of nervous factors on endocrine activity may be obvious in short-term situations: thus fright causes an immediate rise in blood ACTH levels, and mechanical stimulation of the nipple in women produces a rapid rise in blood prolactin levels. Other effects are more prolonged and are more difficult to demonstrate, though they are no less important. Examples are the amenorrhoea sometimes produced by worry, or the failure of growth that can occur in unhappy children.

Another aspect of the nervous control of secretion is seen in the relation of sleep patterns to hormone release. Sleep is a very complex process, and analysis of normal sleeping patterns has revealed two main phases; orthodox or slow EEG wave sleep, and paradoxical or rapid-eye-movement sleep. The latter is associated with increased cerebral blood flow and with dreams and occurs in 20-minute phases every 90 minutes or so. The release of some pituitary hormones is related to the type of sleep; thus growth hormone is secreted in bursts during orthodox sleep, while ACTH secretion has some association with rapid-eye-movement sleep. The nature of the relation of secretion to sleep differs, however; thus growth hormone secretion is specifically related, and a change of the rhythm (as when nurses go on night duty after normal day duty) is at once accompanied by a corresponding change in the time of growth hormone secretion. In the case of ACTH secretion, however, a sudden change of sleep habits is not immediately followed by a change in ACTH secretion rhythms, so that for several days or even weeks the pituitary, and consequently the adrenal cortex, continue to secrete at the old times, and thus inappropriately under the new circumstances. Ultimately, however, the secretory rhythm comes into phase again with the sleep rhythm. These rhythms are important but we do not understand how they are mediated, and we cannot therefore explain how they are abolished in some disease processes. One of the features of Cushing's syndrome due to adrenal hyperplasia of pituitary origin, for example, is the absence of a diurnal rhythm, but almost nothing is known of the derangement that produces it. Some diurnal or circadian rhythms are apparently not mediated by hormones but must themselves cause secondary effects on the endocrine system; thus there is a diurnal variation in the excretion rate

of sodium and potassium, which is not adrenal-dependent as it is found in cases of Addison's disease who are maintained in fairly good general condition by implanted pellets of DOCA.

The pituitary is the principal path by which the nervous system exerts these acute or long-term changes in endocrine activity, and an understanding of the way in which control is effected is vital for the understanding of disease changes.

The hypothalamus contains some highly specialised neuroendocrine cells, which combine the properties of ordinary neurons with those of endocrine cells. In a very restricted sense, of course, all neurons are 'endocrine' in that they act by releasing chemical messengers at their nerve endings, but in the case of ordinary neurons the messenger is usually a rather small molecule (e.g. acetyl choline or noradrenaline) and it is synthesised at the nerve ending, the axon conveying only an electrical impulse. Such a chemical messenger acts only in the immediate vicinity of the nerve ending and does not enter the blood in amounts of physiological importance. By contrast, the true neuroendocrine cells of the hypothalamus elaborate the hormone in their cell bodies and this then travels down the axon, is secreted into the blood and acts on more or less distant sites. The hormone is usually a polypeptide, though perhaps in some cases it is a simpler molecule such as dopamine.

The hormones of the posterior lobe (vasopressin and oxytocin) are the clearest example of neuroendocrine secretion. The bodies of the secretory cells occur in well defined hypothalamic nuclei (supra-optic and paraventricular), the fibre-tracts leading to the posterior lobe are also clearly demarcated and the hormone can be seen by histochemical or electron-microscopy studies as discrete granules in the axons. In this case the hormones are secreted into the general blood stream and affect remote sites such as the kidney or the uterus.

Another type of hormone formed in the hypothalamus controls the function of the anterior lobe of the pituitary. In general, the exact sites of the cell bodies and fibre tracts are not known for each type of hormone formed, but the same general process is inferred to occur as in the case of the posterior lobe hormones. However, in this case the hormone is secreted into the special portal blood system which conveys it into the anterior lobe, where it excites or inhibits the release of the pituitary hormones. These hypothalamic agents are therefore called release hormones or release-inhibiting hormones. There is a convention by which the substance is called a release hormone only when it has been isolated and defined chemically. If experiments indicate that the hypothalamus is elaborating

a release-stimulating or release-inhibiting agent, but this has not been characterised precisely, the agent is called a release factor; thus a corticotrophin release factor is believed to exist but its chemical composition is as yet unknown, and this contrasts with the fully analysed tripeptide thyrotrophin release hormone.

By means of these release hormones, the nervous system controls the pituitary secretions and thus indirectly controls the thyroid, the adrenal cortex and the gonads and also more general functions such as growth or milk secretion. A converse mechanism is also present, whereby the activity of these target organs in turn affects the activity of the hypothalamus. This reciprocal effect is called a feedback, by analogy with electronic circuits. The mechanism can be illustrated by a specific example, that of the thyroid. The thyrotrophic cells in the pituitary secrete thyroid stimulating hormone (TSH); this causes the thyroid to secrete more thyroxine and triiodothyronine into the blood. These now partially block the action of thyrotrophin-release hormone (TRH) on the thyrotrophic cells, so that the secretion of TSH falls. For this reason exogenous TRH is ineffective in stimulating TSH secretion when the blood levels of thyroid hormone are raised. In addition, thyroid hormones can also affect the rate of secretion of TRH, so that in primary hypothyroidism excess TRH is released.

As a result of this negative feedback, a balance of secretion is reached so that the levels of the hormones in the blood reach a fairly steady state. Similar considerations apply to other trophic hormones and their release hormones. The equilibrium, however, is very delicate and is easily disturbed by additional nervous impulses or by altering the balance of other hormones. In the case of the pituitary hormones such as growth hormone or prolactin, which act on tissues other than endocrine glands, there is no known simple feedback and the nature of the control mechanisms must be rather different, though even here indirect feedback systems are probably involved.

This type of feedback, in which the pituitary and its target organ reciprocally govern their partner's activity, is conclusively established and explains many phenomena of clinical importance. In addition, animal experiments have suggested that there may be a 'short loop feedback', by which the pituitary hormone regulates its own secretion by acting on the release hormone mechanism without the intervention of the target organ hormones. So far the concept of short loop control has not greatly helped to elucidate any important disease states.

Although the negative feedback is a fundamental regulatory mechanism, it applies only in a general way and does not involve minute-to-minute control. Thus cortisol levels in the blood show irregular peaks of a few

minutes' duration; ACTH secretion is also episodic, but the bursts of activity of the two glands are not correlated, so that it is clear that these very short-term variations do not quickly affect function of the partner gland. The same remarks apply to the irregular episodic spurts of secretion of gonadotrophins and of testosterone or oestradiol. Thus feedback regulation is concerned with the mean level of hormone secretion over a period of an hour or so, not with the transient fluctuations.

The negative feedback, whereby a raised blood level of target organ hormone lowers the secretion of the corresponding pituitary trophic hormone, is by far the commonest type of feedback. A positive feedback control, however, is occasionally seen; an example is the sudden massive release of luteinising hormone at the mid point of the menstrual cycle, which seems to be triggered off by the rising titre of blood oestrogens.

In the above initial description the assumption was implicit that each hypothalamic release hormone stimulated or inhibited the secretion of only one functional cell type in the anterior lobe, e.g. it was assumed that TRH stimulates the secretion only of TSH from the thyrotrophic cells. This is not, however, wholly true; TRH also stimulates the secretion of prolactin from a quite different cell type. Several other examples of this relative non-specificity will be found in the more detailed descriptions given later. How then does the body avoid inappropriate 'side effects' of the release hormones? The complete answer cannot be given, but several possibilities may be suggested. (a) Sometimes the side effect is only shown by a relatively large dose of the release hormone, and in physiological circumstances only the main effect is produced. (b) The peculiar blood supply through the special vascular complexes ('gomitoli', see later) to the portal system may be a device for directing the release factor to a fairly localised area of the anterior lobe where the appropriate cell type is concentrated. (c) The response of a pituitary cell to a release hormone can be modulated by variations of the cell environment; thus so-called luteinising hormone-release hormone acts on normal adult pituitaries to produce more luteinising hormone (LH) than follicle stimulating hormone (FSH), but in children, or in adults with anorexia nervosa, the same release hormone produces secretion of FSH but little secretion of LH. (d) When a release hormone tends to stimulate release of two hormones, it is possible that simultaneous secretion of a release-inhibiting hormone may suppress only one of the two hormones. By some such mechanisms, it must be supposed, the required hormone balance is maintained.

The cells elaborating release hormones are neurons, albeit rather atypical, and they share with other neurons the inability to divide, so that

the overproduction of release-factors due to secreting tumours of central nervous tissue is not seen. However, pedunculated hamartomas of the tuber cinereum region may be associated with premature puberty and it is possible that the hamartoma cells may be producing gonadotrophin-release factors which stimulate the pituitary. Since the discoveries (a) that a substance similar to growth hormone release-inhibiting hormone occurs normally in the upper gastrointestinal tract, (b) that various tumours of non-endocrine tissues can form release factors and (c) that general tissue trauma can liberate a substance with corticotrophin-release properties, the possibility that the pituitary function may be disturbed by non-hypothalamic humoral factors in disease states is being realised.

The concept of negative feedback in governing the reciprocal relations of the pituitary and the target organ is established, and in some cases the site of action is partially known, i.e. the target organ hormone is thought to act by blocking the action of release hormone on the pituitary cells, or by altering the amount of release factor secreted. We do not, however, know how the mechanism is set to work at its normal level, so as to maintain the blood cortisol, for example, at about 5 to 20 μg per 100 ml (140 to 550 nmol/l). Consequently we have no idea what goes wrong in the important diseases which are due to the governor being set at the wrong level. In the common type of Cushing's syndrome, for example, the feedback only comes into play when the blood levels of cortisol are markedly above normal, though suppression still occurs if large enough amounts of cortisol are present. An exactly similar situation occurs in an extremely rare type of thyrotoxicosis, where the pituitary secretion of TSH is only suppressed by a supernormal level of thyroid hormones. What causes the faulty setting of the 'thermostat' remains to be discovered.

The pituitary, controlled in this way, in turn governs, by means of its trophic hormones, the activity of the thyroid, gonads and cortosol-secreting cells of the adrenal cortex. The adrenal medulla is controlled by sympathetic nerves, and other nerves control the juxta-glomerular bodies in the kidney. These secrete renin, which forms the angiotensins; these play a major part in regulating the activity of the aldosterone-secreting cells of the adrenal cortex. Thus aldosterone secretion too is indirectly under nervous influence, though the potassium concentration of the plasma may directly affect secretion. The secretion of parathormone by the parathyroids and of calcitonin by the thyroid is mainly governed by the level of plasma ions, in this case calcium and phosphate, and neural mechanisms do not seem to play a part in regulating activity.

TYPES OF PATHOLOGICAL CHANGE LEADING TO ABNORMALITIES OF HORMONE SECRETION

Endocrine disorders can be divided into those with excessive hormone secretion, those with clinical features of subnormal hormone production and those with secretion of abnormal hormones. However, it should be realised that there is considerable overlap among these groups. For example, impaired hormone production because of enzyme deficiency may lead to excessive secretion of hormonally active precursors. Similarly end-organ refractoriness or production of abnormal hormones may produce clinical features of glandular hypofunction although the endocrine organ concerned may be hyperactive.

EXCESSIVE HORMONE SECRETION

1 Overproduction of a normal hormone can be due to a tumour of the appropriate endocrine gland. Thus Cushing's syndrome can be caused by a carcinoma of the adrenal cortex arising from a previously normal gland. This merely presents a specific case of the general problem of carcinogenesis. In addition, endocrine tumours can arise by progression from a long-continued hyperplasia. For example, chronic renal failure causes disturbances of calcium and phosphate metabolism which lead to stimulation of the parathyroid glands. At first these respond by diffuse hyperplasia, then by nodular hyperplasia; finally an autonomous adenoma develops, which continues to oversecrete parathormone even if the stimulus to secretion is withdrawn by treatment of the renal disease ('tertiary hyperparathyroidism'). Adenoma formation by analogous processes can occur in the chronically stimulated pituitary or adrenal cortex.

2 Tumours, usually malignant, of non-endocrine tissue can secrete hormones such as ACTH or anti-diuretic hormone ('Ectopic Hormone Syndrome'). Tumours of endocrine glands can also give rise to 'foreign' hormones. These freaks of synthesis can give rise to interesting clinical syndromes and have attracted much attention in the last 20 years, but they are really only examples of the aberrant differentiation of tumours, and a bronchial carcinoma secreting ACTH is no more surprising than a soft-tissue tumour forming bone. The usual explanation for such abnormal differentiation is that the neoplastic process causes derepression of the genes, present in all cells but normally repressed, for ACTH formation or bone formation respectively. A quite different hypothesis, based on cell fusion, has also been suggested.

3 The controlling mechanism for hormone secretion can be set at the wrong level as a result of some functional change. The example of Cushing's syndrome associated with bilateral adrenal hyperplasia has already been mentioned, and some types of inappropriate anti-diuretic hormone secretion (Schwartz–Bartter syndrome) apparently arise by a somewhat analogous mechanism.

4 The body can develop an abnormal stimulating substance which acts on one of the endocrine glands. It seems likely that most cases of thyrotoxicosis arise by the immune system producing two or more types of gamma globulin which possess the peculiar property of stimulating the thyroid function by a mechanism similar to that of normal pituitary thyrotrophic hormone. This production of gamma globulins is a totally abnormal process, not an exaggeration of a normal control mechanism.

5 Some cases of overactivity arise from unknown causes; for example, in primary parathyroid hyperplasia all four glands enlarge and secrete increased quantities of hormone, and in idiopathic hyperaldosteronism the aldosterone-secreting cells of the adrenal cortex can undergo hyperplasia and nodule formation, but the nature and origin of the stimuli responsible for these changes in the two cases are unknown.

6 Finally, a degenerating gland, such as the thyroid in autoimmune disease or the posterior lobe of the pituitary after stalk section, can leak stored hormone into the blood stream and thus cause a special and transitory type of 'overactivity'.

SUBNORMAL HORMONE PRODUCTION

The main causes of diminished or absent secretion by the endocrine glands are:

1 Congenital absence or malformation. Examples are the failure of the thyroid or anterior lobe of the pituitary to develop, and the causes are presumably much the same group of genetic and environmental factors as in other systems. In the particular case of gonads, the absence or duplication of a whole X chromosome is compatible with life but leads to maldevelopment of the ovary or testis.

2 The endocrine gland develops fairly normally morphologically but an enzyme essential for hormonogenesis is partially or wholly absent, causing deficiency of one hormone, often combined with compensatory changes leading to hyperplasia and overproduction of other hormones. Examples

are seen in the thyroid (some types of goitre) or adrenal cortex (congenital adrenal hyperplasia).

3 The hormones are produced normally, but a congenital defect in the end organ leads to insensitivity to hormone action and the result is functionally equivalent to absence of secretion. In some cases the cause is believed to be deficiency of the receptor protein from the target cells, in others the cause is not known. Examples are nephrogenic diabetes insipidus, where the cells of the lower nephron are refractory to anti-diuretic hormone, and testicular feminisation, where the tissues do not respond to testosterone.

4 Destruction of endocrine glands by granulomatous or expanding lesions need no particular discussion.

5 Ischaemic necrosis of the endocrine glands is important. The pituitary, and less commonly the adrenals, may be infarcted, common triggering mechanisms being bacterial (endotoxin) shock, as in the Waterhouse–Friderichsen syndrome; this is probably an example of the immunological process known as the Schwartzman Phenomenon. In late pregnancy the blood vessels seem to be in a very sensitive state and spasm of the pituitary vessels can give rise to post-partum necrosis of the pituitary, which is usually due to vascular collapse from blood loss at labour.

6 Autoimmune processes are important causes of endocrine gland destruction; sometimes only one gland is involved, sometimes multiple glands, as when Hashimoto's disease is associated with Addison's disease. The mechanisms initiating this process are not usually known, but often a virus infection is suspected. It is prone to occur in certain individuals, presumably of a particular genetic type, and it is becoming probable that the HLA tissue type may in some cases act as a genetic marker for this genotype.

7 Experimentally, some chemicals destroy endocrine cells more or less specifically, e.g. alloxan destroys the islets of Langerhans, and hexadimethrine destroys the anterior lobe of the pituitary and the adrenal cortex. However, no analogous process has been proved in spontaneous human disease.

A further possible cause of disturbed endocrine function lies in the occurrence of abnormal binding to proteins in the blood. The thyroid hormones and the steroids secreted by the gonads and the adrenal cortex are mostly bound in the blood to fairly specific carrier proteins. Thus there is a thyroxine-binding globulin, a sex-hormone-binding globulin and transcortin, or cortisol-binding globulin. The blood contains a mixture of bound and free hormone in dynamic equilibrium, and although the bound form is

quantitatively in great excess, it is only the free hormone which is physiologically active. The blood levels of these binding proteins are altered in a variety of congenital abnormalities, in pregnancy, as a result of drug action and in a number of diseases. These alterations lead to corresponding changes in the blood levels of the hormone, and a recognition of this phenomenon is of great importance in interpreting laboratory reports of plasma levels of such hormones. In most cases, however, the levels of free hormone are little affected and so no important physiological changes are induced. It is, however, a possibility that a qualitative or quantitative change in the binding proteins could lead to a clinical endocrinopathy, and cases of this have been claimed. Conclusive proof is as yet lacking.

SECRETION OF ABNORMAL HORMONES

An abnormal hormone may be produced, often from a tumour of an endocrine or non-endocrine organ, but sometimes from a non-neoplastic gland. In the early days of endocrinology this mechanism was invoked rather recklessly to explain at will any unusual symptoms, and it was a big advance when the concept was advanced that 'in different pathological states of such a gland it may produce too much or too little specific compounds but it does not produce abnormal compounds' (Cameron). This dictum remains true in the majority of diseases, and helped to check facile speculation, but recently it has been shown that abnormal hormones can be secreted. Thus rare types of dwarfism are due to a biologically inactive variant of the growth hormone molecule being secreted by the pituitary, and other examples will be discussed later.