

Lecture Notes on
ENDOCRINOLOGY

RONALD F. FLETCHER
SECOND EDITION



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Preface

This book is intended as a guide to clinical endocrinology for medical students but the material presented covers the management of the majority of endocrine disorders in everyday practice and most of what is required in the subject for diplomas in medicine and surgery. In order to present the subject in compact form each gland is dealt with in turn and whenever possible there is emphasis on clinical presentation and management. Most space is devoted to common diseases although others are mentioned and defined. Less attention is given to matters of little practical significance at present, despite their great theoretical and physiological interest.

Terminology has been kept as simple as possible and most eponyms avoided. Methods of biochemical analysis and tests vary widely and are developing rapidly, so that it is not helpful to give detailed instructions or many normal results, but general indications are given. In practice it is necessary to know the current protocols and the normal values for the laboratory with which one is dealing.

In recommendations about treatment, well established preparations are preferred and the many commercial alternatives are not discussed.

The lists of references for further reading at the end of each chapter consist of recent sources to which I have found it useful to refer and the reader may find the same. Most of the references are to books and reviews rather than to publications of original research.

For brevity the historical, embryological and comparative aspects of endocrinology have for the most part been omitted. Similarly, it has often been necessary to give the most conventional or plausible doctrine without discussing the alternatives.

In the preparation of the text of the first edition I was helped directly by many colleagues. For this edition I have gained tremendously from the opportunities for frequent discussions with the many experts in endocrinology who now practice in this city, but I must acknowledge particularly my debt to Professor R. Hoffenberg. The errors and omissions are my own.

RONALD F. FLETCHER

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Chapter I

Introduction

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ROLE OF ENDOCRINE SYSTEM

The last few years have seen a sudden rapid increase in knowledge about hormones and endocrine disease. The prime factor in this has been the introduction of many methods of measurement, most particularly immunoassay, able to measure the minute concentrations of circulating hormones. This expansion of understanding is still in progress and no doubt many of the present apparent certainties will soon be modified.

The role of the endocrine system is to act with the nervous system as the means whereby the function of the mammalian organism is controlled. The endocrine system has three distinguishing features. Firstly, its speed of response which is relatively slow, being in minutes to days in comparison with the fast responses of the nervous system. Secondly, its information is conveyed via hormones which are liberated into tissue fluids or the circulation. Thirdly it is largely self-regulating. There are probably a number of links between the two nervous and endocrine systems but the hypothalamic/pituitary connection is of outstanding importance.

INTERNAL CONTROL

The ways in which the endocrine system is controlled are gradually being revealed. Three separate arrangements can be made out but as they are interrelated the overall organisation is highly complex.

Cyclical variations

There are many rhythmic variations in the endocrine system, mediated via the anterior pituitary. The monthly menstrual cycle is perhaps the most obvious and depends on interactions between the glands involved. Controlled more directly by the brain are the circadian rhythms which modulate the release of the anterior pituitary hormones during each twenty four hour period. The underlying neuronal activity is inherent but is continuously retimed by the alternation of light and dark and the associated periods of consciousness and sleep. This rhythm will adjust to a modification of the cycle, or a complete reversal as in shift work, but the adjustment takes several days. This rhythm does to some extent control how we feel as evidenced by the syndrome of 'jet lag' which occurs while an adjustment of the timing is taking place. The main trends of variation in the plasma level of the anterior pituitary hormones under the influence of this circadian rhythm are shown in Fig. 1.1.

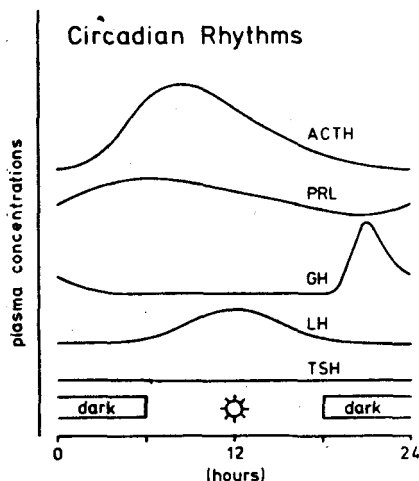


FIG. 1.1. Circadian rhythms of the plasma levels of some anterior pituitary hormones. The curves are idealised. The scales are arbitrary and unrelated.

Response to environment

The release of cortisol and catecholamines in response to physical or emotional stress is well recognised but there are many other changes which may be important, for example after surgery. The intake of food releases gut hormones and insulin.

'Feed-back'

The self-regulation of the endocrine system is achieved by a number of 'feed-back' arrangements, many of considerable complexity. Both negative and positive feed-back are involved. Figure 1.2 shows the

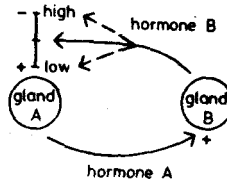


FIG. 1.2. A typical 'feed-back' loop. Gland 'A' liberates hormone 'A' which stimulates (+) gland 'B'. This releases hormone 'B' which modulates the liberation of hormone 'A'. The responsiveness of the receptor at gland 'A' can be moved up or down. The purpose of this arrangement is to control the plasma level of hormone 'B'.

essential features. The sensitivities and responses of the receptor apparatus at various parts of the loop are such that the system tends towards an equilibrium but in many instances the equilibrium point varies with circumstances. Most of the known feed-back loops involve the anterior pituitary and its target glands but the same considerations apply, for example, to the parathyroid glands, plasma calcium and bone.

Examples of these control arrangements will be found in many aspects of endocrine physiology and disease. Also, use is made of them frequently in endocrine investigation and treatment.

HORMONE RELEASE

An unexpected and curious fact to emerge recently is that many hormones from the pituitary and other glands are released in sudden

pulses at intervals of minutes or hours. As many hormones have a fast turnover in the circulation this means that their plasma levels rise and fall rapidly over a few minutes which no doubt contributes to the difficulty of interpreting isolated measurements.

CIRCULATING HORMONES

The steroid and thyroid hormones are carried in the plasma largely bound to proteins and several specific carrier proteins are involved. It is presumably the free hormone fraction which is biologically active and in equilibrium with the hormone in the tissues. Total plasma concentrations may depend more on the concentration of carrier than anything else and give a misleading impression about tissue effects. Peptide hormones also may be present in combinations of various molecular sizes and fragments of the larger polypeptides may be present also.

HORMONE ACTION

There is now much information about the nature of hormone action. For the peptide hormones there are specific receptors on cell membranes, e.g. for hormones from the anterior pituitary, posterior pituitary and parathyroid. The activation of receptor sites by the arrival of these hormones releases (or suppresses) adenylyl cyclase and the cyclic adenosine monophosphate (cAMP) produced then moves to other parts of the cell to activate protein kinases. The resulting reactions lead to the appropriate hormone effect. As the cAMP is the 'second messenger' mediating the action of many hormones it must be directed to its proper destination in the cell according to the nature of the stimulus but this directing system is unknown.

Steroid hormones act differently; they pass the cell membrane, enter the cell cytosol and are then bound to specific receptors. The resulting molecular complex enters the nucleus and there initiates gene transcription and the production of specific proteins. Thyroid hormones act at various sites within the cell and cAMP may be involved. The mode of action of insulin is still uncertain.

The study of hormone receptors offers exciting possibilities in the measurement of hormones by specific binding and in the exploration of hormone/cell interactions.

HORMONE METABOLISM

In general, very little of any hormone which is synthesised exerts an action on the tissues and even the little that does is not necessarily destroyed in the process of doing so. Nearly all the mass of hormone is degraded by systems quite independent of its site of action and the metabolic pathways vary with the individual hormones.

ENDOCRINE DISEASE

Definition

Many features of endocrine disorders result from an excess or a deficiency of a chemical which is present in normal health. The concentrations of hormones vary considerably in normal people so there can never be an exact dividing line between normal and abnormal endocrine function. Biochemical analysis in an individual can be related only to a reference range for a population and this restricts the value of tests in the borderline case. Fortunately, time will resolve the problems and without harm to the patient. Accurate diagnosis is particularly important because in most instances once treatment is started retesting is difficult or impossible. Unless treatment is urgent some confirmatory tests should be done even in obvious disease.

Aetiology

Little is known of the cause of endocrine disease although there are many sex-linked and genetic factors. Atrophy of endocrine glands is common and often autoimmune responses are involved but the primary fault is uncertain. Gland failure may occur also because of destructive processes. Sometimes, glands may synthesise abnormal or incorrectly balanced hormones. Endocrine glands form tumours readily but most of them are benign. Although the tumours often retain the capacity to synthesise the hormones of the parent gland, they tend to lose the normal control system so that excessive hormone secretion results. Some of the tumours are non-functioning. Despite the general principles, the aetiology of common endocrine diseases such as diabetes and Graves' disease is largely unknown.

Although it forms a coherent subject and it is easiest to learn about it as such, endocrinology is linked closely with general medicine and gynaecology and cannot be considered in isolation. Endocrine diseases

are eminently treatable and so it is well worth while to be on the lookout for them.

FURTHER READING

WEITZMAN E.D. (1976) Circadian rhythms and episodic hormone secretion in man. *A.Rev.Med.* 27, 225.

GENERAL REFERENCES

There are a number of books which can be consulted usefully on many endocrine topics. To avoid listing them at the end of every chapter, they are grouped here.

BACON G.E., *et al* (1975) *A practical approach to pediatric endocrinology* Year Book Medical Publishers, Inc. Chicago.

BUTT W.R. (1975) *Hormone Chemistry* (2nd Edition, 2 vols). Ellis Horwood Ltd., Chichester.

CLINICS IN ENDOCRINOLOGY AND METABOLISM (1973 *et seq*) W.B. Saunders, London.

CRYER, P.E. (1976) *Diagnostic Endocrinology*. O.U.P., London.

HALL, R. *et al* (1974) *Fundamentals of Clinical Endocrinology* (2nd Edition) Pitman, London.

LORAIN, J.A. & BELL, E.T. (1976) *Hormone Assays and their Clinical Application* (4th Edition) Churchill Livingstone, London.

MONTGOMERY, D.A.D. & WELBOURN, R.B. (1975) *Medical and Surgical Endocrinology* Edward Arnold, London.

WILLIAMS, R.H. (Ed) (1974) *Textbook of Endocrinology* (5th Edition) W.B. Saunders, London.

Chapter 2

Pancreas and Carbohydrate

Pancreas
 Islets
 Insulin
 Release
 Plasma
 Metabolism
 Action
 Glucagon
 Carbohydrate Metabolism
 Ketones
 Hypoglycaemia
 Causes
 Diagnosis
 Hormone Secreting Tumours
 Further reading

PANCREAS

The adult pancreas weighs between 50 and 70 g and lies behind the peritoneum with its head in the curve of the duodenum and its tail near the hilum of the spleen. Most of the pancreas is concerned with its exocrine function, the production of pancreatic secretion for intestinal digestion. The endocrine portion is only 1–2% of the gland by weight and consists of about 2 million *Islets of Langerhans*. These are highly vascularised areas ranging in size from a few cells to nodules 300 μm across.

In the islets four cell types have been identified so far:

Cell Type	Proportion of Islet %	Hormone produced
β	80	Insulin
α_2	15	Glucagon
α_1	5	Gastrin
?	?	Somatostatin

The islet has a complex internal organisation of unknown purpose. The outer layers of cells contain glucagon, with a few cells containing

somatostatin. The core of the islet consists of insulin containing cells; the gastrin containing cells are scattered throughout (Fig. 2.1).

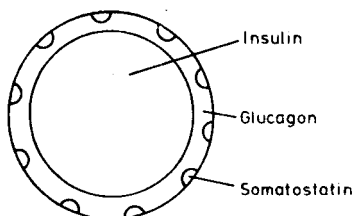


FIG. 2.1. The distribution of some of the hormone secreting cells of the Islet of Langerhans implying a complex internal organisation.

INSULIN

The β cells synthesise a single chain polypeptide called pro-insulin (Fig. 2.2). This molecule is cleaved as indicated to yield insulin, and

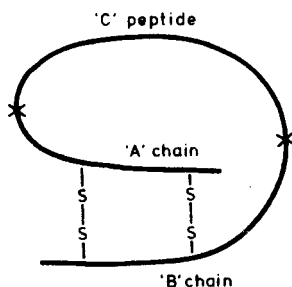


FIG. 2.2. The molecule of pro-insulin. Cleavage occurs at the positions indicated by the two crosses to release insulin (A & B chain with two disulphide bridges) and 'C'-peptide.

'C' peptide; all three substances are released into the circulation. Insulin contains an 'A' peptide chain of 21 amino acids and a 'B' chain of 30 amino acids joined by two di-sulphide bridges. The beef and pork insulins used in treatment differ from human insulin in respect of one and three amino acids respectively. This makes them immunologically distinct, but does not affect their potency in man.

Release of Insulin

The rate of synthesis and release of insulin is determined largely by the level of blood glucose, a rise in glucose causing a rise in insulin. Many other factors can cause insulin release including amino acids, some lipids, vagal stimulation and glucagon. Probably of more physiological importance is the effect of glucose absorption from the intestine which produces a greater insulin release than would be expected from the rise in blood glucose alone (Fig. 2.3). This effect is thought to be mediated by a hormone from the gut.

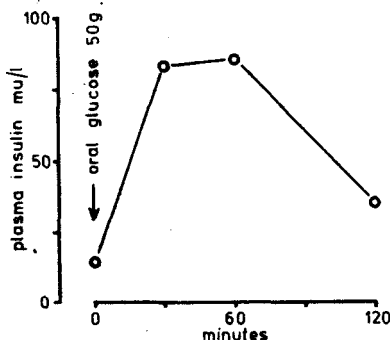


FIG. 2.3. A normal response of plasma insulin to oral glucose.

Insulin in plasma

The concentration of insulin in normal plasma varies over the wide range of 10 to 50 mu/l depending on the state of absorption. Such low concentrations can be measured routinely only by the immunoassay. The insulin activity in the plasma as measured by bioassay does not necessarily equate with the immunoreactive insulin—other substances such as somatomedin and proinsulin may interfere. Insulin antibodies may reduce insulin action. In some diabetics there seems to be a resistance to the action of endogenous insulin which may even be present in increased amounts (see below).

Metabolism of insulin

Insulin is removed rapidly from the plasma with a half-life of about four minutes. It is disposed of by degradation in many tissues, particularly the liver and kidney.

Insulin action

The most important tissues on which insulin has a direct action are the liver, muscle (including heart) and adipose tissue. Nearly all tissues are affected in some way but in many the effects are secondary. In tissues subject to direct action there are specific receptors for insulin on the cell membranes and it seems that insulin does not penetrate the cell. The major action of insulin is to permit the penetration of glucose and other closely similar sugars into cells but some of the actions of insulin are additional to and independent of glucose penetration (Table 2.1). Insulin has no effect on the intestinal or renal handling of glucose.

TABLE 2.1. Effects of Insulin

INSULIN	
<i>Normally causes:</i> Synthesis of glycogen Synthesis of protein Synthesis of triglyceride Glucose oxidation	<i>Deficiency causes:</i> Glycogen $\longrightarrow$ glucose Protein amino acids $\longrightarrow$ glucose Triglycerides $\longrightarrow$ ketones* + Reduced glucose oxidation* $\downarrow$ ketosis
Clinical results of insulin deficiency: Rise in plasma glucose Glycosuria Osmotic diuresis Dehydration Wasting of fat and muscle Ketosis	

* See 'Diabetes' below

GLUCAGON

This is a single chain polypeptide of known structure containing 29 amino acids; it can be measured by immunoassay. Glucagon stimulates the secretion of insulin but paradoxically its major metabolic effect is to raise blood glucose by stimulating glycogenolysis in the liver. Many other effects have been demonstrated but the role of glucagon in human physiology and pathology remains uncertain. It seems that the presence of glucagon is not essential for the genesis of diabetes mellitus.

CARBOHYDRATE METABOLISM

In the average British diet about 45% of the calories are derived from carbohydrate and most adults take between 100 and 300 g a day. The carbohydrate is mostly starch, sucrose, cane and beet sugar and lactose (milk) but these are digested in the small intestinal lumen and mucosa so that only monosaccharides are absorbed, the ratios being approximately—glucose 80%, fructose 15% and galactose 5%. The fructose and galactose are extracted by the liver, even in the absence of insulin, and enter the glucose and glycogen metabolic pathways. In clinical practice only glucose is significant; it has not been possible to use other sugars in the management of diabetes.

In the normal person after food the blood glucose is controlled by insulin release and subsequent disposal of glucose into tissues. During prolonged starvation the blood glucose is always maintained. At first, this is done by glycogenolysis in the liver and muscles but this store is soon exhausted and glucose then has to be synthesised from amino acids as it cannot be made from fatty acids.

Many factors, including hormones, alter carbohydrate metabolism in complex ways but few are of clinical significance. An excess of glucocorticoid and growth hormone tends to diminish carbohydrate tolerance perhaps by interference with the action of insulin. Glucocorticoid deficiency increases insulin action. Glucagon and adrenaline tend to raise plasma glucose by promoting glycogenolysis.

KETONE METABOLISM

The oxidation of fatty acids leads to the production of acetyl CoA. Normally, this:

1. Joins with oxaloacetate and enters the Krebs cycle to release energy.
2. Condenses to form acetoacetyl CoA and thus ketone bodies.

The changes in diabetes are not fully understood but it seems that when carbohydrate utilisation is defective there is an increased oxidation of fatty acid and at the same time a deficient supply of oxaloacetate so that the excess acetyl CoA is deflected into the production of ketones (Fig. 2.4). Ketone bodies can be oxidised in muscle but in severe diabetes production is so high that the disposal system is overloaded and ketones accumulate. Starvation also increases ketone production sufficiently to produce positive urine tests but the increase is only slight and does not produce symptoms.

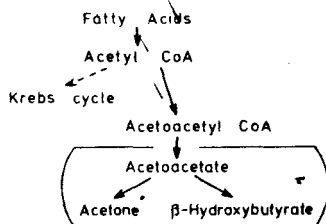


FIG. 2.4. Ketone production in diabetes. Insulin lack accelerates fatty acid oxidation but restricts the disposal of acetyl CoA through the Krebs cycle. The ketones are bracketed.

HYPOGLYCAEMIA

This may occur in many circumstances but levels low enough to cause symptoms, (i.e. below about 2.5 mmol/l)* are uncommon. Nearly all hypoglycaemic states are intermittent and depend on the pattern of food intake, the lowest levels occurring two hours or more after the last meal. The symptoms are a mixture of direct effects of glucose lack on the brain ('neuroglycopenia') and the results of adrenaline release. The latter are characterised by nervousness, weakness, palpitations, hunger, fear and sweating, while the former tend to produce irritability, agitation, confusion and sleepiness. However, the pattern of symptoms is very variable and depends perhaps on the speed of fall of the blood glucose as well as age, and chronicity. Certainly there may be considerable difficulty in diagnosis.

Causes

A full list of known causes of hypoglycaemia is enormous; the commoner types are:

- Primary pancreatic
- Toxic
- Reactive
- Hepatic
- Endocrine
- Childhood forms

Primary Pancreatic

This is due to insulin secreting tissue escaping from physiological control. Usually there is an *insulinoma* which is a small, benign adenoma of islet tissue but which may rarely be multiple ('microadenomatosis') or malignant.

* 45 mg/100 ml.