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Clinical Paediatric Endocrinology

William Hamilton

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Foreword

The successful paediatrician behaves like a benign uncle with a built-in computer. A sensitive and studied feeling for children has to be combined with the rigours of scientific method. By my definition 'A paediatrician is a measuring doctor', for the quintessence of paediatrics is growth and without measurement what can we know about growth? Because the whole child is so complex each component, physical or non-physical, tends to be measured and studied in isolation and a function of the comprehensive paediatrician is to reintegrate the isolated parts. If the child is taken to pieces for study, as often he must be, somebody must remember to put the pieces together again, One of the pieces is endocrinology.

The best is the least we can offer children. For though their whole lifetime can be scarred by illness, yet their ability to help themselves or ask for help (to communicate) is limited. Inevitably the children's doctor develops not only special skills but a special philosophy. Within the wide range of child health the general paediatrician's skills and philosophy are almost bound to differ from those of his colleagues, the specialists in a system or tissue or a technique and the academic research workers. Yet he must continuously absorb and use their discoveries to remain himself the expert in children.

It is primarily for the general paediatric physician that the *Postgraduate Paediatric Series* has been conceived, but it is intended also for surgeons and specialists in any branch of paediatrics who wish for authoritative information on another. Each volume aims to cover one section of paediatrics. Each is written by an acknowledged authority, or at most two co-authors, for in a restricted area individual experience adds pungence and flavour which multi-authorship dilutes. One of the prospective advantages of a series in which the individual volumes are devoted to restricted themes is that each book can be kept up to date by re-writing as often as proves

necessary, without the delay imposed on more encyclopaedic works by slow developing subjects—or slow writing authors.

The author of this volume continues to make original and valuable contributions to paediatric endocrinology yet, to his great credit, has remained a paediatrician. Consequently the text combines a sufficient background of essential theory with an approach that is down to earth. The book is a guide to practice, so a selected rather than an indiscriminate list of references has been preferred. The author has written here not for his fellow specialists in endocrinology but for practising paediatricians at all stages of their careers. As Editor I am firmly lined up with the readers.

JOHN APLEY

Preface

Endocrinology has expanded to a remarkable degree during the past 50 years. Much of the early information came from animal experiments, the work of physiologists, but an equal contribution later came from chemists and biochemists, who characterized many of the hormones. Now the endocrine field is so extensive that it is quite impossible to know it all in depth. Within this clinical speciality there are those whose interests are confined to understanding fully the endocrinology of one gland, while at the same time practising approved diagnostic and therapeutic principles in the other endocrine areas. This book is not offered to the specialist in endocrinology, but rather to the practising paediatrician with practical clinical interests.

To give a reasonable understanding of the various subjects, biological and chemical data have been included when judged necessary, but an attempt has been made to keep such sections to a minimum.

The current vogue of enumerating all published clinical investigative procedures for hormone assay has been resisted. For example, in the estimation of growth hormone, there are now techniques using insulin, glucose, arginine, Bovril and glucagon as provocative agents and in such a situation one procedure, most calculated to give informative results, has been quoted.

In certain sections, the reader may encounter an unfamiliar classification of disease, for example, in the thyroid chapter. This is not an attempt to break with tradition, but rather to maintain a uniformity of approach to clinical problems. The reader will immediately appreciate the similarity of layout in the chapters dealing with the adrenal and thyroid glands. Inborn errors of metabolism, hypoplasia or agenesis, intrinsic functional inadequacy, extraglandular factors causing functional failure and effects of

therapeutic agents are considered in both chapters in that order.

Some well-worn terms have been given scant use. For example, 'congenital adrenal hyperplasia' is not used at all in the accepted section. This term has come to indicate only a few of the clinical syndromes due to an inborn error of cortisol synthesis. It is now recognized that not all of the inborn errors of cortisol synthesis result in adrenal hyperplasia and hence the term is restrictive. Further, congenital adrenal hyperplasia connotes masculinization in the female and macrogenitosomia in the male, but again not all examples of the inborn errors of cortisol synthesis can incorporate these clinical features. These features are associated only with a high adrenal production of androgens and not all the enzyme defects permit this.

An attempt has been made to present the facts faithfully and sequentially but simply. While such an approach may oversimplify a relatively obscure subject, it is hoped that the instruction will remove many of the perplexities which for some surround endocrinology.

Authentication of every statement in the text has been judged unnecessary. Instead, further reading material is suggested. Sometimes this is a standard textbook, sometimes a chapter in a well recognized tome, but mostly it is recently published reviews, articles or case reports in readily available journals, which either review well the subject under discussion or present an additional aspect of the problem.

A multi-author book by experts presents a formidable broadside. This volume by a single author is intended as a practical guide to the paediatrician who may not always be working in salubrious academic surroundings, but who, none the less, practises that type of medicine which aims at diagnosis and treatment.

In the preparation of the manuscripts I have had assistance from many. Outstanding help has come from Dr. John Apley, who invited me first to put pen to paper. His is the mind behind this and subsequent volumes in the series and throughout the exercise his encouragement, down-to-earth recommendations, his firm but cheerful censorship, as general editor, has made the writing a great pleasure. 'Writing a book is an adventure. To begin with it is a toy, an amusement. Then it becomes a mistress, then it becomes a master, then it becomes a tyrant. The last phase is that just as you are about to be reconciled to your servitude, you kill the monster, and fling him about to the public'. (Winston Churchill, 2 November, 1949).

Glasgow

WILLIAM HAMILTON

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CHAPTER 1

Introduction

Endocrinology is the science of the discharge of ductless glands. It was only in 1904 that the term 'hormone' was introduced by Bayliss and Starling who defined it as 'any substance normally produced in the cells of some part of the body and carried by the blood stream to distant parts, which it affects for the good of the organism as a whole'. Since then the nature of hormones has been elucidated, target organs for many of them have been identified and their mode of action suggested.

The hormones of the adrenal cortex, testis and ovary are steroidal in nature while those of the hypothalamus, pituitary, thyroid, parathyroid and pancreas are either proteins or polypeptides. Thymosin, the hormone of the thymus, has yet to be characterized.

The precise mode of action of hormones is still not fully known. There is some evidence that they are activators or inhibitors of enzyme systems such as is seen in the action of epinephrine and glucagon on the phosphorylase system. The action of insulin on the migration of glucose into cells suggests also that they have a mechanism controlling membrane transport, while the fact that thyroxine induces metamorphosis in the tadpole indicates that hormones can stimulate protein synthesis and ribonucleic acid (RNA) turnover.

In this work we are more concerned with the disorders of the endocrine system.

An endocrine gland may be congenitally absent. The resultant failure in hormone production delays the development of hormone-dependent tissues in the foetus and the newborn may have overt stigmata of endocrine failure. A gland may be the seat of disease, infective, neoplastic or autoimmune, while in the 'idiopathatic' or 'essential' endocrinopathies an obvious disease process cannot be identified. Much of paediatric endocrine disease is due to inborn errors of metabolism, enzyme defects which are genetically determined. Occasionally in this group, clinical evidence of the action of hormone metabolites, as is seen in the masculinization of the female

foetus when there is an error in cortisol synthesis, is the presenting feature. Chromosomal abnormalities involving the sex chromosomes give rise to endocrine failure. Classical examples are Klinefelter's syndrome, Turner's syndrome and XO/XY mosaicism. Finally, increased hormone production, due either to abnormal stimulation of an endocrine gland, as in thyrotoxicosis or to neoplasia, as in adrenal carcinoma, gives rise to the symptoms and signs of disease.

There are three basic therapeutic principles in the treatment of endocrine disease. Hormone substitution is required when hormone synthesis is absent or defective. Hormone suppression is necessary when there is overproduction. Ablation of a gland, chemically, surgically or by irradiation is the treatment of choice when the disease process is malignant or when the gland, by virtue of the intrinsic defect, may become malignant.

The chapters which follow expand these considerations, emphasizing primarily, the clinical, diagnostic and therapeutic aspects of paediatric endocrinology.

CHAPTER 2

The Hypothalamus and Pituitary

For long the pituitary gland enjoyed pride of place in the title role as conductor of the endocrine orchestra. Within recent years however the hypothalamus, because of its metronomic activity, has come to be regarded as the controller of endocrine function. By virtue of releasing factors, polypeptides elaborated by its nuclear aggregates, the hypothalamus controls the release of the trophic hormones of the adenohypophysis. Despite the change in leadership, the interrelations between the two are so intimate that it is convenient to consider them together.

ANATOMY AND PHYSIOLOGY

Anatomical relationships

The hypothalamus is part of the diencephalon and lies between the wall of the third ventricle medially and the thalamus laterally. Anteriorly the optic chiasma and posteriorly the corpora mamillaria are its limits. Above is the anterior commissure and foramen of Monro and below, the hypothalamus is continuous with the infundibulum or pituitary stalk. This structure leads into the pituitary gland and its fibres ramify in the neurohypophysis. The pituitary itself lies in a hollow of the sphenoid, the sella turcica, lined by a layer of dura mater. There is neither subarachnoid nor subdural space within the sella although the pituitary stalk is surrounded by both. Lateral to the pituitary, on each side, is the cavernous sinus and anteriorly and posteriorly small venous radicles surround the infundibulum. Above and in front of the pituitary is the optic chiasma.

It will immediately be appreciated from these anatomical relationships that lesions of the hypothalamus and pituitary are likely to present with ophthalmological, vegetative–endocrine and pyramido–cerebellar signs.

Structure and function

Within the hypothalamus are nuclear aggregates named according to their position. From these, non-medullated nerve fibres arise and passing downwards, they converge to form the median eminence. Their subsequent course to the pituitary is the tubero–hypophyseal tract. Within recent years it has been recognized that these hypothalamic nuclei elaborate polypeptides having neuroendocrine activity. In the supra-optic and paraventricular nuclei, oxytocin and arginine vasopressin are elaborated and are transported via the supra-optico–hypophyseal tract to the neurohypophysis where they are stored at the nerve ending. Release of these substances into the blood results from vascular and neural stimuli acting on the neurohypophysis. It is possible that even the neurosecretory cells of the anterior hypothalamus are osmoreceptors and volume receptors.

From the other nuclei, a group of chemically related polypeptides has been isolated. Several are known to regulate the secreting activity of the anterior and intermediate pituitary lobes. These polypeptides have been termed 'hypothalamic releasing hormones' and act with predictable selectivity on the release of six different pituitary trophic hormones. Corticotrophin releasing hormone (CRH) and thyroid stimulating hormone releasing hormone (TSH-RH) originate in nuclei above and posterior to the median eminence respectively. Gonadotrophin releasing hormone (GRH) has been found in nuclei in the area of the mamillary bodies. Hormones releasing growth hormone (GH-RH), follicle-stimulating hormone (FSH-RH) and luteinizing hormone (LH-RH) have also been identified. Lactogenic hormone (LTH) secretion however is inhibited by a hypothalamic factor. Thus lesions of the hypothalamus, by disturbing the normal secretory activity of the nuclei, give rise to endocrine and autonomic disturbances.

The pituitary gland consists of the pars tuberalis, pars distalis and pars intermedia and together these form the adenohypophysis derived from an ectodermal outgrowth of the primitive buccal cavity (Rathkes' pouch). Remnants of Rathkes' pouch occasionally persist, at the site of origin in the nasopharynx, mainly as chromophobe cells. The neurohypophysis is a downgrowth of the diencephalon from the floor of the third ventricle. From the pars distalis, six polypeptides have been isolated. Three (GH; TSH; ACTH) have metabolic activity and three (FSH; LH; LTH) are gonadotrophic. TSH and LH are glycoproteins, the others do not have a carbohydrate in their molecule. A seventh hormone, melanocyte-stimulating hormone (MSH) is secreted by the pars intermedia.

Most of the pituitary hormones can now be estimated by a radioimmunoassay technique.

Hypothalamic control over the adenohypophysis is maintained via a common blood supply (*Figure 1*). The anterior pituitary lobe has a plexus of twigs from the internal carotid and posterior

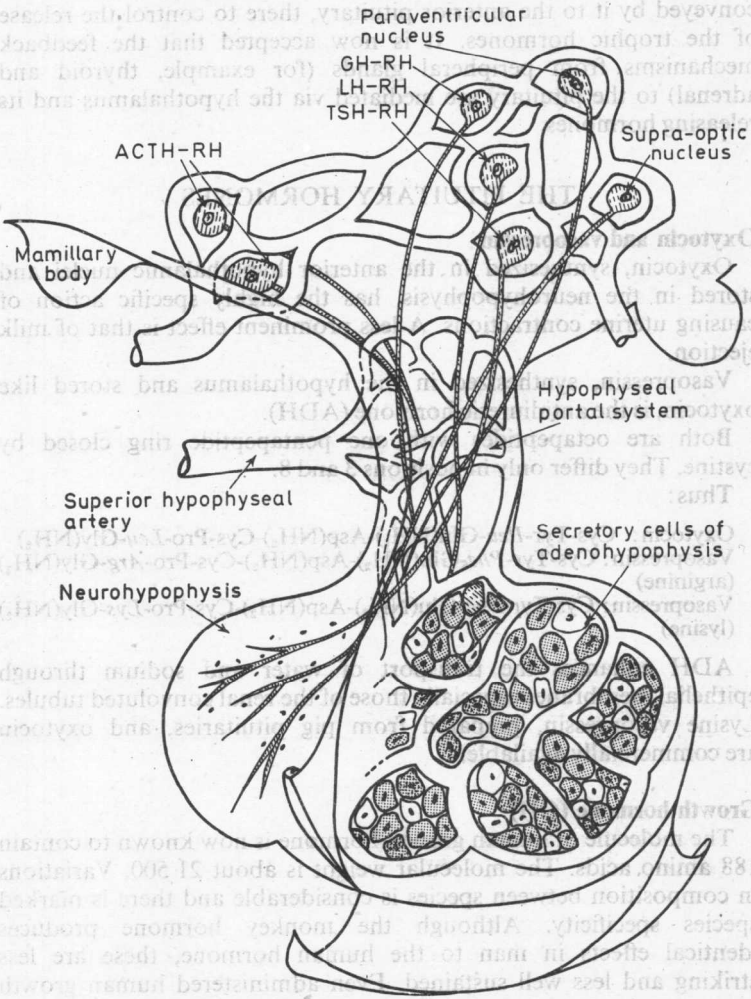

Figure 1. Schematic representation of the hypothalamus, its nuclei, the pituitary gland with the vascular network known as the pituitary portal system

communicating arteries. Capillaries from this plexus extend upwards to supply the median eminence in the hypothalamus. Return blood from that area drains into large capillaries or portal trunk, which pass around the pituitary stalk, finally penetrating the pars distalis as large sinusoids. This is the pituitary portal system and its importance is that the releasing hormones from the hypothalamus are conveyed by it to the anterior pituitary, there to control the release of the trophic hormones. It is now accepted that the feedback mechanisms from peripheral glands (for example, thyroid and adrenal) to the pituitary are mediated via the hypothalamus and its releasing hormones.

THE PITUITARY HORMONES

Oxytocin and vasopressin

Oxytocin, synthesized in the anterior hypothalamic nuclei and stored in the neurohypophysis, has the highly specific action of causing uterine contractions. A less prominent effect is that of milk ejection.

Vasopressin, synthesized in the hypothalamus and stored like oxytocin, is the antidiuretic hormone (ADH).

Both are octapeptides with one pentapeptide ring closed by cystine. They differ only in positions 3 and 8.

Thus:

Oxytocin: Cys-Tyr-*Ileu*-Glu(NH_2)-Asp(NH_2)-Cys-Pro-*Leu*-Gly(NH_2)
Vasopressin: Cys-Tyr-*Phe*-Glu(NH_2)-Asp(NH_2)-Cys-Pro-*Arg*-Gly(NH_2) (arginine)
Vasopressin: Cys-Tyr-*Phe*-Glu(NH_2)-Asp(NH_2)-Cys-Pro-*Lys*-Gly(NH_2) (lysine)

ADH enhances the transport of water and sodium through epithelial membranes especially those of the renal convoluted tubules. Lysine vasopressin, prepared from pig pituitaries, and oxytocin are commercially available.

Growth hormone (GH)

The molecule of human growth hormone is now known to contain 188 amino acids. The molecular weight is about 21 500. Variations in composition between species is considerable and there is marked species specificity. Although the monkey hormone produces identical effects in man to the human hormone, these are less striking and less well sustained. Even administered human growth hormone, in man, may produce antibodies, resulting in loss of effectiveness. Its growth promoting effects require the presence of

insulin. Injected growth hormone increases the rate of protein synthesis and decreases the breakdown of amino acids. Also the oxidation of carbohydrates is restricted with resultant hyperglycaemia and glycosuria. These carbohydrate effects depend on the presence of ingested carbohydrate and are not seen in starvation. Phosphorus, calcium, sodium and potassium are retained in the proportions found in bone and muscle. When the patient cannot respond to growth hormone by linear growth and protein synthesis, diabetes mellitus develops. This effect is not seen in children. The diabetogenic effects of the hormone result from hydropic degenerative changes in the β-cells of the pancreas and reduction in islet tissue. If available for therapeutic use the dose is 0·2–10 mg daily by intramuscular injection. The stimulus for growth hormone secretion is not known.

Thyroid stimulating hormone (TSH)

The stimulus for the release of TSH is a fall in circulating thyroxine. This negative feedback mechanism is only in part mediated through the hypothalamus, the pituitary itself probably reacting more rapidly to alterations in plasma thyroxine concentration. It has a molecular weight of 28 000 and contains glucosamine, galactosamine, mannose and fucose. Its effects are to increase the thyroid weight, the accumulation of iodine in the thyroid and the secretion of thyroxine, the latter by stimulating the enzymic breakdown of thyroglobulin.

Corticotrophin (ACTH)

The stimulus for corticotrophin secretion is a fall in plasma cortisol. It is composed of 38 amino acids. Alterations at position 1 in the chain inactivates the hormone but the sequence 25–39 can be removed without altering its biological activity. Synthetic corticotrophin (β^{1-24}corticotrophin) has physiological activity similar to the natural hormone.

The primary action of corticotrophin is to stimulate the conversion of cholesterol to pregnenolone which takes place in the cells of the inner two zones of the adrenal cortex. It thus stimulates the enzyme C20,22-desmolase but contributes nothing to the hydroxylating mechanisms of the adrenal gland. None the less, the end result of corticotrophin stimulation is an increased adrenal production of cortisol. Continuous daily injection of corticotrophin (20–40 mg) causes a doubling in size of the cortex within 7 days.

Metyrapone blocks 11β-hydroxylation within the adrenal cortex. This is an essential step in the synthesis of cortisol. Its oral use therefore results in a fall in plasma cortisol with a resultant increase in corticotrophin secretion. The adrenal is thereby stimulated but it is