Modern Trends in

Endocrinology — 4

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Preface

It is some five years since the Third Series of *Modern Trends in Endocrinology* appeared in print and the reader will be familiar with the objective – a periodic critical survey into certain fields of endocrinology rather than a general review.

This volume has the same objective and, apart from one or two minor changes, the planning of the book is the same as heretofore. In the first chapter, which is in effect a symposium in some seven sections, the hypothalamic and pituitary axis, and the relations of the brain to the endocrine system and the pathways, anatomical, neurohormonal and functional, are reviewed as far as they are at present known. It is to be hoped that this will provide a comprehensive picture of the subject as a whole.

The remaining eleven chapters follow the usual form, and deal with current topics in the endocrine system as a whole.

Each contributor has had in mind to highlight salients on advancing fronts, as well as to hint at future possibilities in the field, if any such could be inferred.

The Editors and Publishers have, as always, been anxious to ensure publication with the utmost speed. They are inevitably worried by the fact that certain contributors who present their material promptly may feel, with justice, at a disadvantage with their public from apparent delay. Such concern is regrettably inherent in the project owing to the well known fact that contributors can never all be stimulated sufficiently to produce their material simultaneously!

We trust that the symposium at the start will speak for itself. Topics in the second part range widely over the field and the usual balance between clinical and biochemical data has, we hope, been held.

The male gonads, congenital adrenal hyperplasia, and catecholamine-secreting tumours are illustrations of this. The slant in these chapters is mainly clinical but based on an up-to-date biochemical background.

In the first of these, for instance, there is a full discussion on androgen metabolism and the assessment of hormone secretion, as well as up-to-date views on spermatogenesis. In the second there is an account

of the clinical syndromes associated with deficiencies in specific enzyme systems and abnormalities of sex development. In the third there are the clinical pictures associated with catecholamine-secreting tumours on a background of their metabolism and hormone biosynthesis.

The thyroid topics in this volume emphasize therapy and carcinogenesis, being based on modern experience and the current data available. The first deals in detail with recent trends in the treatment of thyrotoxicosis; the second gives a now longer-term view of the effects of radiation on the thyroid and the risks of carcinogenesis.

Hyperparathyroidism has a chapter to itself, too, dealing with the advances in classification and practical importance of distinguishing the different groups.

Finally, there are chapters on the prostaglandins, calcitonin and gastro-intestinal hormones, salients in which at the present moment the biochemical background is well ahead of the clinical front.

Such is a brief summary of the contents of this volume, which we trust will be as useful to readers as these volumes have been previously.

We are much indebted to the contributors for their invaluable work, and also, of course, to the Publishers for their infinite care in the preparation of the book.

THE EDITORS

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1 The Brain and Pituitary Function in Health and Disease

Section I: INTRODUCTION

F.T.G. PRUNTY

At the present time the role of the brain in controlling the activity of the portion of the endocrine system governed by the pituitary gland is rapidly becoming more fully appreciated, but the sources of relevant knowledge cover an extremely wide field. For this reason a break with tradition has been made in the planning of the presentation in this volume of 'Modern Trends', so that in effect a small symposium involving a number of relevant areas of investigation follows within the confines of a single chapter. The first section briefly outlines current thought on the anatomical considerations involved in the relevant nervous pathways leading to the ultimate control of the two portions of the pituitary gland. There follow sections on the gonadotrophins, corticotrophin, growth hormone, thyrotrophin and, finally, the posterior pituitary; in addition further relevant observations will be found in Chapter 2 by Jeffcoate on male hypogonadism.

The first account of a situation in which the higher nervous system might be involved in governing the activity of a peripheral endocrine gland may be attributed to Parry (1825). He cited the case history of a girl who evidently developed thyrotoxicosis immediately after being thrown out of a wheel chair which ran amok careering fast downhill. Since then many have thought that emotional and other stress can be an important initiating factor in the development of thyrotoxicosis (e.g. Werner, 1955). However, mainly owing to the lack of controlled observations and the confusing effects of other environmental factors, others have thought that convincing proof of this association is lacking (*see* Harris, 1955; Morgans, 1964; Rawson, Money and Grief, 1969).

The subject is taken further here in Section V where the limited extent to which such an association can be substantiated by objective criteria is shown.

More definitively it came to be recognized by Marshall (1942) that there was an association between a multiplicity of environmental, or exteroceptive, factors and sexual function in the animals observed by him. In the light of this it was first mooted by Harris (1937) that there might be a humoral transmission of stimuli from the hypothalamus to the anterior pituitary gland. Subsequently the role of a host of stressful stimuli in inducing increased activity of the adrenal cortex has been delineated, and is too well known to be elaborated here.

Recently anatomical advances have indicated some of the ways by which the hypothalamus has connections with other nervous components, even to the cerebral cortex, and through them has access to the effects of endogenous and environmental stimuli. The increasing importance ascribed to structures such as the limbic system and amygdaloid nuclei needs recognition.

The resulting integration of impulses passed to the hypothalamus determines its endocrine effects which are mediated by two independent pathways. Both involve the neurosecretion of hormonal peptides which are transmitted from the cell body along the axon. The posterior pituitary mechanism is the simpler in so far as the gland functions as a storehouse and site of release of the neuronally conducted secretory products, vasopressin and oxytocin. These octapeptides are held available in a bound form in association with a specific protein, neurophysin, and when released are able to exert their effects on target organs without the intervention of a peripheral endocrine gland.

The adenohypophysis is more complex in its function of mediation of endocrine function. The role and anatomy of the hypothalamic–anterior pituitary portal vascular system (Section VI, *Figure 1)* is now understood in considerable detail. Although in the original description of this structure it was thought that the blood flow was upwards towards the hypothalamus (Popa and Fielding, 1930) it in fact transports its neurosecretory products to the anterior pituitary from the hypothalamic nerve endings. These hormones are apparently mostly stimulatory in action, although occasionally they may have an inhibitory function, as instanced in the case of prolactin, and perhaps also of growth hormone and of corticotrophin.

Considerable advances have been made in the elucidation of the structure of these neurohormones. Whilst the detailed structure of gonadotrophin and corticotrophin releasing factors is relatively unknown, that of growth hormone and thyrotrophin releasing factors is established, and the last of these, a tripeptide, is easily synthesized.

To study the physiology and pathophysiology of this intricate control system an essential step is the development of suitable assay procedures for all the hormones concerned. Traditionally the evolution of assay techniques commences with bioassay in order that the hormone concerned may be characterized and its structure determined. These techniques may be followed later by the development of specific chemical procedures, and most recently, by the application of immunological procedures monitored with the use of radioactive tracers. The capacity to carry out large numbers of determinations in dynamic situations then results in the rapid accumulation of knowledge. Not only must suitable assay procedures be available, but also practical means of obtaining suitable samples of material containing the hormone from the appropriate site.

In the case of the releasing factors assay procedures are still in the bioassay stage, but with their availability in pure form, radioimmunoassay can be rapidly developed. The problem of sampling the blood in the portal vessels is a formidable one, but is technically practicable in the experimental animal. Such sampling is nonetheless fraught with the danger of disturbing the physiological state owing to the trauma involved in making the approach. On the other hand, the great dilution of the releasing factors in the peripheral blood is clearly a potential disadvantage and local changes in concentration might be obscured by the sampling of a remote source.

All the anterior and posterior pituitary hormones can now be assayed by radioimmunological means and much recent knowledge has been obtained in this way. Circumstances exist in which doubt remains concerning the correlation of such estimates with biological activity within the organism, and caution is advisable therefore in their interpretation. In the previous volume in this series a review of this subject was presented by Greenwood (1967). In Section III, and also in Chapter 2, attention is drawn to the secretion and effects of the gonadotrophins and the complex problems involved in the simultaneous and separate secretion of the two hormones, FSH and LH. The critical activity of LH at the time of ovulation in the female has now become appreciated. Detailed knowledge of the actions of these hormones must be available in order to consolidate our ideas on the mechanisms involved in the stimulation and suppression of their secretion in accord with the needs of the organism. Such knowledge is being gained and is becoming applicable to complex pathological circumstances that are encountered in clinical practice.

It is clear that the hypothalamus acts as a focal point in governing the activity of the anterior pituitary and acts as an integrator of many impulses. Stimulation of the hypothalamus electrically is well known

to cause the discharge of several hormones, including ACTH, TSH and possibly growth hormone. Conversely, lesions in the area may have the opposite effect. Further, stimulation above this area, of the amygdaloid nuclei, has an excitatory effect on LH. The precise ways in which, for example, light and smell affect gonadal function, glucose concentration affects growth hormone release, and stress affects the anterior pituitary function are becoming capable of future definition. Whilst excitation, or in some instances inhibition, is of cerebral origin, complex feedback mechanisms have been defined which operate on the higher nervous system. These can be separated into the long and short feedback systems and are predominantly negative in effect. The long feedback system is exemplified by the actions of gonadal steroids, corticosteroids and thyroid hormones. But the special excitatory effect of a brief increase in oestrogen concentration at the appropriate moment in relation to ovulation draws attention to the subtlety of the system. The short negative feedback mechanism is mediated by the anterior pituitary trophic hormones, as exemplified by gonadotrophin, ACTH and growth hormone.

The power of the response of the anterior pituitary to stressful stimuli in releasing corticotrophin and growth hormone, in spite of the simultaneous operation of inhibitory stimuli, is an important physiological mechanism requiring further understanding, as indeed does the purpose of the responses involved.

More intricate problems to be mastered are the ways by which deeply established rhythmical secretions are regulated and the nature of the impulses involved. Such are the nyctohemeral rhythms, rhythmic changes in growth hormone secretion during sleep and the long rhythmic cycle of ovarian function. A number of drugs are known to have effects on endocrine function which are probably mediated through the nervous system. These effects may be of value, as for example in the case of the adrenergic blocking agents, in the understanding of neurogenic control mechanisms, or for therapeutic reasons as exemplified by the stimulatory properties of clomiphene. In these days of ubiquitous use of tranquillizers the clinical importance of their inhibitory effects, as for example in the case of chlorpromazine, on the release of gonadotrophins must not be overlooked.

A natural phenomenon, the mechanism of which we are almost completely ignorant, is the onset of puberty. This is discussed by Donovan and by Jeffcoate and it becomes clear that a special prepubertal balance exists within the nervous system and that in turn there may be unusual responses by it to peripheral hormones. The gonadal hormone status of juvenile subjects is, to date, in the early stages of

evaluation but doubtless, with the advent of sensitive assay techniques, will be more extensively assessed in the near future.

In theory at least the control mechanisms of posterior pituitary activity should be easier to resolve, as the intermediate stage of a neurohormonal control mechanism is bypassed in this instance. In this area special problems exist. One of these is lack of knowledge of the circulating levels of oxytocin in various circumstances. Most fundamental is the question of the mode of release of these two hormones and the pathways by which the increased release of one may occur in the absence of change in the other. In general the afferent pathways of posterior pituitary control might at first sight appear simpler than in the case of the anterior pituitary, as these are neurogenic and do not involve complex negative feedback mechanisms. Nevertheless the definition of this aspect of the control mechanism of oxytocin release still requires much detailed examination.

The following contributors have assembled much information concerning the pathological aspects of the subject. The possibilities of reduced anterior pituitary activity resulting from intracerebral lesions involving superior structures are now comparatively well recognized. Much needs to be known about the mechanisms involved. In some instances, for example the male hypogonadotrophic syndromes discussed in Chapter 2 and the female counterparts, disorders of the nervous system or of its integration of external stimuli need to be defined. Also, disturbances of the rhythmic secretion and timing of release of gonadotrophins, as in some instances of precocious puberty including those associated with overt intracranial lesions, are recognized but not understood.

The possibility of increased secretion of trophic hormones in response to increased stimulation by releasing factors is being postulated in the case of Cushing's syndrome and perhaps in some acromegalics. Such disorders might follow a failure in negative feedback mechanisms. It also appears likely that these may be abnormal in certain gonadal syndromes. On the other hand, in Graves' disease convincing evidence of normal feedback control is now forthcoming.

To date investigation of function of the nervous system and of long feedback mechanisms has been mainly by indirect means, by observing peripheral hormone changes in response to stimulants such as insulin, pyrogen and clomiphene. Little is known of abnormalities of the short feedback systems. The advent of purified preparations of releasing and inhibiting factors will greatly improve our capability of defining situations involving deficiency of stimulation by the hypothalamus. The ability to assay endogenous release of these factors will doubtless not be

too long delayed, but application of these techniques to disease in man is likely to prove a difficult enterprise. We already have reports of preliminary investigations into the effects of the administration of thyrotrophin-releasing factor in man and its effectiveness as a stimulant has been confirmed.

As El Kabir (Section VI) points out, this early work with releasing factors presages the availability of an important tool in distinguishing lesions involving the anterior pituitary gland from those in the nervous system above. The long-term need is for means of separating abnormalities arising within the nervous system itself and evaluating their detailed effects on the endocrine system mediated through the pituitary gland.

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Section II: THE NEURAL CONTROL OF PITUITARY FUNCTION— ANATOMICAL CONSIDERATIONS

B.T. DONOVAN

Although understanding of the neuro-anatomical relationships involved in the control of endocrine secretion has not kept pace with advances in endocrine knowledge, the morphological basis of the neuro-endocrine relationships to be described cannot be ignored. Most attention is given to the hypothalamus, for this provides, as it were, the funnel through which the secretion of pituitary hormones is influenced, and relatively minor damage to this area can have serious physiological consequences. Nevertheless, it is as well to point out that the hypothalamus forms but one component of several complex neuronal systems and that 'any consideration of "isolated" hypothalamic functioning is pure subcortical phrenology at its worst' (Morgane, 1969). It is also argued that it is impossible to assign particular functions to certain structures connected to the hypothalamus, such as the hippocampal formation, septal area and amygdaloid complex, because these areas operate by influencing the activity of the whole core of grey matter stretching from the septum through the pre-optic region, hypothalamus, and caudally to the midbrain.

THE HYPOTHALAMUS

Introduction

The boundaries of the hypothalamus are marked superficially by the optic chiasma, the optic tracts, and the mamillary bodies, but these anatomical limits are of little functional significance. Anteriorly, for example, the hypothalamus merges with the pre-optic area and no border can be defined. The nuclear composition of the hypothalamus has been mapped on a number of occasions, but the meaning of particular cell groupings, with a few exceptions, has proved elusive. The cells of the