RECENT ADVANCES
IN
ENDOCRINOLOGY

By

A. T. CAMERON

C.M.G., M.A., D.Sc. (Edin.), F.R.I.C., F.R.S.C.

Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital

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PREFACE TO THE SIXTH EDITION

In the rather short interval since the publication of the last edition no outstanding advance has been made, though there has been steady progress necessitating slight revision of a number of chapters, revision in the nature of extension, rather than of correction of previous work.

The production of artificial iodo-proteins with thyroid-like action and more active than desiccated thyroid, has reached the stage where commercial utilization is possible.

The employment of thiouracil in prolonged treatment of hyperthyroidism has, at least in mild or only moderately severe cases, become justifiably a means of replacing or postponing surgery, although thiouracil still remains for each patient a substance which, until proved otherwise, is potentially toxic. There is promise, however, that related compounds of inherently lesser toxicity may prove as efficacious or even more efficacious in combating thyrotoxicosis.

I am greatly indebted to Professor H. P. Himsworth, and to his patient whose case I have recorded, for furnishing me with the details of what is probably the most successful and prolonged treatment of a severe case of Addison's disease, and for allowing me to publish them. The earlier treatment of this disease with adrenal cortical extracts seemed disappointing, but this case again rouses our hopes that proper treatment may prove as efficacious for Addison's disease as insulin has proved to be for diabetes mellitus.

I am grateful to Dr. Harold Cookson and to the Editor of the "Lancet" for permission to reproduce the excellent illustration of a result of thiouracil treatment that is shown in Fig. 12.

A. T. CAMERON.

Winnipeg, Canada.

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RECENT ADVANCES IN ENDOCRINOLOGY

CHAPTER I

INTRODUCTION

THE pre-history of endocrinology is the story of gradual failure of detoxication theories to explain accumulating facts, demonstrable by experiment, concerning certain "ductless glands." All such theories are not even yet universally rejected.

The history of endocrinology as an exact branch of science scarcely antedates the present century; the name itself is still younger. Until chemical studies progressed sufficiently to result in isolation of several of the "internal secretions," and to emphasize the fact that these are specific compounds, with specific physiological functions, endocrinology was nebulous, and necessarily inexact. Now that we know the chemical nature of most of these compounds, and have learned much about their physiological activities, endocrinology has become an exact science, or branch of science, inseparably related to physiology, pharmacology and biochemistry.

It seems desirable to stress at the outset two fundamental concepts, whose truth, though still unadmitted by numerous investigators, is becoming more apparent with each advance. *The normal function of an endocrine gland is not a detoxication, but the production of one or more specific chemical compounds essential to the normal life of the whole organism. In the different pathological states of such a gland it may produce too much or too little of these specific compounds, but it does not produce abnormal compounds.*

The term *hormone* (from Gk. *hormōn*, rousing or setting in motion), originally proposed by Bayliss and Starling, has been universally adopted for endocrine compounds, though in its original sense it scarcely applies to all of them. Other suggested terms as *chalone* and *autacoid* are no longer used. *Endocrinology* (Gk. *endon*, within; *krinein*, to separate) is generally accepted as the name of that branch of science which concerns itself with the hormones, while the glands concerned are *endocrine glands*, and their "internal secretions" are *endocrine secretions*.

The terminology applied to the hormones themselves is gradually becoming simplified and more definite, as these compounds are gradually being obtained in pure crystalline form. There is still too great a tendency to coin new names to avoid those employed by the larger pharmaceutical companies. Many of these firms are now employing the scientific names, as well as those they use for patent purposes. The physician is, therefore, more easily able to apply his own knowledge to the selection of his therapy.

Hormone production is associated with the thyroid, parathyroid, pituitary, and adrenal glands, the islet tissue of the pancreas, the mucous membrane of the upper part of the intestine, and the gonads and placenta. The thymus and pineal probably produce hormones. Apparently the kidney must also be included. Various claims have been made for others, to which short reference will be made.

By far the most perplexing problems in endocrinology are those concerned with the interrelationships of the actions of two or more endocrine compounds. Such interrelationships cannot be dealt with very systematically; they intrude into the majority of discussions of clinical cases exhibiting endocrine disturbances; they even intrude when normal functions are under consideration. They have suggested a multitude of syndromes, involving much unnecessary differentiation; the inaccurate conceptions underlying many of these suggested syndromes have led to much inaccurate therapy.

In so far as therapeutic treatment is dealt with in this volume, I endeavour throughout to indicate the logical treatment in light of present knowledge. If the assumption be true, as I believe, that almost all endocrine disorders are primarily associated with either hypo- or hyperfunction of only one endocrine gland, then this logical treatment seems obviously to consist in the application of replacement therapy for hypofunction and application of some means of depression for hyperfunction of that gland.

Rational replacement therapy must always take into account the fact that only two or three endocrine principles have been definitely demonstrated to be effective when administered by mouth. Our knowledge of the actual nature and of the actions of the others creates a demand for properly standardized concentrates suitable for injection, and such a demand is being met. Only such properly standardized preparations should be employed.

A useful addition to methods of treatment is the implantation of crystal pellets (suitably sterilized) of potent hormones. A single implant can produce a desired effect for weeks. The method has proved of service with the hormones of the gonads and the adrenal cortex. The essence of the method consists in selecting material of very slight solubility, so that tablets of insulin, fairly soluble, are useless for the purpose (Parkes and Young), though the injection of insoluble protamine zinc insulin achieves the same purpose in much lesser degree.

Surgical treatment is an obviously correct procedure for the majority, if not all, conditions in which a hyperfunction exists. Claims for employment of X-ray therapy are frequent; the relative benefit to be obtained from it and the types of case which will obtain most benefit have not yet been fully established.

The *correct therapeutic dosage of endocrine preparations* is not a subject for generalization, but rather for individualization. It is not possible in this volume to do much more than indicate some of the many potential errors which may arise in connection with dosage.

Where pure endocrine principles or active derivatives are available, such as thyroxine, or crystalline insulin, then dosage can be based upon specific amounts of them. But if the treatment be in the nature of replacement therapy, each individual requirement must be different, for the amount of non-functioning endocrine tissue whose normal output has to be replaced differs in each patient. This is illustrated by Collip's *principle of inverse response*, which he defines: "The responsiveness of an individual to administered hormone varies inversely with the hormone content or production of the individual's own gland." This dictum aptly illustrates the impossibility of accurate dogmatism in endocrine therapy. Even when total replacement is necessary, as, for example, following total thyroidectomy, the requirements of individuals will be related to their body-volume or body-surface or both, while sex and age will also modify them.

When such pure preparations are not available, not only is accurate standardization necessary, but a correct basis of standardization. The same weight of desiccated thyroid may give very variable results if different preparations are at different times given to the same patient. Thyroid should be standardized according to its iodine content—it now frequently is.

Precision of dosage of preparations from the anterior pituitary is and will remain difficult, till complete separation of the hormones of that gland has been achieved; at present all commercial preparations are mixtures of several hormones in uncertain amounts.

Pratt, some years ago, published a thoughtful paper on this subject of dosage in endocrine disorders. He pointed out that the necessity of considering each individual separately is by no means limited to endocrine therapy, and that the ordinary dosages prescribed for such established drugs as digitalis, arsphenamine, the belladonna group and sedatives frequently produce very varying, and sometimes dangerous, consequences, so that it is not surprising that precision of dosage is still not possible for the much newer endocrine compounds. He laid down the obvious but too often neglected dictum that *the reactions of the individual patient to any therapeutical agent should be the criteria for the final determination of the manner and amount to be administered.* It is equally obvious that error on the side of low dosage is the safest error.

Two of Zondek's fundamental hypotheses may well be quoted here; the first also has a bearing on the variation of dosage for different individuals, and for the same individual at different times. "Hormonal effect is not an absolute but a variable quantity, depending not least upon the momentary condition of the organ on which it acts—more especially, the physico-chemical condition of its cells. Functional and anatomical changes in endocrine glands should not always be regarded as the cause of disease, but in many cases the reaction of the glands to morbid processes located in certain other organs."

Complete knowledge of the chemical constitution of certain hormones has led to attempts to improve upon nature. Oestradiol was produced in the laboratory and shown to be more potent than the natural oestrone, but, later, oestradiol was proved to be the true hormone of the ovary. Desoxycorticosterone was a laboratory product before it was isolated from the adrenal cortex. In those two cases nature was ahead of man's efforts. More recently Dodds and his collaborators have found synthetic oestrogens unrelated chemically to those produced in the ovaries (cf. Chapter VIII) and this type of research has already proved of very great value.

Since of all the endocrine glands the pituitary, by virtue of its control of many of the most important functions of the body, seems to be by far the most important, it seems at first sight logical to deal with that gland first. Yet a considerable part of the activities of the pituitary lies in the control of other endocrine glands, and these activities cannot be appreciated until those of the glands it controls have been dealt with. Thus in reality it is more logical to defer consideration of the pituitary until most of the other glands have been considered.

It is therefore useful to give at this place a very brief account of the general functions of the pituitary and its relationship to other endocrine glands. The posterior pituitary produces, probably, only a single hormone, of such labile character that even solution in various organic solvents changes it to the two forms customarily considered as the hormones of this lobe. Through this hormone the posterior pituitary controls kidney tubule re-absorption of water, and the contraction of uterine muscle, and possibly also regulates capillary size.

The anterior pituitary by means of a still uncertain number of hormones controls (i) the thyroid gland, and thereby its control of certain oxidative and other chemical reactions in the tissues, (ii) the adrenal cortex, and thereby its control of electrolyte and carbohydrate metabolism, (iii) the gonads, and through their hormones the secondary sex organs and functions and the reproductive processes, and (iv) directly, by a specific hormone, the secretion of milk by the mammary glands. It also seems to possess direct control of certain growth processes, and thus to some extent of general growth, and of certain reactions which affect protein, carbohydrate and fat metabolism. It does not directly control the parathyroid glands, the islets of Langerhans, or the adrenal medulla.

The parathyroid glands control phosphorus and calcium metabolism, the islets of Langerhans, through their output of insulin, control carbohydrate metabolism, and the adrenal medulla, secreting adrenine, can increase blood pressure and mobilize glucose into the general circulation.

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CHAPTER II

THE THYROID GLAND

INTRODUCTION

THE thyroid gland is built up of a large number of follicles of varying size and shape but tending to be spheroidal (cf. Fig. 1).

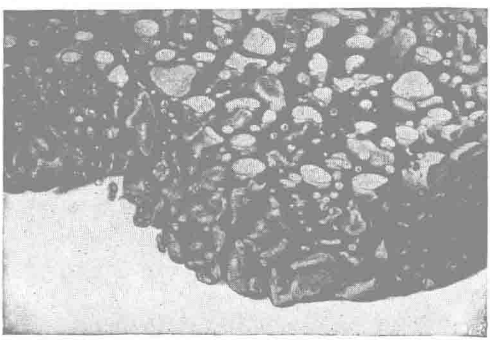


FIG. 1. Top and side view of wax model of normal human thyroid gland. (From Rienhoff, Medicine, 1931, x, 293.)

Follicles measuring 0·05 to 0·12 mm. in length predominate in the human gland. Each consists of a closed vesicle containing colloid material and lined with epithelium, the cells of which are columnar, cubical or flattened, according to the state of activity of the gland and degree of distension of the vesicles. The intervesicular substance is areolar tissue, which may contain lymphocytes and other cells, including epithelial cells (Sharpey-Schafer ; Jackson). The lymphatic system of the gland is a closed system, playing no rôle in the transmission of its hormone (Rienhoff).

In early foetal life vesicles develop from solid epithelial masses ; a little later colloid is produced and is stored in them. After birth secretory activity is marked throughout infancy and childhood ;

a small reserve of colloid is always present. Subsequent to puberty the colloid store increases, and, as judged by the histological picture, activity slowly decreases (cf. Cooper), and this is in agreement with a slow decrease in basal heat production. Cooper has stressed the striking histological resemblance of the gland of the human adolescent and that considered characteristic of (untreated) Graves' disease, and Abbott finds that this is true also for young domestic and wild animals; the thyroids of older animals, as of man, store more colloid and present a histological picture suggesting lessening activity. Hoar has reported a somewhat parallel picture in the thyroid of the Atlantic salmon.

The interfollicular epithelial cells can produce new follicles whenever adequate stimuli activate the gland. This has been shown for rats by Baillif, using cold as stimulus. Seasonal changes in temperature are accompanied by histological changes in the thyroids of farm animals (cf. Kendall). Somewhat similar changes occur in the thyroids of women during the menstrual cycle. Pregnancy appears to produce a hyperplasia, probably accompanied by an increase in function (Verdozzi; Abbott and Prendergast). Different diets also produce some degree of change in the histological picture.

Since under normal physiological conditions the histological picture of the thyroid can show such definite variations, it is evident that too great a differentiation of thyroid histology in pathological states may lead to error.

The blood volume of normal man moves through his thyroid once an hour (Lerman).

The blood supply of the thyroid is of importance in studying its pathological changes. Besides the four main arteries (paired superior and inferior thyroid arteries) and the occasional fifth (thyroidea ima) there are numerous unnamed irregular arteries, small in size under normal conditions, but capable of great enlargement in goitrous conditions; they arise chiefly from the pharyngeal, oesophageal and tracheal arteries. Beneath the true capsule of the gland there is a rich arterial anastomosis. The veins commence as a perifollicular plexus and follow the small arteries to the periphery of the gland, there developing into a plexus covering the whole gland. The finer lymphatic radicles are present in intimate association with the follicular epithelium and a plexus exists around each follicle. By their union a coarser network is formed, with ultimately a close-meshed anastomosis enveloping the whole gland (cf. Joll).

Control of Thyroid Secretion. It is frequently assumed that the thyroid gland is under control of the sympathetic nervous system, and that this is affected in abnormal thyroid states ; in Graves' disease nervous excitation of the patient is a cardinal symptom.

According to Sunder-Plassmann each thyroid cell is under sympathetic nerve control through a terminal reticulum. Bachromejew and Ter-Ossipewa observed, following stimulation of the peripheral end of the superior laryngeal nerve, histological changes in the thyroid suggesting increased activity.

Nonidez has adduced anatomical evidence that the blood supply to the thyroid is under close control of the nervous system, which can thus indirectly influence the rate of secretion and discharge of the hormone. He found evidence for a specific thyroid nerve, and this has been confirmed and extended (in the dog) by Ross and Moorhouse. This nerve is made up of fibres from the superior cervical ganglion of the sympathetic, and parasympathetic fibres from the superior laryngeal branch of the vagus (or, frequently, from the ganglion nodosum or the vago-sympathetic trunk). The thyroid nerve terminates in branches which enter the gland with branches of the superior thyroid artery.

Stimulation of the thyroid nerve consistently slows the flow of blood through the gland, although histological changes in the gland from repeated stimulation in acute experiments have not been demonstrated (Ross and Moorhouse). Thus there seems to be an important *indirect control of the thyroid gland through nervous regulation of the blood supply and therefore of the output of hormone.*

Haney found that stimulation of the cervical sympathetic nerve in rabbits caused elevation of the basal metabolic rate, and this was partially confirmed by Friedgood and Bevin. Brock *et al.* found that bilateral cervical sympathectomy in rabbits caused a decrease in the basal metabolic rate. These changes also indicate sympathetic control of thyroid activity.

The thyroid gland is largely controlled by the thyrotrophic hormone of the anterior pituitary (cf. Chapter IX, p. 342).

Galli-Mainini concludes from *in vitro* studies of guinea-pig thyroids by the Warburg technique that the thyroid and thyrotrophic hormones are antagonistic, and that the amount of thyroid hormone in the blood itself acts as regulator of thyroid gland activity, which is inhibited by a rise in its level, and *vice versa.*

Iodine and the Thyroid Gland

It is now agreed that thyroid function is associated with the elaboration of a specific hormone rich in iodine, and that insufficient ingestion of iodine is one of the chief causative factors of simple goitre.

Iodine is widely distributed, though few materials are rich in it. The amount of it in plant food and in drinking water depends on the amount in the soil in which the plants grew or from which the water drained, and varies from practically nil to a few micrograms per cent. The same is true for land animal products such as meats, eggs, butter and milk. Such materials from different sources show great variations in their iodine content, due to corresponding variations in the content of the soils in different land areas. Marine animals are richer in the element, and many marine algae still richer. McClendon (1) has compiled valuable summaries of the available data (cf. also Lunde, and Salter).

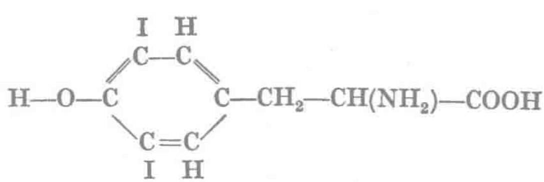
Iodine is present in measurable amounts in all mammalian tissue. Most endocrine glands contain relatively more than non-endocrine tissue, but the thyroid is relatively much richer still (adrenals and ovaries being next in order). The most accurate figures for *normal* human thyroids are still those of Zunz, who found that fresh glands of adult man from nineteen to forty-four years of age averaged 0·056 per cent. (extremes 0·023 and 0·068 per cent.); the corresponding figures for dried glands were: average 0·229, extremes 0·119 and 0·286 per cent. The human thyroid gland in Iceland is small and unusually rich in iodine, averaging 0·083 per cent. in fresh tissue; this is presumably related to a diet unusually rich in iodine (Sigurjonsson).

Unusually high figures (about 0·8 per cent.) have been reported for beef and hog thyroids from the south of India (Dey, Krishnan and Giriraj), and (up to 1 per cent.) for the desiccated glands of sheep pastured on kelp-strewn shores or fed iodide, and of elasmobranch fishes (cf. Cameron).

Iodine is present in both the cells and the colloid of the thyroid, the colloid being somewhat richer in it (Tatum; Van Dyke).

The Iodine Compounds of the Thyroid Gland. Three compounds have been isolated, diiodotyrosine, and thyroxine, both iodized amino-acids, and iodothyroglobulin, a pseudoglobulin.

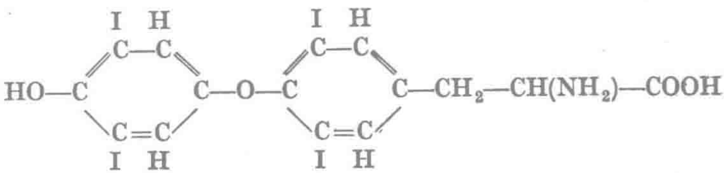
Diiodotyrosine contains 58·7 per cent. iodine. It has been



isolated from the horny axial skeleton (gorgonin) of certain corals (sea-fans) and the corresponding keratin-like spongin of sponges.

More recently Harington and Randall isolated it from the hydrolysed products of thyroid tissue and by enzymic hydrolysis of thyroglobulin, while Foster obtained it from chemically hydrolysed thyroglobulin. It is physiologically inactive.

Thyroxine contains 65·3 per cent. iodine. Kendall isolated it from thyroid tissue. Harington and Salter isolated *l*-thyroxine



from enzymatically digested thyroglobulin. The physiological activity of the racemic compound is due to its laevo-component; the dextro-form has little or none (Reineke and Turner (2)).

Iodothyroglobulin appears to have a constant composition except for an iodine content varying from practically nil to 1·7 per cent. It hydrolyses to the usual amino-acids (White and Gordon), and, as indicated above, to small amounts of diiodotyrosine and thyroxine. The amount present in the thyroid varies considerably. Ultracentrifuge and similar methods suggest a molecular weight of the order of 675,000 (McClendon (2); cf. Salter); it shows a tendency to dissociate to smaller molecules (cf. Fraenkel-Conrat).

Harington and Salter, when digesting thyroglobulin enzymatically, obtained a fraction very resistant to peptidases; this proved to be a mixture of thyroxine and a thyroxine-containing tri- or tetrapeptide.

Harington has prepared thyronine (thyroxine minus its iodine), diiodothyronine (with half the iodine content of thyroxine), and di- and tetrabromthyronine. Their physiological properties have some bearing on theories concerned with the etiology of Graves' disease.

Present evidence indicates that the normal gland contains no appreciable amount of any iodine compound other than thyroglobulin.

When thyroglobulin (or desiccated thyroid tissue) is hydrolysed by alkali, and the hydrolysate is acidified, thyroxine is precipitated, while diiodotyrosine remains in solution. Harington and Randall found the proportions of the two to be roughly equal. Blanchard and Simonnet found the ratio of thyroxine-iodine to total iodine in horse thyroid to vary from 28 to 60 per cent. However, this ratio, and the content of both diiodotyrosine and