MODERN TRENDS
IN
ENDOCRINOLOGY

Edited by

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PREFACE

A VAST AMOUNT of research has gone into endocrinology, one of the results being the massive output of literature on the subject. It is generally agreed that it is virtually impossible for any busy worker to keep abreast of latest developments and there is therefore a great need for the volume which presents the broadest outlook, emphasizes the modern approach and relegates the trite and well-worn theories.

The authors of the chapters are all experts in their particular fields and their objective has been not only to present the up-to-date approach but also to give their personal views, with a tie-up of loose ends, and with a critical evaluation of the trend of events possibly pointing to the future. The chapters are more, therefore, than a routine and stereotyped summary of the present position. In general the aim has been to highlight the advances in a particular field and to bring the present position into perspective.

Particular fields of advance in recent years have been associated with the adrenal hormones and a number of chapters deal with this subject. New work on the thyroid hormones forms the opening chapters and the subject of radioactive iodine and its uses in thyroid disease is dealt with extensively. The female sex hormones are the subject of later chapters and a comprehensive article on hormonal factors in breast development and milk secretion has been included, as has one on human infertility in the female. In the study of endocrinology the interaction and inter-relationship of hormones can lead the reader from one subject to another with little difficulty. As Editor it has been my responsibility to present a compact volume. The choice of subjects has been an arbitrary one and the scope of the work is not intended to be comprehensive. To decide which subjects must await a possible second series has proved to be a most difficult problem and as the anterior pituitary hormones are considered separately in various papers it was decided that an over-all review should not be included. This also applies to the parathyroid glands and to the subject of infertility in the male.

Briefly, this volume has covered many interesting and valuable additions to endocrine knowledge acquired in the last decade, and it will be a helpful addition to the library of physicians, endocrinologists, postgraduates and others whose work necessitates an up-to-date knowledge of modern trends in endocrinology.

I would like to take this opportunity of expressing my cordial thanks to all those who have contributed to the present volume.

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London
October, 1957

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CHAPTER 1

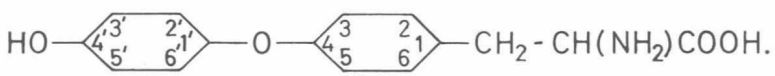
PRESENT KNOWLEDGE OF THE THYROID HORMONES

ROSALIND PITT-RIVERS

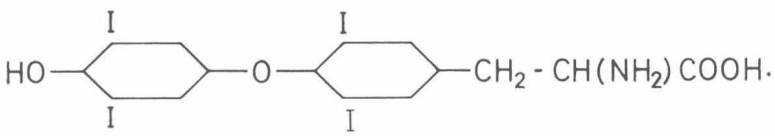
INTRODUCTION

THE PRESENT survey of our knowledge of the thyroid hormones is not intended to be comprehensive. Limitations of space make it impossible to deal adequately with the great volume of work which has been done in this field in the past 20 years; only the more salient biochemical and physiological discoveries will be considered here.

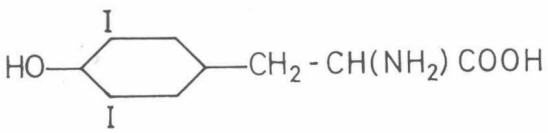
The first advance in our knowledge of the active principle of the thyroid came with Kendall's (1919) isolation of pure thyroxine from pigs' thyroid. The second advance came with the identification of thyroxine by Harington, by degradation and synthesis (Harington, 1926; Harington and Barger, 1927). Desiodothyroxine (thyronine) was at first shown to be β-[4-(4′-hydroxyphenoxy)phenyl] alanine:



In thyroxine, the iodine atoms were shown to occupy the 3 : 5 and 3′ : 5′ positions:



Harington (1933) then showed that natural thyroxine possessed the *L*-configuration and was structurally related to *L*-tyrosine. Diiodotyrosine



and iodide were also shown to be present in the thyroid, and together with thyroxine were thought to account for all the thyroidal iodine.

A NEW THYROID HORMONE

Triiodothyronine

In recent years two new techniques, chromatography and autoradiography of compounds labelled with the radioactive isotope of iodine, ^{131}I, have made a great contribution to our knowledge of thyroid metabolism. The former enables us to separate minute amounts of material; the latter to locate iodinated products on

chromatograms (Gross, 1954). Using these methods, Fink and Fink (1948) first demonstrated the presence of 3-monoiodotyrosine in rat thyroid hydrolysates. Later Gross *et al.* (1950) and Gross and Leblond (1951) showed that the administration of ^{131}I to iodine-deficient rats gave rise to the presence of hitherto unknown compounds in their thyroids, sera and other tissues. One of these compounds (Unknown 1) was demonstrated by Gross and Pitt-Rivers (1951) in the plasma of patients who had received therapeutic doses of ^{131}I. These authors (Gross and Pitt-Rivers, 1952a) identified Unknown 1 as 3 : 5 : 3′-triiodothyronine, and at the same time Roche *et al.* (1952) found triiodothyronine among the products of thyroglobulin hydrolysates. Gross and Pitt-Rivers (1952b) investigated the physiological activity of triiodothyronine in preventing thiouracil-induced goitre in rats, and Gross, Leblond and Trotter (1952) showed that it was highly effective in alleviating myxoedema in man. The high biological potency of triiodothyronine, which will be described in detail later, has made it generally accepted as one of the thyroid hormones.

BIOSYNTHESIS

The biosynthesis of the thyroid hormones may be divided into two main stages: (1) the concentration of iodide from the circulation; and (2) the organic binding of the accumulated iodine.

Iodide-concentrating mechanism

The iodide-concentrating mechanism, or iodide trap, has been the subject of numerous experiments, especially in the last few years. The separation of the two biochemical stages for individual study has been made possible by the discovery of two types of antithyroid drugs: (*a*) thiocyanate and certain inorganic cations, notably perchlorate, which inhibit the iodide trap, and (*b*) the thiocarbamides (thiouracils, aminothiazoles) which inhibit the organic incorporation of iodine. By administering the thiocarbamides, the iodide trap may be investigated independently.

It must, of course, be realized that separation of one stage of hormone synthesis from another may result in abnormal function. Nevertheless, this method of investigation has enabled workers to study effects of hypophysectomy, iodine deficiency or excess, and other factors in the stages of thyroid biochemistry. Many *in vivo* studies have been carried out, notably by Chaikoff (*see* Chaikoff and Taurog, 1948; Taurog *et al.*, 1947; Vanderlaan and Vanderlaan, 1947; Vanderlaan and Greer, 1950; and Halmi *et al.*, 1953, 1954). *In vitro* studies have been carried out by Chaikoff, and more recently by Wyngaarden *et al.* (1951).

Notwithstanding, the mechanism whereby the thyroid concentrates iodine is still unknown, as are the enzyme systems which produce the energy required for this concentration.

Organic binding of accumulated iodine

Organic binding of iodine is generally thought to involve the following reactions:

(1) Oxidation of iodide to iodine.
(2) Iodination of tyrosine to monoiodotyrosine and diiodotyrosine.
(3) Oxidative coupling of diiodotyrosine to thyroxine.
(4) Formation of triiodothyronine.

There are two possibilities: partial de-iodination of thyroxine, or the coupling of one molecule each of monoiodotyrosine and diiodotyrosine; no direct evidence in favour of either reaction exists, but as Roche and Michel have been unable to demonstrate any de-iodination of thyroxine by thyroid slices *in vitro* (though monoiodotyrosine and diiodotyrosine do undergo de-iodination) they therefore favour the latter possibility.

Chaikoff and his colleagues have been responsible for much enlightenment on the nature of thyroid hormone synthesis (Chaikoff and Taurog, 1948), as have Leblond, Gross and their group of workers (Gross and Pitt-Rivers, 1952c; Gross, 1954). We are, however, without any real knowledge of the enzymes which oxidize iodide to iodine and those which potentiate the coupling of diiodotyrosine to thyroxine, apart from the histochemical evidence for a thyroid peroxidase (Dempsey, 1944). Other enzymes in the thyroid have been detected by this means including a protease (De Robertis and Nowinski, 1946). The thyroid protease has recently been isolated and purified (McQuillan and Trikojus, 1953; McQuillan *et al.*, 1954), and conditions governing its action on thyroglobulin determined. This enzyme is responsible for the release of the iodinated amino acids, which are mainly present in the gland, incorporated into the storage protein, thyroglobulin.

Small amounts of free iodinated compounds have been detected after the administration of ^{131}I to animals (Gross, 1954); these may consist of an equilibrium mixture of iodinated amino acids about to become incorporated into thyroglobulin and those about to pass into the circulation.

At present there is no evidence as to whether tyrosine is iodinated in the free state and then bound in protein linkage or whether it is iodinated in the bound state, but both theories have their advocates.

THE CIRCULATING THYROID HORMONE

The nature of the circulating thyroid hormone was for many years a matter of debate. Trevorrow (1939) first suggested that thyroxine itself was the circulating hormone and that it was in some way bound to protein, but at the time her work was largely ignored. Later, Lerman (1940) produced immunological evidence that thyroglobulin was not the circulating hormone. It was not until 1948 that Taurog and Chaikoff produced convincing evidence that thyroxine was the principal hormonal constituent in blood, a fact which is now established (Laidlaw, 1949; Rall, 1950; Gross *et al.*, 1950; Rosenberg, 1951). That thyroxine is loosely bound to a protein in the blood (Gordon *et al.*, 1952; Larson *et al.*, 1952; Robbins and Rall, 1952; and Petermann *et al.*, 1954) has also been demonstrated, but as yet this protein has not been identified.

The thyroxine-building protein migrates in an electrophoretic field between α_1 and α_2 globulins, and possesses properties similar to those of Schmids' α_2-glycoprotein. Changes in the thyroxine-binding pattern in pregnancy and in certain pathological conditions have been studied. (Peters *et al.*, 1948; Danowski *et al.*, 1950; Horst and Rösler, 1953; Horst, 1954; and Dowling *et al.*, 1956.)

Abnormal blood-iodine components have been detected, but their physiological significance is not known, while abnormal proteins have been found in the blood after large therapeutic doses of ^{131}I. Triiodothyronine also circulates in the blood,

though in relatively small amounts, and it is associated with protein; its binding is, however, not nearly so specific as that of thyroxine (Deiss *et al.*, 1953).

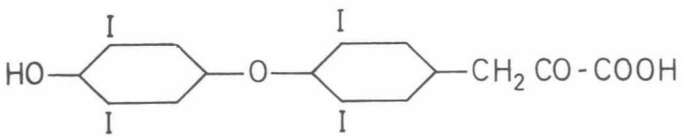
Monoiodotyrosine, diiodotyrosine and thyroglobulin are not found in normal sera, but they do appear after massive therapeutic doses of ^{131}I and in certain patients with congenital goitre (Stanbury *et al.*, 1955, 1956); further, diiodotyrosine has been demonstrated in the urine of nephrotic subjects (Rasmussen, 1956); the origin of this diiodotyrosine is not known, but it probably appears as a metabolite of thyroid hormone rather than from the thyroid gland via the circulation.

METABOLISM

Quantitative aspects of iodine metabolism in man under normal and pathological conditions have been investigated by workers too numerous to mention individually. In the present article, only the biochemical nature of thyroid metabolites will be considered.

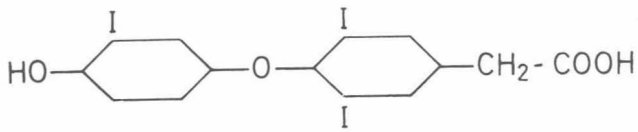
For detailed study the reader is referred to the review by Riggs (1952): later works include the study on endemic goitre by Stanbury *et al.* (1954), and papers by Berson and Yalow (1954), Ingbar and Freinkel (1955) and Sterling and Chodos (1956).

As has been said before, monoiodotyrosine and diiodotyrosine do not appear in the blood in normal subjects; their metabolism is entirely intrathyroidal. After proteolytic release from thyroglobulin (but *not* before) they are de-iodinated by the dehalogenase of the gland. The fate of ^{131}I labelled thyroxine and triiodothyronine has been studied in patients and in laboratory animals (Gross and Leblond, 1947; Albert and Keating, 1952; Taurog *et al.*, 1952; Briggs *et al.*, 1953; Roche *et al.*, 1954; and Myant, 1956). After injection, thyroxine is rapidly distributed between the blood, liver and tissues; it then passes into the gastro-intestinal tract via the bile. In the liver, both thyroxine and to a lesser extent triiodothyronine are present as conjugates, probably glucuronides; these glucuronides have not been synthesized, but treatment of the conjugates with β-glucuronidase leads to the regeneration of the parent amino acids. The formation of these glucuronides can be inhibited by liver damage, induced by allyl formate intoxication (Beraud *et al.*, 1956). There is also evidence, obtained from a number of colour reactions of carbonyl compounds, that bile contains carbonyl derivatives of thyroid hormones. Roche *et al.* (1954) identified these compounds as pyruvic acid derivatives of thyroxine and triiodothyronine.



In rats a considerable amount of iodine is excreted in the faeces (up to 60 per cent), mainly as thyroxine, but in man the most important identifiable metabolite of the thyroid hormones is the iodide found in the urine; this of course only applies to man in a healthy state. Brief mention has already been made of abnormal metabolites found in certain pathological conditions.

Triiodothyroacetic acid.—Roche and his colleagues have recently provided evidence of the presence of triiodothyroacetic acid (Pitt-Rivers, 1953) in kidney homo-



genates of rats which had received doses of ^{131}I labelled triiodothyronine; this compound could well be derived from the keto acid analogue of triiodothyronine. So far, however, it has not been found in tissues after administration of radio-iodide, and the possibility exists that the acetic and pyruvic acid analogues do not represent the normal metabolic pathway of thyroid hormones, but arise from the body's inability to deal with greater than physiological doses of drugs. These findings await confirmation.

Conversion of thyroxine to triiodothyronine

The conversion of thyroxine to triiodothyronine *in vivo* has been demonstrated in the mouse (Gross and Leblond, 1951), to a slight extent in athyreotic man (Pitt-Rivers, Stanbury and Rapp 1955) and in the rat (Hogness *et al.*, 1955). It may well be that the conversion of thyroxine to triiodothyronine is not an essential step in thyroid hormone metabolism; the original hypothesis of Gross and Pitt-Rivers (1953) that thyroxine was a precursor of triiodothyronine has not been justified by subsequent findings.

Albright, Larson and Tust (1954) found that rat kidney slices can consistently convert thyroxine to triiodothyronine *in vitro*; Barker, on the other hand (personal communication), has only had very occasional evidence of de-iodination *in vitro*. Sprott and Maclagan (1954) have also obtained de-iodination of thyroxine by rat liver homogenates with some chromatographic evidence that triiodothyronine was formed.

The presence of diiodotyrosine in invertebrates (corals, sponges) has been recognized for many years, and recent work on the metabolism of ^{131}I in invertebrates has revealed, in one instance, the biosynthesis of considerable amounts of thyroxine.

Gorbman *et al.* (1954) found that after 24 hours' immersion in a solution containing ^{131}I the bivalve *musculium partumeium* had concentrated over 40 per cent of the environmental iodide, and had converted as much as 20 per cent of it to thyroxine. Whether triiodothyronine was also present could not be determined, because the solvent used for chromatographic analysis (butanol-acetic acid) does not separate thyroxine and triiodothyronine. Roche *et al.* (1951) detected thyroxine, but only in traces, in the gorgonine *Eunicella verrucosa* Pallas, though monoiodotyrosine and diiodotyrosine were present in considerable amounts.

The formation of thyroxine in invertebrates is of great interest, since it demonstrates that diiodotyrosine-coupling enzymes must exist in nature in the absence of the thyroid gland. From the evolutionary standpoint, thyroxine biosynthesis has preceded the development of the organ specialized for its production.

PHYSIOLOGICAL ACTIVITY

Effects *in vivo*

Myxoedema in man

Although the absence of thyroid function in man and in animals results in myxoedema, cretinism and stunted growth, these conditions can be overcome by the administration of desiccated thyroid or thyroxine. Triiodothyronine has been shown to have, qualitatively at least, a thyroxine-like effect in myxoedematous subjects. Gross *et al.* (1952) showed that small daily amounts of triiodothyronine (80 micrograms) restored the basal metabolic rate, serum cholesterol and weight to normal levels in two patients. Since then many workers have studied the effect of triiodothyronine in man. Rawson *et al.* (1953) and Blackburn *et al.* (1954) considered the potencies of thyroxine and triiodothyronine to be the same, while Deltour and Bekaert (1953), Lerman (1953) and Asper *et al.* (1953) found triiodothyronine to have a much greater initial activity, as much as 5–10 times that of thyroxine. Although Deltour and Bekaert (1953) found no difference in their latent period of action, it is now generally agreed that in man, triiodothyronine has a very rapid effect—changes in temperature and pulse rate may be detected an hour after administration of the drug—but these same effects would take days rather than hours to be obtained with thyroxine.

The very rapid relapse of myxoedema patients after withdrawal of triiodothyronine has been noted by Frawley *et al.* (1956), who also discerned some side-effects (headache, tachycardia, angina). It was not, however, suggested that triiodothyronine was more likely to produce these symptoms than other thyroid preparations.

Kurland *et al.* (1955) described a response to triiodothyronine in hypometabolic (non-myxoedematous) patients who had not responded to treatment with desiccated thyroid. Striking clinical improvement was obtained in some cases.

Starr and Liebhold-Schueck (1953) have studied the relative effects of thyroxine and triiodothyronine in normal subjects, especially with regard to their depressant action on ^{131}I uptake by the thyroid.

In laboratory animals

Triiodothyronine is able to raise oxygen consumption in intact rats: Gemmill (1953), Heming and Holtkamp (1953a), and Maclagan *et al.* (1952) all found a potency of 1–2 in favour of the drug, while Colville and Bonnycastle (1953) and Tomich and Woollett (1953) gave the higher ratios of 3–5 in its favour. In thyroidectomized rats, the differences were more striking, and most workers have found that triiodothyronine shows a consistently higher potency under these conditions. Donhoffer (1956) has recently shown that the drug has an immediate action on the basal metabolic rate of hypophysectomized rats.

Goitre prevention assay

The discovery of antithyroid drugs of the thiouracil type provided us with a new assay of thyroidal activity. Dempsey and Astwood (1943) showed that goitres produced in rats by feeding thiouracil could be reversed by simultaneous administration of thyroxine; the effect was proportional to the dose of thyroxine. In this assay, triiodothyronine was found to be from 3·5 to 7·4 times more active than

thyroxine (Gross and Pitt-Rivers, 1952b, 1953; Tomich and Woollett, 1953; Heming and Holtkamp, 1953b; and Colville and Bonnycastle, 1953). Ferguson and Warson (1953) emphasized the importance of the route of administration of these compounds.

Mouse anoxia test

The administration of thyroid preparations has been shown to accelerate the death of mice from anoxia (Smith *et al.*, 1947). Tomich and Woollett (1953) found that triiodothyronine was 4·5 times as active as thyroxine in this test, but Gemmill (1953) found only slight differences in potency, while Anderson (1954) obtained values in agreement with those of Tomich and Woollett. The thyroid-stimulating hormone of the pituitary accelerates both the uptake of iodide by the thyroid and the discharge of hormone from the gland, though Wolff (1951) found that this discharge was inhibited in rats by small doses of thyroxine. Gilliland and Strudwick (1953) showed that triiodothyronine was more effective than thyroxine in suppressing the discharge of iodine from chicks' thyroids—a finding confirmed by Anderson (1954).

Amphibian metamorphosis test

Thyroid substance and thyroxine were early shown to accelerate metamorphosis in amphibia and this effect has been widely used for assay of thyroid-like compounds. Roth (1953) found only a relatively low potency for triiodothyronine in his first assays, but later (Roth, 1954) obtained values similar to those of Shellabarger and Godwin (1954) and of Bruice *et al.* (1954); the potency of triiodothyronine was 3–4 times that of thyroxine in this test.

Miscellaneous effects

Bartlett *et al.* (1954) investigated the galactopoietic effects of *L*-thyroxine and *L*-triiodothyronine in lactating cows and found that, when both compounds were given orally, 64 milligrams of triiodothyronine daily had much less activity than 75 grammes of thyroxine. When the compounds were injected subcutaneously, daily doses of 5 milligrams of triiodothyronine were somewhat more effective than 5 milligrams of thyroxine; it appears that the method of dosing is important—the lower oral activity of triiodothyronine may be due to its greater solubility and destruction by bacteria in the rumen. Triiodothyronine was more active than thyroxine in increasing the heart rate of cows; its galactopoietic activity apparently does not parallel its other metabolic effects, even when administered by the most advantageous route.

Tusques (1953) has shown that 3 daily intraperitoneal injections of thyroxine, or of triiodothyronine, in newborn rats shortly after birth will induce opening of the eyes on the ninth or tenth day, whereas spontaneous opening does not occur until the fourteenth day. Maturation of the lachrymal glands, opening of the external auditory orifice, and other processes, were also hastened. The two compounds had the same potency and the same latent period of action.

Triiodothyronine has also been shown (Bruce *et al.*, 1954) to reverse the effects of hypothyroidism on the plumage of birds treated with radioactive iodine. Thyroxine has long been known to effect this reversal (Parkes and Selye, 1937), but