THE ENDOCRINES IN THEORY AND PRACTICE

This article is one of a series on Endocrinology contributed by invitation

PHYSIOLOGY OF THE THYROID GLAND

BY

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The thyroid gland was first described anatomically in 1656; for more than two hundred years, however, no agreement was reached as to the nature or, indeed, the very existence of its function in the normal organism. As in the case of the chemistry of the thyroid, knowledge of the physiology of the gland has its origin in the study of the commonest disease to which it is subject—namely, simple goitre.

In the previous article reference has been made to a medical treatment of great antiquity, which ultimately led to the discovery of the association of iodine with thyroid activity; we have now to see how the alternative surgical treatment revealed the normal physiological function of the gland.

In most cases of simple goitre which were treated surgically in the latter half of the last century and earlier a part only of the enlarged gland was removed at operation; in the more severe cases, however, where pressure symptoms were troublesome, complete removal of the thyroid was sometimes practised. It was observed almost simultaneously by the Swiss surgeons Kocher and the brothers Reverdin that while patients who had suffered partial thyroidectomy showed no untoward after-effects, those from whom the thyroid had been completely removed presented a different picture. The immediate result of the operation was relief of the acute symptoms, but after the lapse of some months the patients passed into a condition which was likened by Kocher to cretinism and by Reverdin to the newly described myxoedema, which had been associated by Ord with atrophy of the thyroid.

The clinical observations were extended by the study of experimental extirpation of the thyroid in animals, and although the results of this work were greatly confused in certain species by the effects of the parathyroidectomy which was unconsciously performed at the same time, they served, nevertheless, to confirm the conclusion that the thyroid was essential to the normal life of the body. Rapidly following upon this work came the first demonstration of the possibility of restoration of deficient thyroid function by replacement therapy with thyroid gland, which proved that the effect of the latter must be exercised through an internal secretion.

Although, however, these investigations proved beyond question that the thyroid performed an essential function, they did nothing to explain what was the real nature of this function. Light was first thrown on this problem by the observation that administration of excessive amounts of thyroid was followed by increased nitrogenous excretion, while the latter was diminished in myxoedema. The obvious interpretation of this observation—namely, that the thyroid secretion influenced the metabolic rate—was amply confirmed by the measurements of the gaseous exchange in various conditions of hyperthyroidism and hypothyroidism which were made by Magnus Levy. Administration of thyroid or the hyperthyroidism of Graves's disease caused increased oxygen consumption, and in myxoedema the oxygen consumption was abnormally low.

General Physiological Effects of Thyroid Secretion

Metabolism.—The stimulation of metabolism as a whole which was thus established as the predominant effect of the thyroid secretion lies at the root of all the individual effects of this secretion which have since been observed. In so far as metabolism is concerned, reference has already been made to the increased nitrogenous excretion which is to be observed in hyperthyroidism; this excessive loss of nitrogen is due not only to increased tissue breakdown, but also to increased oxidation of exogenous nitrogen. Carbohydrate metabolism is also affected, in that excessive thyroid secretion causes impairment of the glycogenic function of the liver, with the result that the alimentary tolerance for glucose is diminished, and in severe hyperthyroidism—for example, in Graves's disease—glycosuria may occur. The emaciation which is a prominent symptom of hyperthyroidism is an obvious indication of the increased rate of oxidation of fat that occurs in response to the increased demand for energy. The effect of hyperactivity of the thyroid on inorganic metabolism is most evident in the great loss of calcium from the body which occurs in this condition; the increased excretion of calcium is chiefly to be observed in the urine and differs from that caused by hyperparathyroidism in that it is not accompanied by hypercalcaemia. In prolonged hyperthyroidism, as in Graves's disease, the loss of calcium may be so large as to cause osteoporosis, indicating that the excess of calcium excreted is derived from the bones.

Growth and Development.—The influence of the thyroid secretion on growth and development is best illustrated by its well-known accelerating effect on amphibian metamorphosis; the effect is essentially an acceleration of the rate of development at the expense of quantitative growth. The predominant importance of normal thyroid activity during the period of growth is further shown by comparison of cretinism with adult myxoedema. In cretinism, which amounts to foetal myxoedema, the pathological changes produced are profound and irreversible in character, and a relatively small degree of improvement can be obtained by thyroid medication. An adult suffering from myxoedema, on the other hand, can be restored to a completely normal condition by adequate replacement therapy with thyroid gland.

Heat Regulation.—The subjective sensations of warmth and cold which are associated with hyperthyroidism and hypothyroidism respectively are doubtless largely due to the corresponding variations in the total metabolic rate. Apart from this, however, abnormalities of thyroid activity involve definite instability of the heat-regulating mechanism. This is shown by the exaggerated response to hyperpyretic drugs which is obtained in hyperthyroidism, and the intimate connexion of the thyroid with heat regulation has been further demonstrated by the response of the blood flow through, and the oxygen consumption of, the gland in experimental animals subjected to changes of body temperature.

Effects of Thyroid Secretion on Individual Tissues

Apart from the generalized effects already mentioned, the thyroid secretion exercises what are apparently more specialized influences upon certain organs, predominant among which is its effect in increasing the heart rate with ultimate production of irregularities of rhythm. This action on the heart is, however, only a special manifesta-

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FIG. 1.—Normal human thyroid. Male, aged 39. Chronic nephritis. Magnification $\times 95$. Iodine content 3.6 mg./g. of dried tissue.

FIG. 2.—Human thyroid showing moderate glandular hyperplasia. Magnification $\times 95$. Iodine content 0.615 mg./g. of dried tissue. (From Marine.)

FIG. 3.—Human thyroid from a case of Graves's disease showing marked glandular hyperplasia. Magnification $\times 95$. Iodine content 0.292 mg./g. of dried tissue. (From Marine)

FIG. 4.—Human colloid goitre. Magnification $\times 95$. From a case of Graves's disease after treatment with iodine. Iodine content 4.614 mg./g. of dried tissue. (From Marine.)

tion of the general effect of the thyroid secretion on the body as a whole. Neither thyroxine nor any preparation which can be made from the thyroid has any direct effect on the isolated perfused heart. On the other hand, it is clear that the action on the heart is peripheral in character and not conveyed through the nervous system, since the isolated perfused heart of an animal treated with excess of thyroxine continues to beat at an abnormally high rate. The same remark applies to the action of the thyroid secretion on tissue respiration; no effect can be demonstrated by addition of thyroxine or thyroid to the fluid bathing an excised normal tissue, but excised tissues of thyroid-treated animals exhibit increased oxygen consumption.

Mode of Action of Thyroid Secretion

Finally, we have to recall the delay in onset and the prolonged character of the physiological reaction to a single large dose of thyroxine. Administration of 5 to 10 mg. of thyroxine intravenously to a normal man produces no perceptible effect for at least twenty-four hours. Thereafter the metabolic rate rises until it reaches a maximum after about a week, and a completely normal condition may not be regained until after two or even three weeks have elapsed. This mode of action is peculiar to thyroxine and remains entirely unexplained. In conjunction with what has just been said, however, it indicates that the influence of the thyroid secretion is diffused throughout the organism by a chemical (non-nervous) mechanism, and suggests that the ultimate effects on individual tissues may not be exercised directly by the thyroid hormone as we know it, but indirectly through the intermediation of a second mechanism.

Biochemical Factors Affecting the Structure and Activity of the Thyroid

Variations in the physiological activity of the thyroid are accompanied by considerable changes in its structure, and these in turn can be reasonably explained upon a biochemical basis.

It is well known from the work of Marine that the maintenance of normal thyroid structure is dependent on an adequate supply of iodine. The iodine content of dried thyroid tissue, which averages 0.2 to 0.5 per cent., may be as high as 1 per cent. in localities where the food is rich in iodine, and in such cases the gland will retain its normal appearance. If, however, owing to deficiency of iodine in the diet or to other causes, the iodine content of the thyroid falls below 0.1 per cent. of the dried weight the gland begins to show histological abnormalities.

The familiar normal structure of the thyroid is illustrated in Fig. 1. The vesicles are well filled with deeply staining colloid and are lined with a single layer of cubical or slightly flattened epithelium; in this particular case the iodine content was 0.36 per cent. Fig. 2 illustrates what is found when the iodine content falls below the critical level of 0.1 per cent. (in this case to 0.06 per cent.); the colloid is vacuolated and stains poorly; the epithelium has altered in character, the cells assuming a tall columnar form, and has increased in amount. Fig. 3 shows a further stage of the process (iodine 0.03 per cent.), in which the colloid is disappearing altogether and the epithelial hyperplasia is still more evident.

The explanation of this series of changes which is advanced by Marine, and which seems to me to be acceptable, is that the thyroid responds to deficiency of exogenous iodine or to any interference with the access of iodine to the gland, first by loss of colloid (stored secretion) and secondly by a "work-hypertrophy." The latter process consists of an overgrowth of the active glandular tissue in the effort to keep pace with the

demands of the body for the normal amount of secretion while the supply of the essential raw material (iodine) is deficient.

If the deficiency of iodine is maintained exhaustion atrophy of the gland may supervene and myxoedema will result. If, on the other hand, the supply of iodine is restored to a gland which has undergone much epithelial hyperplasia colloid will be stored rapidly and in excessive amount with production of a colloid goitre (Fig. 4); here the vesicles are distended with colloid and are lined with a thin layer of much-flattened epithelial cells.

It is evident that when the exogenous supply of iodine is no more than sufficient for ordinary life a relative deficiency of iodine, which will lead to changes in the thyroid similar to those just described, may be produced by a temporary increase in the physiological demand for thyroid secretion. In this way may be explained the fluctuations in the size of the thyroid in women, in whom the gland tends to be enlarged at critical stages of the sexual cycle, particularly in localities where goitre is prevalent owing to environmental scarcity of iodine.

Interrelationships of the Thyroid with other Endocrine Organs

There are few, if any, of the other endocrine organs with which the thyroid has not at one time or another been supposed to be interrelated. The evidence for many of these relationships is, however, very questionable, and it is proposed here to limit the discussion to one possibility and one established fact—namely, the supposed relationship of the thyroid and the suprarenal cortex, and the connexion which is known with certainty to exist between the anterior pituitary and the thyroid.

THE SUPRARENAL CORTEX AND THE THYROID

Concerning the suprarenal cortex relationship there is little to be said. The evidence for its existence rests on two observations.

(a) A few days after birth the suprarenal cortex of the normal child undergoes involution, and this process coincides with an increase in heat production. Since heat production is controlled by the thyroid this suggests that activity of the latter is increased by diminution of that of the cortex.

(b) Marine and Baumann have shown that severe injury to the suprarenal cortex in adult animals will cause increased heat production so long only as the thyroid is intact.

It has, however, so far been impossible to relate these observations to any naturally occurring condition of hyperthyroidism or hypothyroidism, and the suggestion that the suprarenal cortex normally exercises an inhibitory control over the thyroid remains, therefore, no more than an interesting possibility.

THE ANTERIOR PITUITARY AND THE THYROID

The position with regard to the anterior pituitary is entirely different. Here there is a large amount of satisfactory evidence that the connexion between this organ and the thyroid is direct and important. Among the numerous hormones elaborated by the anterior pituitary is one which has the specific property of stimulating the thyroid to hypertrophy. Moreover, injection of pituitary extracts containing this hormone into a normal animal causes not only hypertrophy of the thyroid, but hyperactivity, so that all the symptoms typical of hyperthyroidism appear; these symptoms even include that of exophthalmos, which cannot be produced experimentally in any other way than by treatment with the thyrotropic hormone of the anterior pituitary.

The histological changes undergone by the thyroid under the action of the thyrotropic hormone are precisely similar

to those described above as the result of the hypertrophy of the gland in response to iodine deficiency; the colloid disappears, the glandular epithelium undergoes hyperplasia, and coincidentally with these changes the iodine content of the gland diminishes. It is clear, therefore, that the thyrotropic hormone stimulates both the growth and activity of the glandular epithelium of the thyroid and the release of the active secretion into the blood stream.

Nothing is known of the way in which the pituitary controls thyroid activity in normal life. From what has been said, however, it will be clear that the possibility, and indeed the likelihood, of the existence of such control is now beyond dispute. The possible pathological implications of the work which has been done on the thyrotropic hormone are obvious. They cannot be discussed in detail here, but it may be pointed out that administration of the hormone affords the only known means of producing experimentally a syndrome indistinguishable from Graves's disease, and, further, that the histological and chemical changes which occur in the thyroid in Graves's disease are precisely similar to those elicited by thyrotropic hormone.

A stumbling-block in the way of understanding the normal mode of action of the thyrotropic hormone is that the effect of its administration is only temporary. After about six weeks the condition of an animal under treatment with it becomes again apparently normal, and, moreover, the blood serum at this time acquires the property of neutralizing the effect of thyrotropic hormone given to another animal, suggesting that an antibody against the hormone has been developed. The meaning of these observations remains quite obscure, but the phenomenon which appears to extend to other hormones of the anterior pituitary is one of great interest, and is being intensively studied by several groups of workers. If its explanation can be attained much light may be thrown on the whole question of hormone action.

Summary and Conclusions

The conclusions of this and the preceding article may be summarized as follows:

1. The thyroid has a specific affinity for iodine which enables it to utilize practically all of this element which normally gains access to the body.
2. The iodine taken up by the thyroid is introduced into the molecule of tyrosine to form 3:5-diiodotyrosine; part of this is further converted into thyroxine, which is the only naturally occurring pure compound to exhibit the qualitative physiological properties of the thyroid gland.
3. The thyroxine and diiodotyrosine so formed are then linked, either directly or, more probably, through other amino-acids, and are finally built up into the molecule of thyroglobulin or colloid, which constitutes the storage form of the thyroid secretion.
4. The true thyroid secretion is in all likelihood a peptide containing both thyroxine and diiodotyrosine, and is liberated from thyroglobulin and released into the blood stream in response to the demands of the body.
5. The general effect of the thyroid secretion is to control the rate of metabolic processes, and to this can be referred almost all if not all of the individual effects of the secretion on different organs or tissues which have been observed.
6. The normal function and structure of the thyroid are intimately dependent on an adequate exogenous supply of iodine; deficiency of this essential component of the active secretion leads to a work-hypertrophy of the gland with profound structural changes.
7. The functional activity of the thyroid is possibly subject to an inhibitory control by the suprarenal cortex;

it is undoubtedly influenced by the activity of the anterior pituitary, the thyrotropic hormone of which is able to induce in the thyroid of a normal animal a high degree of glandular hypertrophy and secretory hyperactivity.

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THE RECOGNITION OF FATIGUE, WITH SPECIAL REFERENCE TO THE CLINICAL DIAGNOSIS OF MORBID FATIGUE IN INDUSTRY*

BY

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In his book *The Economics of Fatigue and Unrest*,¹ Sargent Florence rightly remarks, "as is usual with words that have come into popular use, 'fatigue' symbolizes several related things, just as 'unrest' was found to do. Particularly we must distinguish the *feeling* of fatigue or tiredness, the outward *manifestation* of fatigue in reduced efficiency, and a probable inward physiological *state* of fatigue. How far these three things are concomitant is still under investigation." Much of the confusion and vagueness which at present surround the whole subject of fatigue has arisen, as it seems to me, from the fact that the physiologist, the psychologist, and the industrial engineer have each concentrated attention upon a single aspect of fatigue. The isolated studies of these specialists have not been drawn together, nor have they been related to the underlying unity of which each is a part. We have, therefore, a physiology of fatigue, a psychology of fatigue, and a "science" of human efficiency, but we have no clear view of fatigue as a clinical entity—that is to say, of fatigue as a disorder of health from which actual people are suffering. This present discussion represents an attempt to approach the subject of fatigue, and especially the subject of morbid fatigue as it occurs in industry, from the wider angle of its human or clinical manifestations.

Human fatigue is not an abstract entity: it has no existence except as a state of living persons. If, then, we are to bring order into the confusion which surrounds the study of fatigue we must make a fresh start; we must approach it from the clinical angle and must endeavour to relate the discoveries and researches of the specialists to one unifying conception.

The absence of such a unifying conception may have results which are practically dangerous. Thus, by a study of "production rates" the industrial engineer may conclude that the "highest industrial efficiency" can be attained by increasing the rate of production in a certain manufacturing process by a given figure. Yet the engineer, being a specialist, may fail to realize that his added production is only to be won at the hidden cost of ill-health, of premature invalidity of the workers, of serious increases in accident rates, or of a larger amount of spoilt work. That this danger is a real one is obvious to clinical observers. The danger is still further increased by the fact that there exist certain strong emotional and psychological "drives" that are capable of raising human productivity to a level which is "unphysiological." A worker may unconsciously do harm to his health when he is in the grip of these powerful motives. (It is here that we touch upon the field of the expert psychologist.) These hidden costs of unphysiological production are observed by the clinician who is called upon to diagnose unexplained illness, or they can be recognized by the industrial manager when he is confronted by unexplained variations in his production statistics. Finally they may be noted by the observant workman when he himself or his fellow workers fall ill.

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