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Original Articles

THE PHYSIOLOGY OF THE THYROID GLAND IN ITS RELATION TO EXOPHTHALMIC GOITER.*

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The investigations of the last twenty years have given to the thyroid gland a physiologic importance of the first order. So enthusiastic have some observers become in their belief in its primal position in physiology and also, on the part of a few, in therapeutics, that one is almost tempted to compare its supposed potency to the famed fountain of eternal youth whose magic healing and rejuvenating properties was the hope of the aged, infirm explorer. I must confess myself as among those who share the belief that the thyroid is a true gland, whose proper functioning plays such a part in the physiologic rhythm of the body that it stands very near to, if, indeed, not in, the list of viscera to which the term vital is properly applied. I share also in the belief that the thyroid proteids have a wide range of beneficial therapeutic activity, and yet I must, in the beginning of this discussion, call attention to how little scientific knowledge we have of the real significance of the gland and its mode of functioning, and to how large a degree our knowledge is the plainest empiricism.

We know that complete removal of the thyroid apparatus, i. e., thyroid and parathyroid, leads in most species of mammals to a fatal issue in the majority of cases. We may now safely conclude that such a result is due wholly to the removal of the glands and not to a traumatic injury of the nerves in anatomic proximity to the gland. Death from such a complete operation is generally sudden and follows a varying period of severe tetanic convulsions. I think that as a result of the experimental work of the past ten years we may go further and state that the thyroid apparatus is complex and has two well differentiated histologic structures, thyroid and parathyroid, and we have good reasons for believing that the different histologic structure corresponds to a different function. Removal of the thyroid alone is followed in most cases by a cachexia, which may in large part be relieved by the administration of thyroid substance. Removal of parathyroids, if complete, is followed by an acute fatal tetany which supervenes in a few hours or a few days.

During the last few months I have carried out some further experiments on this line which give additional evidence of their different function. The experiments

have in all cases been made on dogs. The acute tetany has been induced by operative removal of the parathyroid glands. While the animal was in severe convulsion, a hypodermic injection of beef parathyroid nucleoprotein has been given with the result that in from thirty minutes to two hours nearly all the animals have temporarily recovered a normal condition. The improved condition does not last, however, for muscular twitchings begin again in from 24 to 60 hours, and the animal rapidly passes into a tetanic condition. Another injection of the parathyroid nucleoprotein a second time will relieve the animal. The whole procedure may be repeated a third time, but we have not thus far succeeded in keeping an animal alive longer than three weeks after such an operation, but we can nearly always prevent death in the acute tetany. We have some evidence that the convulsions following the operation are due to a toxic condition of the blood, for if animals are fasted for a few days or if they are fed on meat-free diet the convulsions are less severe and appear later than they do if meat is given. Severe convulsions can be brought about in two or three hours by giving an operated animal a heavy feeding of meat. MacCallum's experiments have shown that bleeding the animal in tetany and infusing with normal saline will likewise relieve the convulsions. Further, the blood of an animal in tetany was found to be very toxic to an operated animal before enough time has elapsed for the animal to have tetany from its own operation. The globulin from the parathyroid has thus far failed to relieve the symptom, a fact which indicates a difference in chemistry from the thyroid, as in the latter gland the peculiar iodine group is in combination with the globulin and is, therefore, the proteid of particular physiologic activity.

The older experiments did not differentiate between thyroid and parathyroid, so that the acute tetany following the complete operation has been by them ascribed to the thyroid insufficiency. There are observations on record of relieving the acute symptoms by large doses, 4 to 5 grams, of iodothyron per day. Such doses are far beyond the limits of the physiologic and are not to be compared to the very small amount of parathyroid-nucleoprotein required to do the same thing.

The observations on the effect of operative removal of the glands and on the administration of various components of the glands to animals operated on and to normal animals constitute the most important known facts about the physiology of these structures. And the facts are briefly as follows:

1. Removal of the thyroid causes cachexia thyropriva, the symptoms of which may in large part be alleviated by administration of thyroid preparations. Thyroid extracts owe their activity largely to the organic iodine group therein contained.

2. Removal of the parathyroids is followed by an acute tetany. It is on the above observations that all the

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interesting and suggestive theories useful in the physiologic and therapeutic value of the glands have been founded. Some of these theories have sufficient dignity to command serious respect, but in many of them there is a lack of regard for the fundamentals.

It is a well-authenticated fact that thyroid feeding stimulates nitrogenous metabolism, and it may be that such a stimulation is accompanied by a heightened oxydative capacity of the organism by which toxic products of metabolism are rendered harmless. Hunt has recently furnished the first experimental demonstration of the detoxicating action of thyroid by showing that mice fed with thyroid preparations are able to stand larger doses of acetonitrile without fatal effect than control animals. The beneficial effects in these experiments are not to be ascribed to a direct chemical union of thyroid with acetonitrile, but rather through the metabolic stimulation which the gland extract caused. Although the detoxication theory of thyroid function has very little direct experimental evidence to support it, there is some empiric clinical evidence in its favor and it has been used by Moebius as the foundation of his treatment of exophthalmic goiter. The blood of thyroidectomized animals contains a somewhat different distribution of proteids than is found normally, in that there may be an increase in the ratio of globulin and a diminution in the hemoglobin, but there is little experimental ground for supposing that the blood of thyroidectomized sheep contains a toxin, and there is absolutely no reason to believe that this toxin, if it does exist, can combine in quantitative chemical fashion with human thyroid secretion. The supposed mechanism of this therapy is purely hypothetical and is without any analogy in known physiologic action. To Moebius belongs the credit for first formulating our notions of the hypersecretion theory of exophthalmic goiter, but his means of treatment has the most empirical foundation.

A unique detoxication theory of the function of the thyroid and its rôle in exophthalmic goiter has an ardent supporter in Blum, who believes that there arises in the course of metabolism a toxic globulin which is detoxicated in the thyroid by the chemical addition of rodin. The colloid is, therefore, an excretory product and the more perfectly it is iodized the less toxic effect should it have. (According to this theory exophthalmic goiter is caused by the escape into the circulation of large quantities of this partially iodized proteid.) The theory is based principally on Blum's observation that iodine can be added to the thyreoglobulin *in vitro* with the result that its peculiar physiologic properties are completely lost. The latter observation is probably correct, but granting that it is, no conclusions worth entertaining can be drawn from it. Blum's theory contradicts the experimentally demonstrated facts that the iodized proteid from the glands is responsible for much of their physiologic activity, and the equally well demonstrated fact that the activity is proportional to the iodine contained. If potassium iodide be given to an animal there is an increase in the content of physiologically-combined iodine in the gland. Roos has shown that when the glands from animals fed with large quantities of potassium iodide are tested physiologically they show an activity proportional to their iodine content, whereas, according to Blum's theory, such glands should have less physiologic activity than the normal. The artificial iodizing of a proteid *in vitro* is a violent chemical action not to be compared to the behavior *in vivo*. We

know, furthermore, that the beneficial effects of thyroid treatment in myxedema may be produced by the circulation of the organic iodine group, a fact which is directly contrary to Blum's hypothesis. His theory of thyroid function will not bear close inspection, but the cause of the exophthalmic symptoms, by an escape of large amounts of partially iodized globulin into the circulation, is identical with the belief generally held to-day. I am personally inclined to believe that one function of the gland may be a detoxication, but I do not believe that this is accomplished by a direct chemical union of the thyroid secretion with a metabolic toxin, but rather by the stimulating and regulating effect which is exerted on other viscera.

Chemical studies of the gland have demonstrated the presence of three forms of proteid, nucleoproteid, globulin and albumin, in addition to a number of the simpler cleavage products of proteid, the latter being bodies of no especial significance. The normal thyroid contains relatively little of the nucleoproteid, much globulin and a smaller amount of albumin; the parathyroid, on the other hand, contains a large amount of nucleoproteid, a very small proportion of globulin and still smaller amounts of albumin. These findings agree with what we should expect from the histology, and in each case the proteid present in greatest abundance is the one most active physiologically. Since the discovery and isolation of the organic iodine group by Baumann most of the chemical study of the gland has been directed toward that compound and the proteid of which it forms a part—thyreoglobulin. This is proper from a physiologic point of view, but from the pathology of the gland we must not fail to consider the nucleoproteid. I have had an opportunity during the past two years to separate the nucleoproteid and globulin from a large number of thyroid glands, normal, simple hyperemic, glands with marked cellular hyperplasia, simple adenoma, colloid goiter, and glands from practically all stages of exophthalmic goiter. In most of the glands from the latter condition there has been found a much larger proportion of nucleoproteid, particularly in the fatal cases. The normal conditions may be entirely reversed and the nucleoproteid be found in as great preponderance as the globulin in the normal gland. Additional confirmation of this point is found in the statements of Kocher and Aeschbacher, that when the gland is rich in phosphorus it is poor in iodine. The phosphorus comes chiefly from the cell nuclei which are much more abundant in the exophthalmic gland. Histologic evidence supports this finding, as in the late stages of exophthalmic goiter there may be found considerable cellular hyperplasia with relatively little colloid. There is practically no experimental evidence on the function of the nucleoproteid as distinct from the globulin, yet in certain pathologic conditions the former must play an important rôle and one of which we are as yet entirely ignorant.

The study of thyreoglobulin and its content of iodine has been the main chemical contribution of recent years, and it is especially to Oswald that we are indebted for much of the work since Baumann's time. Oswald has determined the content of thyreoglobulin and iodine in many normal glands and simple colloid and parenchymatous goiters. He finds in goiter a great variation in the relative and absolute amounts of globulin and iodine, but his findings may be summarized by the statement that in goiter there is a relatively large amount of globulin poor in iodine. Although he has reported only four analyses of these glands, he bases thereon his latest

theory of the disease, viz., a flooding of the system with a globulin poor in iodine. Such a theory really means a hypersecretion of a product of less physiologic activity than the normal. If we consider, however, that normally the blood supply is so great as to permit the entire volume of blood in the body to pass through the gland fourteen times in twenty-four hours, and consider also to how great an extent this blood supply is increased in exophthalmic goiter, we must conclude that this theory means simply an excess of effective thyroid secretion in the circulation. Even though there is less iodine in the proteid than normally, there is no evidence that this indicates a change in the essential character of the proteid. There may be less activity per unit of globulin, but since there is such an increase in the number of units in circulation the conclusion of the chemical study is in favor of the hypersecretion theory. Oswald entirely ignores other proteids than the globulin, a decision which I wish to emphasize again is not satisfactorily explained. The chemical findings in colloid goiter can not be used in an argument on exophthalmic goiter, since in so many cases the nucleoproteids in these latter glands is quite as important a constituent as the globulin. Although the chemical studies indicate that in exophthalmic goiter the globulin contains proportionally less iodine, such a result does not imply a dysthyroidization as a factor in the disease, for the iodine in the proteid is a measure of a quantitative rather than a qualitative change. The clinical argument that the many types of the disease can only be explained by a dysthyroidization may have some support in the fact that nucleoproteid and globulin are found in glands of exophthalmic goiter in different ratios from those in the normal gland, but an equally probable explanation is to be found in the personal idiosyncrasy toward active proteids.

We know very little of what the thyroid secretion does when confined within physiologic limits, but if given in excess we see as a result many of those symptoms characteristic of exophthalmic goiter. The exophthalmos, tachycardia, tremor, gastrointestinal disturbance, profuse sweating, increase in temperature, rapid loss in body weight, severe mental disturbance, have all been caused experimentally in animals by overdosing with thyroid preparations. It has thus far been impossible to produce the disease experimentally, and the nearest approach has been obtained by giving an excess of thyroid extracts. There is, however, a serious error in technique in most of these experiments in that the commercial thyroid has been given in intermittent doses by stomach in most cases, but if the physiologic conditions are to be simulated a saline extract of the gland from the same animal species should be given in small, frequently repeated doses hypodermatically. Even then we are not providing the most suitable conditions, as the extract of a normal gland has a distribution of proteids somewhat different from those the diseased secretion contains. One of the most interesting experiments of this kind is that reported by Dr. Matthes, who had a patient suffering from exophthalmic goiter operated on with a curative result. Later when the patient was fed portions of his own dried gland there was an increase in the nitrogen excretion with some return of symptoms.

However, granting that, as seems probable, the hypersecretion theory offers the most satisfactory explanation of the origin of the symptoms in the disease, we as yet have no satisfactory explanation of the mechanism by which they are brought about. The tachycardia, for in-

stance, has been variously explained, an acceptable theory to many students being that of Gley, who believes the vagus impulses are inhibited and the accelerator stimulated by the gland extracts; yet very recently some experiments on the isolated heart have indicated that the central nervous system may be in no way concerned in the matter.

The mechanism responsible for the other symptoms of the disease are in a more unsatisfactory condition than the tachycardia. The very rapid loss in weight has been repeatedly given a partial explanation by the stimulating properties which the gland extracts have, but why and how the extracts act in this manner is a subject entirely unknown to us at the present time. The metabolism of patients suffering from exophthalmic goiter has been partially studied in a number of laboratories, and as a result we know that very large amounts of nitrogen are required to maintain an equilibrium during some stages of the disease. Recently in our laboratory more complete analyses of the urine have been made by Dr. Shaffer, and the most interesting new fact which can be drawn from these studies is that the kreatinin excretion is low compared with the normal, and the lower figures always go with the more severe toxic forms of the disease. When the patient improves there is a corresponding rise in the kreatinin output. With the low kreatinin excretion there is an increased kreatinin excretion. We know little of the origin of kreatinin in the body, but Dr. Shaffer has recently advanced the theory that it is a measure of the muscular efficiency; such a theory is supported in this disease by abundant clinical evidence and by the measurements of the strength of selected groups of muscles made by Dr. Frederick Muller, who has found that in patients suffering from exophthalmic goiter the muscles are no more than one-fifth to one-third as strong as in normal individuals.

There are two commonly accepted possibilities which explain the origin of the hyperactivity of the gland. First, as a result of nervous shock; second, as a compensatory hypertrophy during a toxemia.

As to the first possibility, the investigations of the last ten years have given us a fund of information concerning the remarkable control exercised by the nervous system on glandular activity. Particularly with reference to the digestive glands we have seen qualitative and quantitative changes in their activity following an apparently insignificant stimulus. We have no direct experimental evidence to indicate in how far we can apply these results to the thyroid gland, but clinically we see many instances of marked change in the activity of the gland following some profound nervous disturbance. The condition may have been latent before and first becomes evident following some severe fright or sudden sorrow. Why the effect should last beyond the stimulus which called it out we do not know. That a new habit of abnormal activity may result from a series of repeated stimuli is an hypothesis put forward to account for many instances of physiologic overwork, and it may apply here.

As to the second hypothesis, there are some histologic studies which indicate that during the infections and also during chronic toxemias the thyroid undergoes cellular hyperplasia which may serve in the nature of a compensatory hypertrophy, i. e., the additional demand for the detoxicating action of the gland results in its growth. At present we have no method of measuring the activity which the gland has either in a normal or pathologic condition and can form only the crudest no-

tions by the gross appearance and histologic structure. It is, therefore, rash to conclude that in those cases of exophthalmic goiter with no goiter there is no hyperthyrosis. There are many clinical observations that support the theory of compensatory hypertrophy, and it is the mere bulk of this evidence rather than its character which is impressive.

In conclusion I must again call attention to our dearth of knowledge of the physiology of the thyroid gland and the pressing need for systematic, careful investigation, both on the part of the laboratory worker and the clinician. Theories we must have, for it is by these that we grow, but the danger lies in accepting an attractive theory as an established fact.

THE PATHOLOGY OF EXOPHTHALMIC GOITER.*

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The symptom-complex which we know under various names as exophthalmic goiter, Graves' disease, Basedow's disease, etc., has been very extensively studied, but even yet there is not perfect unanimity of opinion as to the anatomic changes which underlie these symptoms. Nearly all writers, except certain clinicians who have not made anatomic investigations, agree that there are always changes in the thyroid, although there has been much debate as to whether these changes are constant in character or not. There are others who think that the lesions must be sought in the sympathetic system or in the central nervous system, while still others regard the disease as the result of a functional disturbance of the nervous system and do not expect to find gross anatomic changes. Other attendant lesions in the eyes, in the skin, the muscles, the digestive tract and in the lymphoid tissue and thymus have been frequently described, and organs of internal secretion other than the thyroid, such as the parathyroids, adrenals, pancreas, hypophysis, etc., have been investigated with varying results. Since Moebius put forward his idea of the fundamental relation of the thyroid to the disease, attention has been centered chiefly on that organ and it has formed the point of attack in therapeutic measures, but the other lesions must still be regarded as worthy of close study, and in this paper the changes found in a rather large series of cases will be taken up in order. It must be observed, however, that none of the changes which have been generally found and which I have found in my series have the character of primary changes. They seem in each instance to be the response or reaction to some fundamental or primary disturbance of which as yet, I think, we have no very clear notion.

Disturbances of metabolism in these cases are obvious, and these seem to be intimately connected with the fundamental activity and corresponding anatomic condition of the thyroid, but whether as cause or effect is not absolutely proved. Similarly pronounced nervous disturbances occur, the heart runs riot, the body trembles, secretions are disturbed and the mental condition and temperament are altered, but whether this is the result of chemical changes or of obscure anatomic lesions in the nervous system we are not certainly informed.

Whatever vague notions we have as to the fundamental underlying cause of all these things we may discuss after describing the anatomic changes.

It has been shown by Halsted and others that if a portion of the thyroid be removed from an animal the remainder shows after some time a curious alteration, which consists essentially in the great proliferation of the epithelial cells by a process of mitosis. So great is this new production of cells that they become too numerous to be accommodated on the smooth wall of the round alveolus and the epithelial lining accordingly becomes folded in the most complicated way, each fold carrying up with it into the original lumen a supporting strand of connective tissue with blood vessels. This change in the alveolar wall is followed by a decrease in the amount of visible colloid, which loses its hyaline dense appearance and becomes pale and ragged. The whole process has been regarded by Dr. Halsted as a compensatory hypertrophy, the proliferation of the epithelium being an attempted repair of the loss of thyroid substance. A similar condition is found in a small percentage of stray dogs in Baltimore and occasionally in sheep and goats, while in certain localities, as reported by Dr. Marine, in Cleveland, in a recent paper, an enormous proportion of the stray dogs are thus affected.

What the cause of this hypertrophy can be is not perfectly clear, but Dr. Marine has observed that if these dogs be given iodids in considerable doses the alveoli again become round and filled with colloid, and Dr. Kocher tells me that the administration of iodin will prevent the development of the folded condition after the operative extirpation of part of the thyroid.

Now in exophthalmic goiter the thyroid presents an appearance practically identical with that found in these animals, and it will be my task to describe in greater detail these anatomic appearances as they occur in this disease. It is true that none of the symptoms found in exophthalmic goiter are observed in the animals operated on nor in those in which the hypertrophied condition occurs spontaneously, but still the analogy is of great interest.

The material which I have had for study consists of sixty patients, most of whom have been operated on by Dr. Halsted for the relief of symptoms more or less typically those of exophthalmic goiter, and I am much indebted to Dr. Halsted for this material. Not all of these cases presented the complete typical picture of exophthalmic goiter; some of them, as will be recounted, showed part only of the characteristic symptoms, while some were complicated by the presence of other lesions of the thyroid and other organs. It will be of interest, however, to determine in how far the anatomic changes correspond with the development of symptoms, and this can be done briefly, more exact data being obtainable from the table on the next page.

From this table it is seen that in certain cases the changes in the thyroid are very well marked and are of a characteristic type, while in others they are less easily recognizable.

The more characteristic changes may be discussed first. In most instances the thyroid is enlarged, although, as a rule, not to a great size; in some cases it is not larger than the normal or it may be actually decreased in size. At operation the superficial veins are found to be very large and easily torn and are distended with blood so that the gland has a very congested appearance. This is not striking in the excised portion, since the vessels collapse and on section the interior of

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