Anomalies of Thyroid Secretion

BY

FREDERICK C. SHATTUCK, M.D.,

BOSTON, MASS.

Jackson Professor of Clinical Medicine, Harvard Medical School

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ANOMALIES OF THYROID SECRETION.*

BY FREDERICK C. SHATTUCK, M.D., BOSTON,
Jackson Professor of Clinical Medicine, Harvard Medical School.

MR. PRESIDENT, MEMBERS OF THE MAINE MEDICAL ASSOCIATION:

I thank you for the honor you do me in inviting me to address you this evening. Perhaps I should apologize for venturing to bring before you a subject which is not new. But all that is new is not true, and my subject is, at all events, replete with interest, practical as well as more strictly scientific, with well laid foundations, though the superstructure is still far from complete. Indeed, it seems to me there is nothing even in modern surgery more striking, I could say more dramatic, than some of the results which flow from our gain in knowledge as to the function of that little gland which is saddled across the trachea just above the root of the neck.

And we shall see that the surgeon's knife has lent its aid in fashioning the links of the chain of evidence, enforcing the lesson of the unity of medicine and of the interdependence of the physician and surgeon, the special work of each being based upon the general principles of anatomy, physiology, pathology and chemistry.

I hope it will not be a waste of time to briefly sketch the evolution of our present knowledge of thyroid function. Of the four chief ductless glands in adult life the adrenals were the first with

* Oration before the Maine Medical Society at the Annual Meeting in Portland, June 2, 1904.
regard to which we gained a definite knowledge, thanks to Addison's classic work which showed that their destruction is followed by mortal disease characterized by more or less well defined symptoms; that these glands, small as they are, are in some way indispensable to health and eventually to life. The far larger and usually single spleen is still something of a puzzle to-day. Its total extirpation seems to be compatible with the maintenance of good health even in the absence of one or more supplementary spleens. In case of necessity the bone marrow and lymph glands appear to be able to do the work of the spleen. Here we have a sharp contrast between the spleen on the one hand and the twin adrenals and Siamese twin thyroids on the other. If they are destroyed the organism seems to be unable to supply their place. The still smaller and single pituitary body is the last to yield up its secrets, in part, at least.

Enlargement of the thyroid gland — goitre — must have been recognized since anatomy, begotten of dissection, was born. Save in its mildest degrees it cannot escape notice. Atrophy of the gland, on the other hand, is not often easy to recognize in life, save indirectly through its symptoms.

While isolated cases of goitre occur everywhere it has long been notorious that in certain localities, some of the shut-in Alpine Valleys, for instance, it is far more common, so common in some places that its absence in an individual may be regarded almost as a deformity. And it was, furthermore, noted that where goitre is endemic a peculiar form of impairment, mental, physical or both, is rife, so peculiar as to deserve a special name — cretinism. Among the fanciful explanations for this endemic disease the drinking of water from melted snow was a favorite, winning credence alike from the profession and the laity. I well remember in 1869 my guide in the Tyrol trying to dissuade me from allaying my thirst from an icy mountain rill, and assigning the danger of goitre as a reason for his advice.

The connection between thyroid disease and cretinism was masked by the fact that there is no obvious relation between the degree of goitre and that of mental and physical health,— that one person with great thyroid enlargement might be otherwise well, while another with far smaller or no tumor might be a repulsive idiot, small in stature and asymmetrical in development. This, with dense ignorance as to the function or necessity of the thyroid gland, was the situation in 1873 when that great physician and acute observer, Sir W. Gull, published his paper entitled, "On a peculiar cretinoid state supervening in women in adult life." Note, please, here, the truly scientific mind. He described what he saw, fully, clearly. He indulged neither in hypothesis nor theory. Note also the word "cretinoid." His keen eye detected the broad resemblance of the acquired to the congenital state. Next Ord in 1877 first follows the trail to the autopsy table and introduces the term "myxedema," on account of the remarkable mucin reaction presented by the puffy but non-pitting integument, so different from the ordinary oedema. He also discusses the relation between myxedema and cretinism, sporadic and endemic, and notes thyroid changes in his fatal case. It is interesting that Curling and Pagge had already called attention to atrophy and absence of the thyroid in sporadic cretinism. Mark again Ord's purely descriptive...
We had now learned to recognize the condition resulting from the total absence or loss of thyroid function, congenital and acquired. We had also learned that the presence and activity of a portion of the gland, or of an accessory thyroid, prevents the development of the group of symptoms to the acquired form of which Ord's term "myxœdema" still remains attached. These symptoms when fully developed are so striking and distinctive as to permit probable diagnosis at a glance. Some years ago I was called to the suburbs to see a man with general peritonitis. While the family physician was going over the history the patient's wife came into the room. One look at her was enough to reach the diagnosis of myxœdema. Subsequent treatment cured a condition which had lasted for years, so near as to be practically in the "Hub of the Universe."

The story of myxœdema, like that of polyneuritis, is an illustration of how much easier it is to see what is pointed out to us than to see for ourselves — how rare is original thought. How many really obvious things now pass under our very eyes without penetrating beyond the retina!

The evolution of the therapy of myxœdema is scarcely less remarkable than that of its pathology. Transplantation of the gland was first practiced, and was followed by marked improvement which was, however, only temporary. The gland did not seem to live and persist amid strange surroundings; but the results showed that we were on the right track. In the first edition of Osler's Practice, 1892, we find "Unfortunately no satisfactory treatment is known. The patients suffer in cold and improve greatly in warm weather. They should, therefore, be kept at an even temperature and should, if possible, move to a warm climate during the winter months."
But while these words were going through the press the light was breaking. It was found that hypodermic, and even rectal, injection of the raw gland prepared and used under strict aseptic precautions was efficacious. Then feeding with the raw, the cooked gland, and, finally with liquid or dried extract of the gland was successively tried with the surprising result that the important active principle is, for practical purposes, unchanged either by the preparation without the body or by the digestive process within it. Thus was the battle won, and thus did we come into a position to readily recognize and cure, the condition first described by Gull less than twenty years before, and which had been uncertain and obscure in pathology and hopeless in outlook.

A year ago a middle-aged man came under my care at the Massachusetts General Hospital. His friends, weary of the burden of his support and care, were ready to send him to the poorhouse. He was practically an idiot, sluggish to the last degree both in body and mind. After several months' treatment he returned home, and his own mother failed to recognize as her son the man, active mentally and physically, whose bald head with here and there a long wisp of dry hair had become thickly covered with normal growth. I have seen him recently; he is perfectly well, self-supporting with steady work. I know nothing in medicine comparable to the change in a myxœdematous patient after treatment unless it be the effect of potassium iodide in certain cases of syphilis.

If the thyroid gland be congenitally absent or if it cease to act in early life, growth is seriously arrested and distorted. A child of eight, weighing twenty-three pounds, a typical cretin, entered my service this winter. Under treatment she has lost nearly six pounds in weight, but gained greatly in strength, intelligence and appearance. If the gland be destroyed by disease or extirpated in adult life certain nutritional and mental changes occur. Cretinism and myxœdema are essentially identical in nature, the only real difference lying in the period of life at which the cause begins to act. The relation of cause and effect is as certain as anything in medicine. But as to how the effect is produced we are still far from clear. The prevalent view is that the ductless glands secrete something which finds its way directly into the blood—internal secretion, so-called. However interesting it might be to touch upon the modern views as to the existence of an internal secretion also in glands furnished with ducts, nay even of the parenchymatous organs, such discussion would be aside from our present issue and would lead too far. I will mention only the relation of Langerhans' islands in the pancreas to, at least some cases of, diabetes. This seems established. The effects, then, of arrested thyroid secretion being so distinctive, what happens if, for any cause, secretion be excessive? For it seems highly probable that myxœdema is due to purely quantitative change. The failure of symptoms to develop if a portion of the gland remains active is one point favoring this view. With regard to this most interesting and important point—excess—we have not as yet succeeded in getting on as firm ground, though it seems as if more positive knowledge might not be far off.

There is one disease the symptoms of which are almost diametrically opposed to those of

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1 It is interesting to note that Englishmen took far the largest part in the solution of the mystery of myxœdema.
myxœdema and in many cases of which the thyroid gland is manifestly enlarged. This enlargement, moreover, is capable of undergoing such variations in size as to suggest that the enlargement must be in part, at least, due to actively increased blood supply, which, presumably, entails increased glandular activity. In passing, the thyroid enlargement—vascular—which occurs sometimes in connection with pregnancy and menstruation is worthy of note. I allude, of course, to that remarkable group of symptoms so obscure in origin until lately, to which the name “Graves’ disease” is attached, though priority of description belongs to Parry. Parry’s observations were lost sight of and, for convenience, I shall use the common English name. Contrast the facies of terror, the nervousness and tremor, the intolerance of heat, the moist skin and vasomotor instability, the emaciation of Graves’ disease with the cow-like placidity, bodily and mental sluggishness, intolerance of cold, dryness of the skin and its appendages, scanty urine, and the swollen and puffy integument of myxœdema. The suggestion that symptoms so absolutely opposed must depend, at least in a measure, on opposed pathological conditions cannot but demand most serious consideration. I think it was Möbius who first, in 1890, maintained this view in print. How is proof to be secured? We know that myxœdema is cured by introducing into the system the thyroid of some animals, the sheep, for instance. Does such introduction produce Graves’ disease in a healthy person? What is the effect on patients already the subjects of Graves’ disease? For obvious reasons full experimental evidence on man with regard to the first of these questions cannot be secured. But that thyroid over-dosage does quicken the pulse, raise the temperature and cause loss of weight admits of no doubt. I have a lively recollection of a patient whom I nearly killed with thyroid extract some ten years ago. He was the first case I recognized as having partial myxœdema, a gentleman who had been treated for all sorts of things, “aropsical tendency” among others. Though I felt sure of the diagnosis I asked Dr. J. J. Putnam to see and examine him without me and without knowing my opinion. He concurred. Putnam had just received the first sample of Parke Davis’ dried extract which had reached Boston, and kindly placed it at my disposal. The patient took 15 gr. three times daily, and it was not many days before the pulse shot up from 70 to 140, the temperature from sub-normal to 103, and anginose pain was severe enough to require several half-grain hypodermics of morphia within a few hours. He has taken the extract ever since, occasionally intermittting its use for a short time; but never in 15-gr. doses. He is now seventy-nine. I have never poisoned anyone else to that degree. The cretin I alluded to before entered the hospital with a pulse of 70 and normal temperature. The pulse now runs 130-140, temperature 100-103, under one grain three times a day. By increasing or diminishing the dose, the pulse and temperature can be raised or lowered. A rapid pulse is the most constant single symptom of Graves’ disease. Exophthalmos and goitre may be absent in severe and even, as Thomson has seen, fatal cases. The name “exophthalmic goitre” is, therefore, wholly inapplicable to the disease and should be dropped as it tends to perpetuate the error from which Kocher himself has not been able to free himself. As a surgeon he naturally sees only the cases with goitre and
hence denies that Graves' disease can exist without goitre. This error reminds one of that of the great Hebra who maintained the identity of varicella and variola, I have always thought for the reason that he had seen but little varicella.

Thyroid extract, then, is capable of producing the most constant, if not essential, symptom—rapid heart action—and some of the minor symptoms of Graves' disease. Improvement in all symptoms often follows partial extirpation of the thyroid, as also it may follow ligation of arteries resulting in diminished blood supply, and hence, presumably, diminished glandular activity. These facts, taken together, constitute strong evidence as to an intimate relationship between the thyroid gland and Graves' disease.

It has been thought that the parathyroid glands may play something the same rôle in Graves' disease that the thyroid does in myxœdema, and keen investigators are studying the question. Extirpation of the parathyroids in animals is followed by acute and convulsive disorders—tetany, while extirpation of the thyroid alone is followed by chronic and nutritional disorders. The parathyroids were formerly supposed to be accessory thyroids and inconstant. They were discovered by Sandström in 1880, rediscovered by Gley in 1892. Positive clinical and pathological evidence with regard to the parathyroids in man is still meager, partly from the short time the work has been going on, partly from the inherent difficulties of the problem. Analogy would suggest that their action is essentially the same in the higher vertebrates. The known sequence of their removal in animals has suggested the possibility that the alarming frequency of pulse and respiration, too often fatal, which sometimes occurs rapidly after thyroidectomy for Graves' disease, may be due to removal of the parathyroids rather than to flooding of the system with thyroid secretion, poured out from the cut surface of the gland and rapidly absorbed from the extensive wound. If the parathyroid theory be true it would seem as if such cases should be invariably fatal, as they are not. The facts do not, as yet, warrant any final conclusion; but for the present, at least, the injunction by Jeandelize to make a point of sparing the parathyroids in thyroidectomy should be heeded by surgeons. MacCallum has fed the parathyroids to a patient with Graves' disease without appreciable effect. Whether the action of the thyroid and parathyroids is antagonistic, complementary, or unrelated we do not to-day know. But what evidence we have does not seem to indicate a vital causal connection between the parathyroids and Graves' disease.

Let us then assume, for the sake of argument at least, that myxœdema and Graves' disease are both dependent on states of the thyroid gland, and that the former represents loss of function of the gland. Does it then follow that the latter—Graves' disease—represents excessive function or purely quantitative changes in secretion? We do not know. Qualitative change may or may not be operative. That glandular activity of any kind may be increased or diminished in greater or less degree, or even arrested, for considerable periods and simply from faulty innervation, we do know. The stomach tube which enables us to extract the gastric contents at any period of digestion has demonstrated to us the existence of both hypochlorhydria and hyperchlorhydria as phases of nervous dyspepsia, so-called. We
have no such direct means of determining the amount and character of thyroid secretion, which, moreover, is probably far more subtle in its nature than that of the peptic glands. However plausible the theory that Graves' disease is the result of purely excessive thyroid secretion may be, proof is still lacking.

I have just received from my friend, Dr. W. H. Thomson, of New York, his most interesting monograph on Graves' disease, fresh from the press. He, as you know, doubts the causal relation of the thyroid gland to Graves' disease, and believes the main factor to be toxin absorption from the intestines. After study of his therapeutic results, which are better than any with which I am acquainted, it is hard to escape the conclusion that diet and mercurials are of great service, while we yet provisionally hold the view that morbid thyroid activity is the central and essential factor in Graves' disease. Thomson tells me that he prefers to get a bad case as his results in such are more striking.

It is certainly conceivable that intestinal toxins should have a peculiarly bad effect on the subjects of thyroidism. We are ignorant as to whether the thyroid puts something into the blood useful for constructive nutrition, though the fact that the earlier in life the gland ceases to act the greater the effect on growth would suggest this to be the case; whether its action is destructive toward toxins; or whether it acts in both ways at once. If the gland has a double action it is possible that either variations in the demand for the one or the other action, or variation in the supply to meet one or the other demand may occur in the complex conditions which constitute life. A double supply, a double demand; the extreme subtlety of the chemistry of the living body; and our fragmentary knowledge of the subject afford ample scope for speculation and hypothesis, which are in place in matters scientific, provided always that they be recognized for what they are.

Thus far I have had in mind fully developed cases of myxedema and Graves' disease. They are easily recognized. But are we as a profession sufficiently alive to the fact that all grades of each exist? Do we recognize the "formes frustes," as the French call them? I think not as often as we should. Personally, I happen to have been interested in the subject, and during the past year I have seen at least four cases of Graves' disease in males and two in females, the nature of whose trouble had in some certainly, in others apparently, not been suspected by their previous attendants. These were, of course, cases entirely without or with only slight exophthalmos and goitre. Only yesterday a gentleman called with a pulse of 150, tremor, sweating. I have seen him at intervals of about six weeks for as many months and feel sure of the diagnosis. His return of rapid pulse of yesterday I think due to recent unavoidable business strain, for on the whole he is decidedly better than he was six months ago. Although the heart's action was violent as well as rapid, shaking nearly the whole chest, he was entirely unconscious of it, though he was conscious of his "nervousness." 2 If we keep clearly in mind the characteristic symptoms, minor as well as

2 Very recently I have seen a lady who was seen by my friend and assistant, Dr. W. H. Smith, some years ago. He tells me that at that time her somewhat rapid pulse and nervous manner led him to look for goitre which, as also exophthalmos, was quite absent. Under recent psychical perturbation the nervousness and tachycardia have greatly increased and goitre is manifest.
major, of myxedema and Graves' disease, I feel sure we shall now and then encounter undeveloped cases of one or the other condition. Among the important symptoms of myxedema a small renal secretion with a still smaller, proportionally, output of urea is not the least. Myxedema, alike partially and fully developed, I think more rare than Graves' disease. ③

In case there be doubt as to the diagnosis of these "formes frustes," tentative treatment, especially perhaps of the myxcedematous class, may confirm or negative our suspicions. Therapeutic truth lies at the bottom of a very deep well, deeper than the philanthropic drug and prepared-food manufacturers, distributing sample bottles, wish us to believe; and it is, of course, not safe to conclude that any gain following the use of thyroid extract is the direct result of its use and a proof of hypothyroidism, any more than that symptoms relieved after quinine were malarial; or that those disappearing after potassium iodide were syphilitic. At the same time a marked gain in physical and mental alertness with the return of a normal relation to cold are significant. Hertoghe seems to me to attach especial probably of the myxcedematous class, may confirm or negative our suspicions. Therapeutic truth lies at the bottom of a very deep well, deeper than the philanthropic drug and prepared-food manufacturers, distributing sample bottles, wish us to believe; and it is, of course, not safe to conclude that any gain following the use of thyroid extract is the direct result of its use and a proof of hypothyroidism, any more than that symptoms relieved after quinine were malarial; or that those disappearing after potassium iodide were syphilitic. At the same time a marked gain in physical and mental alertness with the return of a normal relation to cold are significant. Hertoghe seems to me to attach especial importance to the important symptoms of myxcedema. The presence of notable arteriosclerosis or of degenerative myocardial disease should make us very cautious as to dosage, at first at least. ④ It is easier to add to a deficient or to supply a lost thyroid secretion than to directly restrain or modify one which is excessive or otherwise morbid. The treatment of Graves' disease has long been unsatisfactory at the best. Real recovery is rare, though much may be done in alleviation if a quiet life without much nervous strain can be secured. A cool summer resort is very important. The improvement reported in some cases from mountain resorts and attributed thereto I believe should probably be credited to the temperature rather than to the altitude. Sexual excitement should be infrequent. A shrewd Canadian doctor once remarked to me that he had noticed aggravation of the symptoms of Graves' disease in the wives of commercial travellers coincident with the homecoming from trips.

The diet should be comprised mainly of fats, starches and sugars, with great moderation in or abstention from highly nitrogenous food; due regard being had, of course, to digestive peculiarities, temporary or fixed, of the particular patient. Oatmeal is probably the least desirable of the cereals from its excitable qualities. The bowels are apt to be either constipated or relaxed. Diarrhea, if genuine, may be regarded as an internal sweating and may be treated by some form of bismuth. Personally, I use Squibb's sub-nitrate in teaspoonful doses, less constipating than the smaller doses, perhaps, on account of its crystalline and hence scratchy nature. If there

③ We still heed light on the interesting question as to how often thyroid atrophy, greater or less in degrees, results from thyroiditis complicating or following acute infectious disease.

④ Larger doses are required, or may be used, to cause the disappearance of symptoms than to prevent their recurrence. The thyroid extract must, of course, be taken for the rest of life. A lady whom I saw in consultation eleven years ago came to see me within twenty-four hours about a friend. Under two grams, once, daily, she considers herself absolutely well, but experience has convinced her that this amount is indispensable.
be constipation or any evidence of faulty intestinal chemistry I shall be tempted in future, acting on Thomson's suggestion, to give calomel regularly once or twice a week. And yet I have seen two cases recently, one with fifteen or twenty loose movements a day, the other with constipation, promptly acquire normal defecation under the neutral bromide of quinine alone.

Digitalis, far too frequently ordered under all sorts of conditions simply because the pulse is rapid, should not be used unless there be indication of insufficiency of the heart muscle. Strychnia is to be avoided. Three of the cases of Graves' disease seen lately had been taking digitalis and strychnia for longer or shorter periods without benefit.

Nearly four years ago my friend, Dr. F. Forchheimer of Cincinnati, told me of his results from neutral bromide of quinine. I have used it since and have thought it more helpful than any other drug I have used before. The toleration of quinine in Graves' disease is remarkable, and is seemingly proportional to the severity of the symptoms. I give it in five-grain pills three or four times a day. Two patients, cases of moderate severity, have now taken twenty grains daily almost constantly for more than three years without the least cinchonism, and with decided amelioration of all the symptoms, tachycardia and nervousness especially. A gentleman with acute Graves' disease, exophthalmos and goitre absent, was amazed that he could take twenty grains a day without discomfort, as he had always been highly susceptible to the action of quinine. Another similar case, a lady who has just come under my observation, gives the same testimony. At my suggestion

the treatment has been largely used in the Out-Patient Department of the Massachusetts General Hospital with, as is reported to me, very satisfactory palliative results. The remarkable freedom from cinchonism and the small amount of bromide in twenty grains of the salt make it highly improbable that the latter is the active agent though, doubtless, as diminishing reflex excitability, it helps somewhat.

With thyroidectomy I have little experience, less, I am inclined to believe, than I should have considering my opportunities. The alarming symptoms and rapidly fatal termination after some cases of operation deter one from advising the knife in moderate cases, and the severe ones are bad subjects for serious surgery. On the other hand, a severe and chronic case perhaps justifies almost any risk. I have seen a few cases which have been greatly improved after operation, and Osler tells me within a day or two that they are having good results in bad cases at the Johns Hopkins operating under cocaine. A Massachusetts General Hospital case operated on by Mikulicz a year ago with distinct benefit has, I am told, since relapsed. I now regret not having advised operation in a very severe case in a young Jewess I saw some six months ago. All the symptoms were extreme. The prominence of the eye-balls was so great that corneal ulceration of a week's standing when I saw her had already destroyed her sight. It is the only case that I have seen of this disaster. Under such circumstances death is a true friend; but one shrinks from being the executioner.

With Rodagen, prepared from the milk of thyroidectomized goats or the serum, I have no experience.

To sum up: Graves' disease for the present is
to be treated by rest, diet, climate, attention to the bowels and neutral bromide of quinine. If these measures are not followed by distinct improvement operation is to be seriously considered in severe cases, especially in patients whose circumstances in life are unfavorable for the general management of their disease.

In conclusion it only remains for me to thank you for the patience with which you have listened to me. If I have succeeded in imparting to my presentation a fraction of the interest which I feel in the subject, and, above all, which it merits, I shall be satisfied.

The fascination of the constant advance in knowledge tempts one, even in moments of weariness, to share the wish of Professor Hagen, the celebrated entomologist: "I wish I could be my own great-grandson."