

On myxoedema and allied disorders : being the Bradshaw lecture delivered at the Royal College of Physicians, on November 10th, 1898 / by William M. Ord.

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With the respectful homage of
William M. Ord

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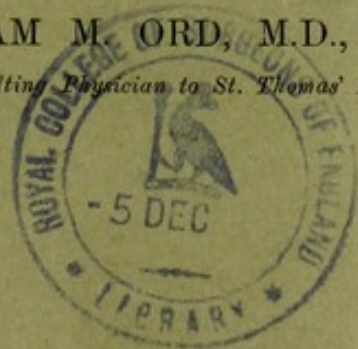
ON
MYXCEDEMA AND ALLIED
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BRADSHAW LECTURE

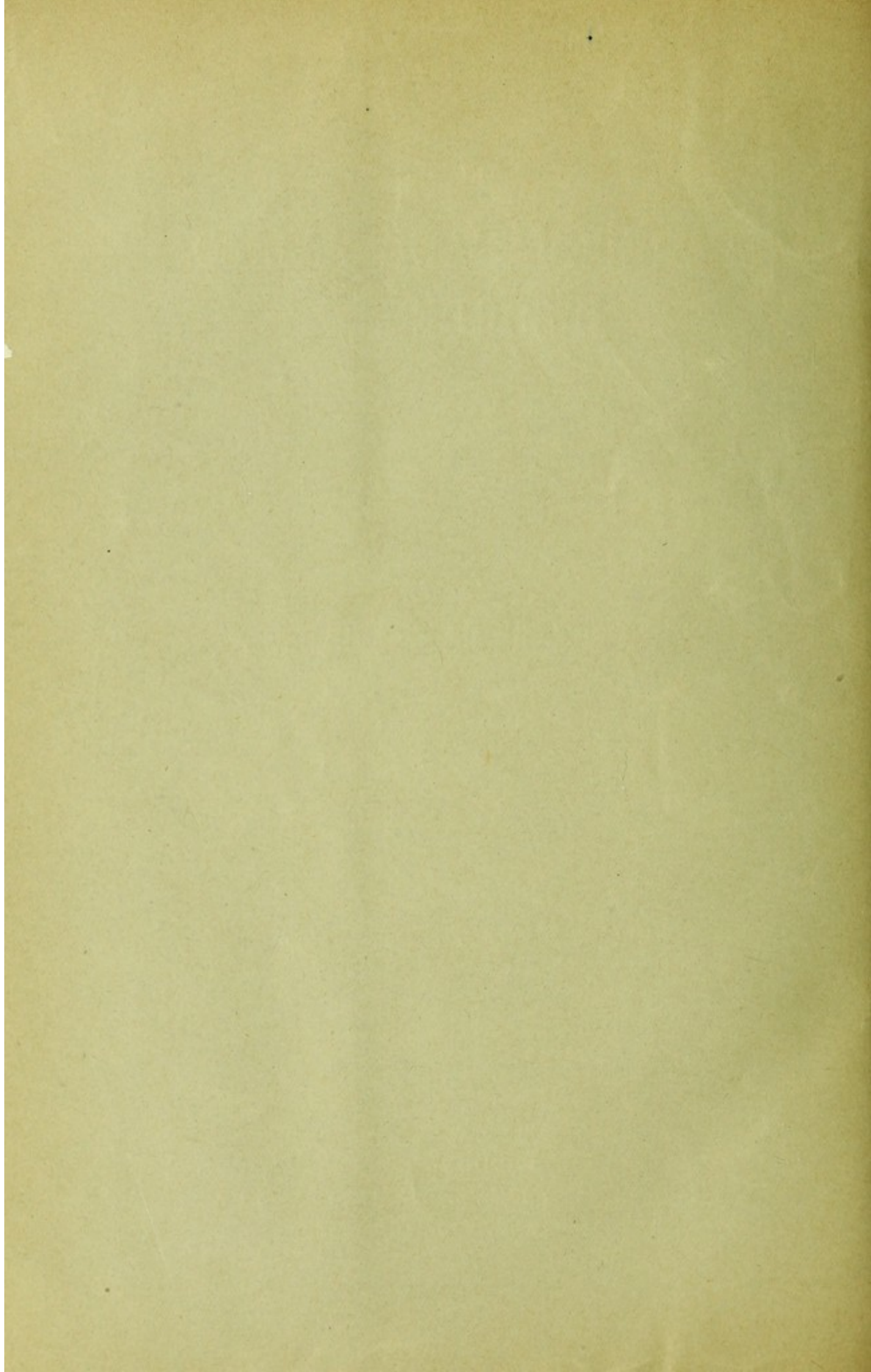
DELIVERED AT THE
ROYAL COLLEGE OF PHYSICIANS,

ON
NOVEMBER 10th, 1898,

BY
WILLIAM M. ORD, M.D., F.R.C.P.,
Consulting Physician to St. Thomas' Hospital.



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MYXŒDEMA AND ALLIED DISORDERS.

THE pathology of myxœdema, so far as it is at present known, will doubtless form a part of the Lectures which Dr. George R. Murray, of Newcastle, will deliver before this College next year. In the present lecture, I propose to devote my attention mainly to the clinical aspect of myxœdema, its recognition, its differential diagnosis and its treatment.

The primary diagnosis of the disease is not always so easy as might be expected from the observation of well pronounced or typical cases. This is true, indeed, of all kinds and manner of disease. Whatever be the disease, it is necessary, in the first place, whether we do it consciously or not, to construct a picture of such disease in its full development, including, first, the main and most important symptoms, then, next, the less frequent and less characteristic symptoms ; thirdly, certain accessory symptoms of varying value in various cases. Such a picture cannot be constructed by making a mere list of symptoms. It is necessary, by careful comparison of a considerable number of cases, and also by bestowing careful regard on the relations of symptoms to etiology, to make the picture a carefully shaded one ; to put into strong relief that which is most important, and that which is less and less important further and further in the background. The picture must, in a word, have its perspective and its colouring carefully drawn and filled in. Such a process, carried on in a more or less methodical manner, must be applied to the separation in our minds of diseases and of their subjects from one another, before we are able to write down the primary naming of any disease, of which there may often be many forms.

Diagnosis.

As the knowledge of myxœdema grows, by the addition of new cases to our original list, it becomes evident that around our well-defined picture are to be found forms more or less obscure ;

in part because of incomplete development of the whole series of symptoms, in part also by reason of curious modifications of myxœdema constituting alliances with diseases to which the term "myxœdema" cannot with propriety be applied.

Classification
of symptoms.

The most
characteris-
tic.

Let us now endeavour to make a classified list of the signs and symptoms of myxœdema. The first lines which we draw in firmly, in limning the disease, are those connected with the external appearance of patients, such as the increase in the size and bulk of the whole body, due, evidently, in part, to changes in the skin, in part to changes in the subcutaneous tissue. Next, the changes in the skin, affecting, more or less, the whole surface, and determining changes in the appendages of the skin; in the hairs, in the glands, and in the organs of touch. In correlation with the changes in the skin, we have to take note also of altered states of mucous membranes, resembling those observed in the skin, and leading again to destruction of appendages, such as the teeth and glandular structures. It is here a point of much importance to remember that the swelling of the skin and mucous membranes is not an ordinary dropsical swelling, does not in any way gravitate from the upper parts of the body to the lower, and does not in any part pit on digital pressure, but is firm and resilient.

Next comes a group of symptoms indicating in various ways impairment of the functions of the nervous system, such as slowness in muscular movement and tardiness in response to impressions made upon the surface of the body, slowness in thought and action, weakening of memory, disturbance of the balance of muscular actions in the limbs. With these we must associate the quality of the speech and the sound of the voice perfectly typical of the disease, and dependent apparently on the combined effects of the swelling of the lips and fauces, of failure of the movements of the muscles within the swelling, and of default of nervous power in controlling the action of muscles. Further beyond the above-mentioned signs of dilapidation, we may find various degrees and kinds of mental aberration, and certain mental phenomena, which may be fairly called "peculiar" up to a certain point.

Symptoms
of second
degree.

The next in the rank of important signs may, I think, fairly be taken to be the lowering of the temperature of the body, rarely, if ever, absent when the disease is fully pronounced. A less common symptom than those already enumerated, is the ten-

dency to hæmorrhage following comparatively slight injury, the hæmorrhage being most commonly in the skin or mucous membrane, but sometimes in internal organs.

Partly with special regard to etiology, we have to consider the question of sex, noting that the affection is very predominantly one of the adult female. In all diagnoses, negatives have to be marshalled among sources of help. We shall find that there is no affection of viscera which can be called characteristic of myxœdema, although in the course of the disease visceral affections may arise, chiefly from the operation of external and new causes, not wearing, so to speak, the uniform of the higher groups.

After passing in review the components of the several groups of symptoms and conditions above classified, the relations of the thyroid body assume great importance, seeing that certain changes in that body and its functions are in effect causative of myxœdema.

Another set of changes belongs to other diseases, which, in this aspect, have some sort of alliance with it and help us to its explanation.

We may now amplify the elements of each group of symptoms in succession.

The often vast and quivering bulk of the body is, I have already said, partly brought about by alteration in the skin, and partly by developments of fat beneath the skin. It is doubtless often due in part to alterations in the muscles and viscera, all partaking of the nature of the change most readily noticeable in the skin. The skin is found to be everywhere dry, and often in many parts is clearly very much thickened in its epithelial layer as well as in the derm. It is exceedingly rough and harsh to the touch, so that, as a patient once remarked, you might almost strike a match upon it—an experiment which, I may say, I have never yet attempted. The varying connections of the skin with the deeper tissues involves considerable variety in the appearance of the swollen parts. For instance, the loss of natural facial expression is at once forced upon one's notice. The skin on the cheeks and forehead is very obviously translucent, dry and firm to the touch, but not nearly so harsh to the rubbing touch as elsewhere. Both upper and lower eyelids are much swollen, and the upper lids droop heavily over the eyeball. They are almost transparent, and look, at first sight, like the eyelids of persons suffering from acute renal disease, but they do not

Detail of
symptoms.

in the least present any pitting on pressure. As a result of the drooping of the upper eyelids, the eyebrows are mostly raised in various degrees, sometimes to a very considerable extent, by the effort to elevate the upper lids above the level of the pupils. The *alæ nasi* are generally particularly thickened and translucent, giving rise to a broadening of the whole nose. The upper and lower lips alike are so swollen as to destroy the natural expression of the mouth, and to reduce it to little more than a chasm between the inflexible margins. The ears are usually both very much enlarged and thickened. The total effect is that of a mask of sorrowful immobility. There is in this a remarkable resemblance of myxœdematous patients one to the other.

In examining the body, one, of course, generally takes note at once of the condition of the thyroid body, although this has no direct relation on the state of the skin. On each side of the neck above the clavicles we usually find large soft projections. Sometimes they are called "dough-like," but they are not plastic like dough, and convey to the touch the same kind of sensation that might be yielded by a large ripe tomato imbedded beneath the skin. These projections, as you know, are partly fat, partly changed connective tissue, and possibly in part veins. They are also very characteristic of that modification of myxœdema which is observed in sporadic cretinism. The abdomen is usually particularly large and often pendulous. In the hands and feet, most noticeably in the former, the changes in the skin determine a great thickening and coarsening of these members. In the hand the digits while swollen are much flattened out, and when the hand is extended no spaces separate one finger from another. The resulting conformation of the hands has been aptly called by the late Sir William Gull "spade-like." The altered hands lose, like the face, what we may call the natural expression, and lose also their delicacy of movement.

Among the earliest manifestations of the disease is a change in the hair, which becomes rough, loses its natural lustre and breaks very readily, becoming after a time very ragged and very intractable in the toilet. The hair thus altered speedily falls off, both from the head and from the eyebrows; not before, however, the latter, if well developed, have passed through a stage of raggedness which is brought into prominence by their raised position. The eyelashes undergo similar disfiguration, are always

much broken, and often are lost altogether. The hair over the body also dwindles and falls off, and the nails, although they rarely go so far as to complete atrophy, are wasted and brittle. It is perhaps mostly in the hands and feet that the extreme roughness of the skin is most developed, the highest degree of this change occurring on the sole and the heel.

All visible mucous membranes exhibit alterations parallel with those of the skin. In the mouth it is evident that the swelling of the lips is very much compounded of mucous membrane. The cheeks project in between the teeth, are marked by them and are very apt to be bitten. The tongue is very large and generally very anæmic. In the fauces we can see the changes of mucous membrane generally most pronounced. The uvula and soft palate press down upon the tongue as a somewhat firm, very translucent and imperfectly movable mass. Similar changes may be seen in the vulva and vagina. The teeth almost invariably undergo impairment of nutrition, sometimes becoming brittle and falling to pieces, sometimes coming out whole without much obvious alteration in structure. The gums are usually greatly swollen, yet recede from the teeth, tending to become ulcerated and to bleed on the very slightest provocation. The most obvious explanation of the decay of the hair and teeth, and of the dryness of the skin, is to be found in an extremely swollen change of the connective tissue in the skin and mucous membranes. The connective tissue becomes firm and resistant, ultimately encroaching on the pulp of the teeth, on the follicles of the hairs and on the sebaceous and sudoriparous glands. Whether these changes in the connective tissue be in part of neurotrophic origin, is a question to be considered, but at present not fully capable of answer. It is important, however, to know that under certain treatment, hereafter to be set forth, the skin, losing its swollen character, resumes its functional activity, and the hair frequently returns also in a healthy form over what have appeared to be bald surfaces. The swelling of the body is, however, not always uniform, or constant. It may, and usually does, appear most strongly in the face and supraclavicular regions. It may, however, be found in the limbs, or in the abdomen, before involving the face and neck. It may in early stages disappear altogether for a time, or it may be transferred from one region to another. The face is particularly subject to alterations in the amount of swelling, generally in association with changes in symptoms, more especially nervous

Mucous
membranes.

symptoms; disappearance being followed by headache or neuralgia, recurrence by relief of these conditions.

Nervous and
muscular
changes.

Tactile sensation all over the body is in typical cases diminished. This can doubtless be explained in part by the alteration of the connective tissue in and around nerve-endings, but it is also in some cases clearly traceable to defect in the central receiving nervous system. The defect of sensation is, of course, particularly noticeable in parts which depend for much of their usefulness upon very delicate and sensitive nerves. The fingers noticeably lose, not only mobility but also accurate sense of touch, which is very plainly demonstrated when a patient endeavours to fasten or unfasten a button or pick up a pin from the floor. There is also a tendency to drop things held in the hand. Not only, however, is the sense of touch blunted, but the recognition by the central perceptive organs of impressions made upon the periphery is distinctly retarded.

In certain circumstances the skin entirely loses sensibility in parts. A lady, whom I have seen recently, and who presents fairly typical myxœdema, has from time to time sudden increase in the swelling of the feet and hands accompanied by a complete loss of sensation over restricted areas of no particular form. When, as happens from time to time, the swelling passes away, sensation is restored to the same condition as in the rest of the body. We may find, therefore, both bradæsthesia and anæsthesia in myxœdema.

The special senses are sometimes affected, particularly the sense of smell and the sense of taste, offensive odours being complained of where no signs of such odours appear to be present, and tastes of excessive sweetness, or acidity, or bitterness, most commonly the sweetness, being present in the mouth.

As regards the muscular system, there is in all cases a marked debility and tendency to ready exhaustion by exertion; sustained action of muscles evidently using up their power very rapidly. The complaint of excessive muscular weariness is one of the next that we have to listen to, and sometimes the failure of muscles leads to very distressing results. Patients sometimes are unable to keep the head erect. For the most part, both in the erect and sitting posture, the head falls forward with the chin on the upper part of the chest and cannot be restored to its proper position without assistance from the hands, either of the patient or of a nurse. Sometimes the head when restored to its position, or a

little beyond the proper position, falls backward with a rapid movement enough to cause anxiety as to the occurrence of injury consequent upon the jerk. Such loss of balance in the movements of the muscles supporting the head seems to exist throughout the whole system, and is readily noticed in the gait of well-marked cases. I have seen this most often of course in women, who are the most frequent victims of the disease. If asked to walk, they rise from the sitting to the erect posture with a somewhat tremulous effort; they sway somewhat in standing, and in walking present a quivering of all the muscles of the body, particularly of the legs with each step. Their movement in walking is such as might be expected to attend great nervous excitement with difficulty to restrain it, and is not altogether without a suggestion of stateliness, such as might be represented upon the stage. Not unfrequently the want of co-ordination in flexors and extensors which leads to this quivering movement, goes so far as to determine sudden falls, not caused by the feet coming in contact with obstacles, but by giving way of the knees. The patient falls suddenly into a kneeling position and often experiences serious injury, sometimes even incurring fracture of the patella. This form of nerve weakness may persist even after the disappearance of the main symptoms already noted.

The speech of the myxœdematous patient is, so far as I know, unlike any other modification of speech in disease. There is an obvious difficulty, in the first place, in getting words out of the mouth. They seem to stick at the lips, and their ultimate pronunciation is accompanied by either a writhing of the upper lip or by a puffing, explosive jerk of the word through the chasm between the comparatively immovable lips of the patient with advanced disease. The quality of the voice is nasal and leathery, the tone monotonous, and at the same time speech is frequently interrupted by little explosions through the nostrils. The words uttered, although somewhat blurred, are usually correctly framed and, for the most part, accurately represent what is in the mind. Sometimes, however, patients will state that they have words in their mind which they are unable to put into speech. In spite of the slowness and painfulness of utterance, the patients are disposed to talk at great length. Once started in conversation, they tend to go on indefinitely. I have known a patient talk continuously for an hour or even more without interruption save for drawing the breath at frequent

intervals, and without taking apparent notice of a remark or question intended to break the prolonged monologue.

In connection with speech, it must be remarked that the patients in many cases write letters, also at great length, and that as a rule the handwriting is good and monotonously regular, the difficulties already mentioned in respect of the movements of the fingers not appearing to interfere with the use of pen or pencil.

The voice, which I have tried to describe, with its monotonous flow and leathery intonation is, once heard, almost in itself a ground for diagnosis of the whole disease. It has occurred to me to hear a patient speak outside the door of my consulting room and to recognise the disease before I had actually seen the subject. It has occurred also under my observation that patients in hospital under treatment for myxœdema would detect in the voice of a newcomer the existence of the malady and would say, "That's my disease." The imperfections in speech are not always so complete as in the typical cases which I have already described. It sometimes happens that the elocution is only comparatively slow, and the existence of a difficulty is not fully understood only after treatment. Then it is frequently found that the patient naturally speaks very quickly and with excellent elocution, which has only been modified in a minor degree. It is, of course, obvious that not infrequently the loss of teeth complicates matters and increases the difficulty of articulation.

If the treatment of myxœdema in any case be successful, natural speech is gradually resumed, but while the mechanical obstacles appear to pass away completely, the tendency to garrulity for the most part persists; so that the physician has still to listen to a long setting forth of comparatively small matters recited volubly and with interminable iteration. That the state of the nervous system is much concerned in this alteration of speech is, I think, abundantly clear. It is perhaps only the first to attract our notice of many nervous symptoms. In some cases, to the difficulty of speaking, a difficulty in swallowing is added. The swollen state of the fauces and of the mucous membrane beyond would make us ready to expect some difficulty, but at times dysphagia of considerable severity together with affection of inspiration, will lead to a suspicion of affection of the medulla oblongata.

Changes in
the mind.

It has been noted already that the aspect of the patients is lethargic. A considerable number are actually lethargic and

unnaturally placid, but it is very common to find, even early in the disease, indication of the disturbance of mental equilibrium. The most common of all is the gradual development of a suspicious frame of mind. This is not, as a rule, a suspicion of conspiracy or of intent to do harm on the part of the people around the patient, but a constant idea that all such people regard the patient unfavourably and are finding fault. This may be developed so far as to make the patient actually violent and protest against the injustice of the supposed attitude of the persons around; and I have seen patients so terrified by the sensation of dread of some ill-defined malignant influence, that they have tried after getting out of bed to throw themselves from windows or downstairs.

It is also interesting to observe that some people who are not suspicious of others, are suspicious of themselves, and spend their time in moaning over their sins and shortcomings, although these cannot be stated in any clear or definite form. Some years ago a patient under my care at St. Thomas's Hospital very well illustrated such conditions. She was a woman of more than middle height, was enormously swollen and weighed over 20 stone. She was afflicted particularly with *cacoëthes loquendi*, and was full of suspicions about everybody who had to deal with her, as well as about the rest of the patients in the ward. "They were all thinking evil of her and no one expressed any sympathy for her sufferings." When I paid my visits to the ward, she often detained me for half an hour with the endless recapitulation of her sufferings, suspicions and fears. One night, under the influence of great excitement, she actually fell out of bed, receiving, however, no obvious injury. One day, after I had been enduring her loquacity for some time, I was passing on to see another patient, when she sat up and reviled me and all present on account of the want of interest shown in her. It occurred then to one of my clinical clerks to take an opportunity of letting her talk herself out. He sat by her bed and listened patiently to her as long as she was able to continue speaking. This lasted for more than an hour and a half. She immediately took a great fancy to him, and said that for the first time she had been properly understood. This was before the days of the use of the thyroid treatment, but the patient certainly improved during a long stay in hospital, and left weighing only 18 stone. I attributed her improvement to prolonged rest in bed, the maintenance of warmth,

and the use of jaborandi. A few months afterwards she appeared in the ward one afternoon during my visit. She was still further reduced in bulk, weighing then only about 15 stone, but while she talked a great deal, her change of mental attitude was quite remarkable. She, indeed, came mainly to apologise to me and to the nursing staff for her rudeness during her stay in hospital. She had known all the time that she was rude and unreasonable, but she was quite unable to repress the feelings which prompted her to rudeness. The case was valuable as illustrating the licence in which persons of unsound mind will sometimes indulge, being fully aware at the time that their conduct is unjustifiable. She did not make her appearance again in the hospital, at least in my ward. Mental improvement following a distinct abatement of the signs of disease has been observed in this case as well as in some others. On the other hand, the suspicions and the garrulity often remain the last symptoms to be overcome. In fact, in some cases they are actually exaggerated in persons who have lost all the other characteristic signs of the malady.

In more than one case, the mental disturbance has become so great as to require restraint.

Taken in conjunction with alterations in the thyroid gland, all the materials for a direct diagnosis of myxœdema are to be found among the foregoing symptoms, but there certainly are cases of myxœdema in which for one reason or another certain of the symptoms may be absent or modified. Thus, for instance, as Dr. George R. Murray has recently shown, instead of the marked swelling of the whole body, a relative tumefaction, accompanied by a yellowish tinge of the skin varying under treatment, would render the first-sight diagnosis a little obscure. The speech is often not characteristic, even when the other parts of the picture stand out well, and the hair and teeth may escape the ordinary degeneration. I have seen recently a lady whose hair at the age of sixty was almost, if not quite, natural, being abundant in quantity, not having fallen out and not being broken or ragged. The teeth, however, in this case had gone early.

There are, indeed, cases in which it must be admitted that diagnosis is very difficult; cases in which, while the bulk of the body is very considerable and the face much swollen, the yellowish, transparent look of the skin is not present, the speech is but little impaired and the hair and teeth have suffered only in

a minor degree. Some of these cases are not easy to separate from cases of simple over-fatness of the body, and it is only by dint of repeated verification that the existence of symptoms belonging to myxœdema and not to simple fatness may be determined.

In the early identification of myxœdema its subjects have much the appearance of being really victims of a form of Bright's disease without albuminuria, and, indeed, after the early publication of observations on myxœdema, it was seriously contended by more than one accomplished physician that the disease really was Bright's disease, associated with an unusual form of dropsy. The compass of this lecture will not allow of my entering into the details of the controversy, but I think that no one now-a-days has any doubt of the absolute difference between Bright's disease and its dropsy and myxœdema and the swelling belonging to it.

We can now proceed to consider some of the associated symptoms of myxœdema, not of such primary importance as the preceding. First among these is the lowering of the temperature of the body. In the well established disease the temperature of the body is usually lowered by from 1° to 3° Fahrenheit. Such lowering of temperature, however, is not by any means always present in the early stages. The heat of the body may be maintained at something like the average temperature or a little above it by the influence of intercurrent disease, particularly that of phthisis. Indeed, an average temperature say of 94° or 96° Fahrenheit observed in a case of well developed myxœdema may be taken to be an indication of a sort of pyrexia calling for the most careful search for any local or general causes, such as in ordinary people raise the temperature to 100°, 101° or more. It will be seen afterwards that one of the first effects of successful treatment of myxœdema is the raising of the temperature. Related no doubt with the lowering of the temperature, we find patients liable to great suffering and aggravation of their symptoms during the prevalence of cold weather. This is certainly the rule, and one may notice in hospital how our old patients come back to us with the frosts. They do not appear so much to feel the cold as to be conscious of the injurious effects of cold. One may see a patient sitting up in bed and complaining of feeling ill because of the cold weather, the hands and feet will often be found then extremely cold and

Associated
symptoms.

Temperature
of the body.

blue, and yet it is far from uncommon to find the complaining person allowing her nightdress to be open so that the air directly impinges upon the skin, and careful questioning will elicit the fact that the patient is not conscious of such impact of cold air, the general numbing of sensation masking the effects of a prejudicial influence.

Independent of various modes of treatment, climate must be regarded as very strongly modifying the progress of the illness. The people who can have well warmed houses and keep out the cold of our English climate pass through the winter with much less suffering and danger than poorer people unprovided with such protection. Still more, if people can exchange our English climate for a warmer one during the winter season, the progress of the disease may be retarded and the sufferings greatly diminished.

Observations of temperature must be made by insertion of a thermometer into the mouth or into the rectum. Axillary determinations may be regarded as practically valueless.

Hæmor-
rhages.

Hæmorrhages from various parts are, as we have noted, not uncommon in myxœdema, though far less general in their occurrence than the alteration in temperature. They occur mostly in the fully established disease. Epistaxis and bleeding from the gums will often be noted. The extraction of a tooth often called for, is always to be dreaded on account of the hæmorrhage which is apt to follow, lasting in some cases for three or four days in spite of plugging and the use of styptics, and involving a drain which the anæmic patient can with difficulty sustain. Hæmorrhages in the skin and from the bowels are less common, but uterine hæmorrhage is often a serious source of enfeeblement, becoming dangerous in association with parturition. Post partum hæmorrhages are far from uncommon in even the early stages of the disease, to an extent almost becoming a rule when the relatively small number of myxœdematous patients who become pregnant is considered. The most serious hæmorrhages are those into the brain. I have seen three cases of apoplexy, in two of which post mortem examination showed bleeding into the brain in the usual position of cerebral hæmorrhage; in the third in a curiously distributed form in the cortex of the brain. In the last mentioned case I had the opportunity of watching the progress of the patient for a considerable time. He was a man of thirty, a waiter by occupation, and was admitted for the first time to St. Thomas's

Hospital, under my care, on June 14th, 1892. It appeared that his illness commenced six years before his admission. He began at first to feel dull, heavy and depressed, and became clumsy, especially with his hands. His friends complained of his dull and muffled voice. All exertion became a trouble and he would occasionally fall. His abdomen and body generally began to swell and his face became round, puffy, and yellowish-brown, with flushed cheeks, earning for him the nickname of "The fat boy in Pickwick," which replaced the nickname of "Skin and Buttons," which had before the illness been bestowed upon him on account of his pale and hollow-eyed countenance. The two photographs which I now indicate represent respectively the condition of the patient some years before his illness and not long after his admission to hospital. His hair had begun to fall out sometime before admission and his skin was always very dry. He stated that he was rather worse in the winter-time than in summer, and had lost interest in the outside world. He was conscious of being very irritable. At the time of admission his skin was exceedingly harsh and dry, also much pigmented, his hair dry, scanty and broken, particularly on the face and head. His features were heavy, his expression was somewhat fatuous, and there was a strong suggestion of his having undergone a sort of Mongolian change of physiognomy. He was very bulky, there was some fulness about the clavicles, the thyroid gland could be felt but was evidently smaller and firmer than natural. All his movements were sluggish, and his hands were spade-like with impairment of the finer movements. There was no sign of visceral disease and the urine was normal. Glycerine extract of thyroid, prepared after the admirable method of Dr. George R. Murray of Newcastle, was injected hypodermically in doses of 15 minims on the following dates:—July 12th, 16th, 19th, 22nd and 30th. He improved considerably under this treatment, which was however discontinued on account of great swelling and distress following the injections, and was replaced by internal administration of the same preparation in the same doses daily. Under this improvement continued rapidly, his bulk diminished, his skin became moist, and at times he perspired very considerably. His hair grew again very quickly and in great thickness. The third photograph presents his condition after six weeks of treatment. This and the second photograph were kindly taken for me by an exceedingly clever clinical clerk of mine, who wrote on the back of the one I am pointing

out a very appropriate quotation from the *Ingoldsby Legends*:—

“He grew sleek and fat,
In addition to that,
A new crop of feathers
Came thick as a mat.”

Only we must pass over the fact that the patient did not, like the jackdaw, get fatter. The patient left the hospital on the 28th August, 1892, but continued to attend as an out-patient for some months afterwards, taking the glycerine extract regularly, but only now about twice a week. The fourth photograph shows him in a later stage of improvement, almost, if not quite, amounting to cure. His attendance now became irregular. He appears to have taken up service as a waiter. I learned at the time that he was a very good waiter in a general way, but was somewhat expensive in consequence of a tendency to drop plates and dishes when he was handing them. It is certain, however, that at this time he began to indulge in alcoholic stimulants, and to have neglected his thyroid treatment. The signs of myxœdema gradually returned, and at the beginning of July he had a fit, in which he lost consciousness for some hours, and this was followed by a second and a third fit during that year. In the last of these the tongue was bitten. He was again admitted in the St. Thomas's Hospital on the 13th November, 1895. Much of the appearance presented at the time of his first admission had now returned, and his urine now was of a specific gravity 1028, with a trace of albumin. Shortly after his admission he was seized with convulsions and was unconscious for one hour. On the 14th November, he had two fits, after which he became very violent, struggling and talking incoherently. He sweated profusely all the next day and was still very violent, requiring restraint by a male attendant. He then became comatose for some hours and died on the 16th November. The temperature, which had been 98·2 at the time of his admission, rose on November 13th to 100·6. At the post mortem examination the thyroid gland was found to be very small and flabby, the isthmus being little more than a strand of connective tissue. It is important to state that the adrenals were diseased, the left being increased in size by enlargement of the central cavity, which contained several calcareous and caseous nodules, some surrounded by miliary tubercles. The right adrenal showed a similar change, but with all this the mass of

glandular tissue was unaffected; there was now no pigmentation of the skin. On examining the brain there could be seen through the arachnoid and pia mater innumerable minute hæmorrhages dusted, as it were, over both hemispheres, but more numerous on the left side. The cortical vessels were much distended and the brain throughout was hyperæmic, but there was no petechiæ below the surface. Otherwise, the brain appeared to be healthy. As regards the hæmorrhages noted on the surface of the brain, it must be remarked that in his convulsions and struggling he had evidently met with some injury of the scalp, but the distribution of the petechiæ and their superficial character were most probably either the result of his epileptic fits or the cause of them. It is well-known that petechiæ occurring in the face of children are not unfrequently found to be the result of convulsions, and that occasionally their existence may lead to the recognition of fits occurring during the night and not in the day-time.

It is now generally admitted that myxœdema, in common with the sporadic cretinism of children and cachexia strumipriva, is dependent on a destruction or loss of the function of the thyroid gland, and that in many ways myxœdema is allied to cretinism, in which affections of the thyroid gland play an important part. It is commonly the case that, in myxœdema, diminution of the thyroid gland is recognised during life; not, however, always by reason of the difficulty of feeling the thyroid through the massive and unyielding cutaneous tissue. For the most part, the gland is found in a state of atrophy, having the secreting structure partially or completely destroyed by a fibrosis of connective tissue, there being also an associated loss of the colloid secretion. But it is not always a reduced thyroid that is found. In an enlarged gland, the destruction of the tissue may be brought about by a new growth, and furthermore, the history of a certain number of cases of myxœdema indicates that an enlargement of the gland has preceded its contraction and atrophy. To go further than this, it may be stated that, in certain well observed cases, the symptoms presented before the establishment of myxœdema have been more or less the symptoms of exophthalmic goitre. It appears to me probable that we shall recognise in the future more and more the occurrence of a stage of hypertrophy of the thyroid gland with or without the signs of Graves's disease as an antecedent of myxœdema.

Changes in
the thyroid
gland.

I will venture to give here an abstract in as short a form as

possible, of a case, the notes of which have been kindly sent to me by Dr. Alexander Hope Walker of Cranleigh, whom I beg now to thank for his kindness. It is, of course, helpful to me to have the opportunity of quoting the cases of other observers as well as my own. The patient is a girl aged 23, living at Alfold in Surrey, a place where, according to Dr. Walker, goitres are frequent. Being hitherto in the enjoyment of fairly good health, she noticed in July, 1890, that her neck was larger than usual, though neither pain nor inconvenience was experienced from the enlargement. In March, 1891, she began to present signs of exophthalmic goitre, and was subsequently admitted in June of that year to Charing Cross Hospital, under the care of Dr. John Abercrombie. The diagnosis of exophthalmic goitre appears to have been formed and adopted at the hospital, where she was treated with iron, quinine, and digitalis, together with daily galvanization of the thyroid. Under this treatment the swelling became reduced in a somewhat marked degree, and she left the hospital on August 1st, 1891, to all appearance cured. She then went into service at Burgess Hill and continued well until November, 1893, when she noticed her legs, arms and hands to be swelling. She finally gave up her service and returned to Alfold, where she was seen by Dr. Walker on November 20th, 1894. At that time, to quote Dr. Walker's notes, "the face throughout was markedly swollen, the skin feeling thick, looking translucent and waxy, and the eyelids were particularly swollen. The nose was broad, the lips thickened and diverted, the face was devoid of all expression, the pink flush, so constantly present in these patients, was absent, the hands were spade-like, the skin was harsh, dry and pale, the hair was falling out, the speech was slow and monotonous, the temper sulky and uncertain, the movements of the body were all very slow and deliberate; the urine and the viscera appeared to be normal; the thyroid gland could just be felt." I think you will agree with me in accepting the first stage of this patient as one of exophthalmic goitre, the second as one of myxœdema. I may add that the treatment was mainly by the administration of thyroid in the form of tabloids. By the end of January, 1895, she appeared to be quite well, but being at home she neglected to send for her tabloids and drifted back into her myxœdematous condition. She was recovered from this once or twice by renewed treatment, but finally died rather suddenly of heart failure on

June 6th, 1897, that is to say seven years after the first appearance of symptoms connected with the thyroid. No autopsy was made so far as I am aware. It appears probable that the enlargement of the thyroid in such a case, as indeed, in exophthalmic goitre generally, is due partly to hyperæmia, and partly to changes in the gland, which are apt, in certain cases, to determine proliferation of the epithelium surrounding the cells, such proliferation ending in the replacement of the true glandular structure by fibrous materials and consequent destruction of the functions of the gland. The gland being thus destroyed, after a time undergoes a sort of cicatricial contraction, leading to atrophy comparable to that occurring in cirrhosis of the liver.

I am inclined to think that the succession of enlargement of the thyroid, with or without the typical signs of Graves's disease, is much more commonly an antecedent of myxœdema with contracted thyroid than is generally supposed.

In my own experience, and probably in that of many other physicians, young women brought for treatment on account of anæmia and various nerve disorders, are found much more commonly now than formerly, to present some enlargement of the thyroid. Doubtless, with the phenomena of myxœdema and exophthalmic goitre brought more and more prominently before our notice, we have come to take more careful note than formerly of the state of the thyroid gland. It is certainly common to find a definite increase in the size of the gland present where neither the parents of the patient nor the patient herself were conscious of anything of the kind. I do not mean to say that in all these cases the enlargement of the thyroid is followed by atrophic change, but the great frequency of the occurrence of enlargement in adult women justifies the hypothesis that in a much larger number of cases than we know of at present, an enlargement of the thyroid has preceded the development of myxœdema. How this enlargement comes about is certainly not well understood as yet, but it must be remembered that, in the first place, myxœdema, like exophthalmic goitre, is a disease affecting women in an exceedingly larger proportion than men. In fact, the title to Sir William Gull's first paper brings this predominance into strong relief. The title of the paper was "On a Cretinoid State supervening in Adult Life in Women." Temporary increases and diminutions of the size of the thyroid body are certainly not easy to recognise and determine, but certainly where a thyroid is

once enlarged it is often found that there is increase of enlargement at the time of menstrual period. When, as in many women, conditions approaching the inflammatory occur in various parts of the body at the time of menstruation, it is no hasty induction if we suppose that a local exaggeration of such conditions may lead to a permanent enlargement, to be followed by simple subsidence or possibly in some cases by contraction. I know of no changes in the sexual organs of men in any way related with myxœdema where it attacks them, and *primâ facie* I should not expect to find such a relation, there being in men no periodical disturbance comparable to those of menstruation. In sporadic cretinism, which is really only myxœdema occurring in childhood, the affection of the two sexes appears to be about equal, boys and girls alike in those cases being affected by developmental error. It is only after the full development of the sexual organs that the disproportionate implication of women becomes evident. So far as I know, the occurrence of sexual development in sporadic cretinism, for the most part very delayed, does not affect the further course of the disease in either sex. The boy and the girl suffering alike from their myxœdema, carry it on with them equally when they respectively become man and woman.

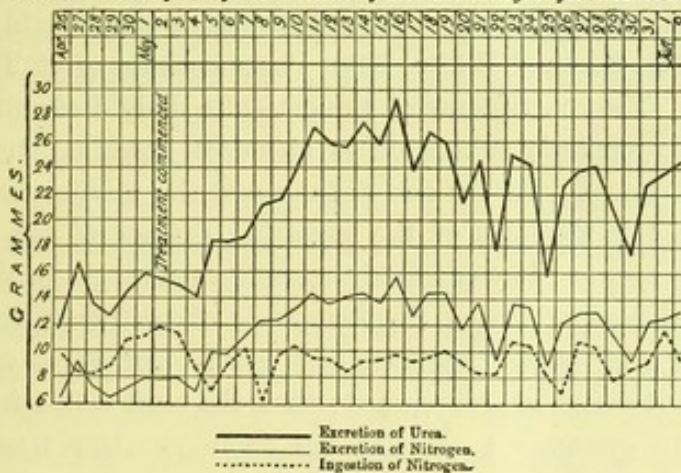
In relation to the points that have just come under discussion, I may draw attention to an exceedingly interesting paper read by Dr. George R. Murray at Edinburgh in July last on "The Diagnosis of Early Thyroidal Fibrosis." The object of this paper is to draw more attention to a class of cases of early disease with partial disablement of the thyroid gland, which are more common than is generally supposed. Dr. Murray points out that the symptoms in these cases are not yet sufficiently well recognised, and he regards the symptoms to be the result of a certain amount of atrophy of the glandular tissue of the thyroid with fibrosis, but he does not think it desirable to discuss the question as to the possibility of fibrosis being primary and leading to atrophy of the secreting epithelium as a secondary result, or to fibrosis as a secondary condition following atrophy.

The urine.

For the most part, the urine in myxœdema contains no albumin, certainly not as a rule until the disease has lasted a very long time, often not at all from beginning to end. Where albumin however is present regularly in the urine together with casts and degenerated epithelium, we may regard it as an indication that the kidney has undergone an internal change com-

parable to that observed in the eyelids, where the glandular tissue is injured by the encroachments of swollen connective tissue. In post mortem examination the kidneys are found somewhat enlarged and exceedingly tough, reminding one in their consistence very much of the kidney of advanced heart disease. This change in consistence is associated with excessive thickenings of the connective tissue around malpighian bodies and between the tubes; changes, at first sight, very like those of the contracting granular kidney. In the case of the young man who died with cerebral hæmorrhage, some increase of interstitial tissue in the kidneys with great degeneration of epithelium, especially that of the convoluted tubes, was noted.

Chart illustrating changes in excretion of urea and nitrogen after treatment.



Average daily excretion of urine and its constituents.	Before treatment.	After treatment.	Increase after treatment.
Volume c.c.	928	1127	199
Total solids grms.	26.16	36.49	10.33
Ash "	7.37	8.84	1.47
Organic Matter "	18.79	27.65	8.86
Urea "	14.21	22.36	8.15
Nitrogen "	7.39	12.08	4.69
Phosphoric Acid "	2.78	3.33	.55
Chlorine "	1.71	2.01	.30
Average daily ingestion of nitrogen in food grms.	9.46	9.30	—

Further, as regards the urine, three things have long been observed as occurring in the treatment of myxœdema by the administration of thyroid :—

First, the urine, below the average quantity before the administration, was very largely increased in the first days of treatment.

Secondly, the quantity of urea present in the urine before treatment, long known to be very deficient, amounting often to less than half of the proper excretion in that fluid, was found under the treatment to be very much increased in quantity, to a point even above the average.

Thirdly, the temperature of the body was found to rise with more or less rapidity from the subnormal range present in the disease to either the normal height or beyond it. After selecting a well-marked case of myxœdema, I obtained the valuable assistance of Mr. Edmund White, B.Sc., Pharmaceutist of St. Thomas's Hospital. The constituents of the patient's daily diet and of the urine were regularly submitted to chemical examination a week before treatment. At the end of the week the administration of the thyroid in the form of the glycerine extract of the sheep's gland was begun. It was found that while the weight of the body diminished rapidly during the first week of treatment, the daily volume of urine passed rose from 928 cubic centimetres to 1127, being an increase of 190 grains; that the total solids increased from 26.16 grammes to 36.49; the organic matter from 18.79 grammes to 27.65 grammes; the urea from 14.21 to 22.36, and the total nitrogen from 7.39 to 12.08 grammes, there being also a distinct increase in the quantity of phosphoric acid and chlorine. It was clear, therefore,

- (1) That the thyroid had a distinct diuretic action.
- (2) That the elimination of nitrogen was largely increased.
- (3) That the increased elimination of nitrogen was almost entirely in the form of urea.

These results appear to indicate that during the process of the melting of the myxœdematous deposit, there occurs some important metabolism of nitrogen containing substance. These observations were brought before the Clinical Society of London some years ago.

Treatment.

Under the head of treatment, it must first be observed that until the introduction by Dr. Murray of the practice of making

hypodermic injection of a glycerine extract of the thyroid gland, no remedies could be spoken of as effective. Arsenic and iron were suggested by the very obvious presence of anæmia; and each in its way often produced some improvement in the general health of the patients. The hypophosphites were used where the nervous weakness was particularly evident, and jaborandi or the salts of pilocarpin were used in order to favour the occurrence of perspiration. In addition to the use of drugs, the introduction of portions of thyroid gland into the tissues of the body has been used by several observers. Some found a resting place for the gland in the peritoneal cavity, others in the tissues beneath the skin. I may say that I myself have made use of the latter method in several cases, choosing a spot over the upper part of the pectoralis major muscle where the portion of the thyroid gland could be deeply imbedded in subcutaneous tissue. In all cases some improvement rapidly followed the operation; the skin began to be moist, the patient's face to fine down, and the hair recovered somewhat of its healthy character, but in no very long time it could be ascertained by the touch that the imbedded gland was diminishing in size and at length it had disappeared. With its disappearance passed away also all the signs of improvement. I suppose that it is just possible that by regular repetition of the process something like cure might have been effected, but I do not know that anyone has performed the operation more than once or twice, the difficulties of such a proceeding being very obvious. It must be stated that the imbedded glandular structure was taken from a goitre, just removed by operation.

After Dr. Murray had made his important discovery, Dr. Hector Mackenzie found that the internal administration of the gland or its preparations brought about as marked an improvement and progress to cure as had been effected by the hypodermic injections, and I suppose that the internal administration of the thyroid gland in one way or another is the method of treatment now usually adopted. It appears to me that the administration of the thyroid gland itself, when it can be carefully and regularly maintained, is the most appropriate form of treatment. The gland may be finely minced and administered raw with sugar or salt or may be lightly cooked. The size of the gland, mainly obtained from the sheep, varies a good deal, and such variation is to some extent a justification of the administration of an extract obtained from a number of glands so as to

get something like an average. In one case still under my occasional notice, an affectionate husband has been at the trouble to procure regularly thyroid glands from sheep and to prepare them in a raw state for administration to his wife. The original quantity administered was one gland a week, but as the patient has improved the frequency of administration has been diminished, but it still goes on as it has gone on for some years, and at the present moment the lady presents no signs whatever of the disease.

It is possible to give the thyroid gland too frequently. When the knowledge of its efficacy as administered internally first became known, I gave to a patient, who was so ill as hardly to present any chance of maintaining life, one gland a day for four days in succession. At the end of that time she suffered from violent headache, vomiting and pains in the limbs with a rise of temperature amounting to 6° Fahrenheit. With such a lesson the gland was administered at longer intervals, namely, of a week to ten days, with ultimately the greatest benefit. But to procure fresh and healthy glands and to prepare them in the proper way involves a great deal of trouble, and its use may be replaced by the administration of Dr. Murray's glycerine extract in doses varying from ten to thirty drops a day, or every second or third day according to the effects produced and to the patient's power of bearing the influence of what we may call now the drug. Still more convenient and not ineffective are the preparations in the form of tabloids now in common use. Some of these contain the dried and crushed gland, others extracts of it, such as the excellent powders devised by Mr. White, the Pharmaceutist of St. Thomas's Hospital. On the whole, I prefer the extracts of the whole gland to any kind of principle derived from it by chemical processes. Perhaps the next best form is the dried and powdered gland of the Pharmacopœia.

A good deal of extremely interesting work relating to preparation has been done by various observers, and I would draw your attention to "Observations on the Chemistry and Action of the Thyroid Gland," by Dr. Hutchison, Demonstrator in Physiology, London Hospital Medical College. According to Dr. Hutchison and others, colloid matter prepared in various ways from thyroid gland is found to contain a definite quantity of iodine, which appears to be present in the form of what has been called "iodothylin" (Bergmann).

We may note in passing that according to Dr. Hutchison parathyroids when administered in myxœdema have no effect upon the disease, although in operations on dogs no myxœdema occurs if the parathyroids are not removed as well as the thyroid.

In conclusion, I may be permitted to say that myxœdema presents for us great interest in the matter of its primary diagnosis; that it presents for our consideration many problems besides those connected with its own etiology and course, and its relations with other diseases in which affection of the thyroid is present; and that in its pathology there are also many points to be investigated and explained. I have dealt only lightly with its pathology for the reason which I have already given, namely, that the setting forth of this before you will presently be found entrusted to more skilful hands.

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