Myxoedema and the thyroid gland / by John D. Gimlette.

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BY

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PREFACE

This account of a comparatively rare disease was originally written in Portuguese to form an inaugural thesis, in accordance with the rules of the Medical School of Lisbon. It being necessary, as part of the State examination, to write and defend an essay on some subject of medical or surgical interest, in order to obtain the title of "medico-cirurgião." Myxœdema was chosen on account of the immense advance in the knowledge of its treatment which has taken place during the last two years, and as a compliment to the work of the Portuguese surgeons in the study of this disease. It was afterwards suggested to me to amplify the essay and publish it in English, with the hope that the general practitioner might find it useful as a convenient epitome of the present state of knowledge on the subject. Space does not allow me to refer to the sources from which these pages have

been compiled; I can only acknowledge my indebtedness in general terms to the many who have investigated and written on the disease, trusting that this review of their valuable labours may meet with their approval.

J. D. G.

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TOPICS RELATIVE TO MYXŒDEMA

CHAPTER I

THE HISTORY OF MYXŒDEMA

The whole history of Medicine is one of progressive differential diagnosis; and Myxœdema, like many other diseases, existed for a long time before it was recognised as a distinct disease.

In primitive times there probably was only one disease recognised,—that is to say, all diseases were considered identical. Even of late years we know how typhoid and typhus fever were considered one and the same, how all venereal diseases were considered identical, and how all forms of kidney disease were classified as Bright's disease. In like manner, in olden times, myxœdema may have been confounded with some other disease, perhaps with leprosy. In the fifteenth century there were many so-called lepers throughout the whole of Europe.

Perhaps some of these may have really suffered from myxœdema; almost certainly some were cretins. Of late years there is no doubt that myxœdema has been classified as œdema originating through disease of the kidneys, although King, as far back as 1836, recognising with Sir Astley Cooper the importance

of the functions of the thyroid gland, had possibly observed the clinical picture now known as myxœdema, which only of late years has been carefully described.

About twenty years ago Sir William Gull was the first to draw attention to this particular disease. On October 24th, 1873, he brought five cases before the Clinical Society of London, being impressed more by the mental and physical peculiarities than by the morbid tissue changes, and defining his cases as examples of a cretinoid state supervening in adult women. To him belongs the honour of the authorship of the first pathological treatise; and to the Clinical Society the satisfaction of having stimulated the first clinical studies of this disease, which have been crowned with such remarkable results.

At the time of Sir William Gull's studies but little was really known of the nature of myxœdema beyond its connection with the cretinoid state; and it was only four years later, when Dr W. M. Ord published observations on seven new cases, that the nature of the disease began to be carefully investigated. Dr Ord brought his cases of the disease before the Clinical Society of London in 1878, and was the first to give an account of its morbid anatomy. He gave the result of the first autopsy, and calling attention to the atrophy of the thyroid gland, was of opinion that the remarkable anatomical modification

of the disease, described by Gull, consisted in the exaggerated formation of mucoid tissue. On account of this histological alteration he gave it the name of myxœdema (*μύξα*, mucus; *οἴδημα*, œdema), defining it thus :—"A progressive disease, in which the tissues of the body are invaded by a mucus-yielding dropsy, unaccompanied by albuminuria or other symptoms of renal disease."

After the publication of these cases many observations on this new disease were published in different countries; in England and the United States by Duckworth, Hammond (of New York), Goodhart, Savage, Thomas Inglis, and Lloyd. In France, however, the disease was still unknown until Charcot independently discovered it. He was the first to record a male case, and was content to call the disease "cachexie pachydermique," as strictly representing the clinical fact of a diathesis having gone on to the production of an actual diseased state; but the name myxœdema, originally given by Dr Ord, is now universally used.

In 1881, Dr Morvan wrote a paper containing notes of fifteen clinical cases, and in it called attention for the first time to the influence of climate and locality upon myxœdema.

Various other observations were published by Olier, Thaon, Bourneville, &c. A very elaborate paper was written by Bazile Féris, in which he

proposes the use of the singular term "Hydroparesie," as it appeared to him that there was a similarity between myxœdema and beri-beri. The remarkable period, however, in the history of myxœdema, which has been very well called the surgical period, began with the discovery of post-operative myxœdema by Reverdin in 1882. The great merit of his work is that he demonstrates that extirpation of the thyroid in man and in animals is followed by morbid symptoms which reproduce a classical picture of myxœdema. An account of the history would be incomplete if the name of Professor Theodore Kocher, of Berne, were not mentioned. This surgeon, at the time of his writing about this disease, did not as yet know the myxœdema of Ord, but describes under the name of "cachexia strumipriva" the extraordinary results which follow extirpation of the thyroid gland. His observations are registered in Langenbeck's 'Archives,' xxiv, 2, 1883. When these are consulted, we see that there is not a single symptom of myxœdema which is not mentioned in them. Only one symptom had been observed by him which is not met with in myxœdema. This symptom, one which sometimes supervenes after thyroidectomy, is the arrest of the growth of the body after the total extirpation of the gland in children. Strictly speaking, however, we ought to confess that myxœdema is properly a disease of adults.

The careful investigations of Kocher did much to prove the remarkable relation which exists between myxœdema, sporadic cretinism, and cachexia strumipriva.

Shortly afterwards a communication by Dr Felix Semon more clearly demonstrated the affinity between these three states, and a commission was organised, under the chairmanship of Dr Ord, by the Clinical Society of London (December 14th, 1883) to study the subject.

Professor Victor Horsley made a series of experiments to investigate the effects of extirpation of the thyroid gland in monkeys, and proved that the loss of the function of the thyroid was accompanied by all the symptoms of myxœdema or cachexia strumipriva, and that cretinism could be regarded as a chronic form of this disease; Professor Bruns, of Tübingen, showing in 1884 that the same symptoms occurred also in man.

Many years before, in 1856, Professor Schiff had proved that extirpation of the gland in dogs was rapidly followed by the death of the animals.

Later experiments made by him, in order to investigate the action of the thyroid, proved that if the gland of a dog were removed and then grafted into another dog, the thyroid of the latter could be removed without producing any ill effect, provided that the grafted gland had not already become absorbed.

These experiments were repeated and confirmed by a great number of physiologists, Albertoni and Tizzoni, Colzi, Führ, Wagner, &c. &c.

Among the many works recently published on myxœdema, one of the most important is by Professor Virchow in the 'Berliner klinische Wochenschrift' (1887), in which he recognises myxœdema as a special disease. Beyond the experiments of Schiff, Munk, Zesas, &c., there are those of Serrano and Bettencourt Rodrigues of Portugal, and those of Dr George Murray, Hector Mackenzie, and other members of the Clinical Society of London, which principally take up the treatment of myxœdema.

CHAPTER II

THE ÆTIOLOGY OF MYXŒDEMA

As happens with all diseases whose nature is complex, the ætiology of myxœdema is still very obscure, it being necessary to consult the different authors who have written on this subject, and to choose, as far as is possible, the ideas which, given in detail and supported by statistics, are most worthy of consideration. As regards this disease, in view of its comparative rareness and more or less obscure nature, a perfect representation of its ætiology cannot be given, for ætiology cannot here be divided into the two classes of predisposing and exciting causes.

We must therefore limit ourselves to a general consideration of the relation of age, sex, heredity, geographical extension, hygienic conditions, preceding illnesses, and common facts.

Age.—In the majority of cases the symptoms begin at the age of thirty to fifty years, and in women it is especially common at the menopause. For example, in two cases, of which a condensed history is given, the ages were forty-four and forty-nine years; in other reported cases the ages are generally about forty-four,

fifty-two, and fifty-four years. At the same time myxœdema has appeared at the age of eight and half years, has rendered itself fatal at the age of twenty years, and has shown itself at the advanced age of seventy-six years.

There are also the curious cases of sporadic cretinism or cretinoid idiots first observed in England by Curling and Fagge, which by many are considered as cases of myxœdema in children. Of these, a very interesting one, of which details are given later, was that of a little boy of hardly two and half years of age, mentioned by Dr Gibson, of Melbourne ('British Medical Journal,' January, 1893). In fact, we may almost conclude that the disease manifests itself at all ages.

As regards myxœdema artificially produced by removal of the goitrous thyroid, the tendency towards its full development diminishes as age advances. It is said to have seldom appeared after forty years of age.

Sex.—Myxœdema is more frequent in women than in men. We have seen that Sir W. Gull considered this disease peculiar to adult women, but it certainly occurs also in the male sex, although more rarely, and of the 109 cases cited in the "Report on Myxœdema" ('Clin. Soc. Trans.' Supplement, vol. xxi) there are 15 male cases to 94 female ones—a proportion of about 1 to 6.

Cachexia strumipriva has been induced very much more frequently in women than in men, on account of goitre being relatively so very common in them.

As regards the result of curative treatment in myxœdema, we may hope for equally good results in both cases.

Heredity.—There is no doubt that in this disease heredity has a great, though perhaps a not well-defined influence. Very often the disease affects two or several members of the same family,—for example, mother and daughter, brother and sister, or twins; that is to say, parents have children who in after life become affected with myxœdema—they are not born cretins; indeed, it is remarkable how often the parents of sporadic cretins born in England are perfectly healthy. Intermarriage and consanguinity do not seem to have any influence.

In certain cases a direct transmission from the father is met with, but more often from the mother. Among the hereditary antecedents there are gout, diabetes, rheumatism, syphilis, alcoholism, and various neuroses, all of which do not seem to have any certain relation to the ætiology.

Geographical extension.—The geographical extension of this disease is probably universal. It has already been met with in many different countries, viz. Bermuda, England, France, Portugal, Queens-

land, and Thibet; it seems to be rare in Germany and the United States. In North Britain it is not uncommon. Some think that the coloured races enjoy a complete immunity; proofs, however, are yet wanting to justify this conclusion. As regards the places where it is met with, it seems that the manifestation of this chronic disease is closely related to what Virchow calls "Gelegenheitsursachen." As an example of this, the fact may be cited that in Edinburgh and Dundee there are certain quarters in which myxœdema and sporadic cretinism have been met with so frequently that they may be said to abound there. One after the other, persons living in these crowded districts, and so in identical conditions, are attacked with this disease.

It is not certain whether there is any relation between the causation of myxœdema and the influence of climate (as happens with endemic goitre), although atmospheric conditions, such as low temperature, scanty rainfall, and diminished sunshine, may have some significance. In England, in the districts such as Derbyshire, where goitre manifests itself, cases of myxœdema are not exceptionally frequent; but in countries such as Switzerland, where cretinism is endemic, climate seems to have had a special tendency towards favouring the onset of "cachexia strumipriva" after thyroidectomy.

Dr Morvan attributes the relatively large number

of cases observed by him to the humid climate of Lower Brittany, and Thaon also mentions the case of one of his clients, a native of the Ionian Islands, whose symptoms were greatly aggravated by the change of climate to London, the regression completely subsiding when the patient returned to her native land. In the treatment of this disease change of climate has been recommended, and sometimes with benefit.

Hygiene.—This seems to have some influence in the causation, because it is noteworthy that, in the majority of cases, those attacked are people belonging to the lower or lower middle class, the hygienic conditions of whose existence are not generally so good as those of the higher classes. However, in the "Report on Myxœdema," which is an admirable and very elaborate treatise by the Clinical Society of London on this subject, and which extends over the period from 1883 to 1888, it is said that social position probably has no influence at all as a predisposing cause.

Preceding illnesses.—It is thought that there is a relation between phthisis and myxœdema; and certainly in the latter disease there is a great tendency towards tuberculosis. The reason for this is not known.

Myxœdema doubtless possesses an affinity with insanity, which in many cases supervenes, while in others it may precede it. In the latter case the co-

existence of the two diseases is probably only a coincidence.

It is said that, if the parents have swellings of their thyroid glands at the time of marriage, their progeny will be either sporadic cretins or "myxœdematous," and that if both parents are goitrous for two generations in succession the offspring of the third generation is sure to be a cretin (Watson). This filiation between goitre and cretinism is an important fact; for it is very evident that although we can probably do but little for the endemic cretin, we can aim at preventive treatment by acting on the goitre. A case has been noted in which a myxœdematous mother gave birth to a child which afterwards suffered from goitre. This case, however, cannot be considered as genuinely hereditary, for, endemic goitre being a miasmatic disease, the influences which predispose to it act not only on the parent, but also on the fœtus *in utero*. At times the symptoms of Graves' disease have preceded the onset of myxœdema; the two diseases have been even considered combined, and it seems certain that a special relation exists between them. As yet, however, there is no proof which justifies us in considering these two diseases as cause and effect. There may be obvious enlargement of the thyroid gland from vascular engorgement without increased secretion of the thyroid juice.

Other observations.—The fact of myxœdema so often

attacking women originated the attentive inspection of the relation of myxœdema to pregnancy.

Many times the patients are multiparæ, and it is frequently seen in the history of the disease that the symptoms have followed the last confinement or an abortion, but it seems that there is no real connection here, although it has been ingeniously argued (Blake) that if the absorption of purulent products abolish the functions of the thyroid, we may have myxœdema.

It is true that myxœdema has very often attacked women who have in a few years conceived many times, but cases of myxœdema have also occurred in persons who have never been pregnant, *e. g.* in men; and there have also been some pregnant women in whom the disease has grown less during the period of pregnancy; but an ingenious explanation of this is given by Dr Blake, in his book, 'Myxœdema, Cretinism, and the Goitres,' in which he says that the thyroid gland of the fœtus may have supplied for a time the place of that of the mother. In a case quoted by Dr Ord, a patient with the typical physiognomy of myxœdema became pregnant, all the swelling of the disease disappearing, but returning after the confinement. The first symptoms have shown themselves after a great affliction or agitation, such as the mortal illness of a husband or child, ill-treatment by a spouse, &c. The action of these depressing moral impressions, fatigue, &c., as ætio-

logical elements should be borne in mind; and though they are not always met with in myxœdema, yet as regards sporadic cretinism they form a common history on the part of the mother before the birth of the child. It is well known that emotion makes itself felt on the secretion of the gastric juice, saliva, bile, and urine, and that a mental shock can even cause atrophy of the liver, chorea, syncope, &c.; and physiological teaching tends to show that emotional states, and anything which lowers nerve force, diminish or arrest secretion in general. Fear even paralyses the action of the salivary glands.

And so it has been asked whether myxœdema has its origin in a neurosis; but this term, like the expression "functional disease," is after all but vague and inconsistent, only indicating an abnormal reflex discharge of nerve force, the nature of whose physical basis and organic cause is undetermined. Mental depression, by producing slowness of the circulation, which may be induced by prolonged grief, is certainly more likely to dry up secretion than to promote it.

CHAPTER III

THE SYMPTOMATOLOGY OF MYXŒDEMA

The symptoms of myxœdema commence so treacherously, and proceed so regularly and slowly, that it is almost impossible to clearly define the period of its onset. Although its nature is essentially chronic and progressive, nevertheless at times there may be periods of interruption in the symptoms, so that without treatment and without complications this disease may last for many years, even twenty, without being fatal.

However, two cases have been noted in which the disease showed itself suddenly; one by Charcot, in which the first symptom was a sensation of intense cold, and the other by Ord, in which the first symptom was hæmaturia.

When the typical symptoms are developed there is no difficulty in recognising the disease, for there is a general degeneration of the tissues, and the nervous system is seriously implicated; while, with the advance of the disease, a cachexia shows itself working changes which, at last, are so great, that if the patient absents himself from home for some time, he is not easily recognised on his return.

There are three remarkable characteristics in myxœdema: a progressive and gradual change in the skin, altering the physiognomy in a noticeable way; a grave complication of the nervous system, producing a series of symptoms characterised by indolence and want of action; and an affection of the intellectual faculties bordering on insanity. These three characteristics are so strange that each one merits a full and separate description. It must always be remembered, however, that they are inseparable, that with the alteration in the skin there is a torpor of the faculties and a loss of activity and will force, from which gradually results the weakness of mind and body.

Alterations in the skin.—In the first degree of myxœdema the skin loses its elasticity, a so-called "solid œdema" being gradually produced. Throughout the body there is a curious, firm thickening or hard swelling in the subcutaneous areolar tissue. It is an œdema which, not being at the surface of the skin, does not exhibit, like true œdema, the signs of pressure. It is especially well seen in the eyelids, lips, cheeks, and nose, the skin being coarse and wrinkled, but with the advance of the disease extensive tumefaction of the subcutaneous tissue may occur, *e. g.* above the ear, and the skin of the whole body may appear in thick rolls, sometimes at the end of the disease becoming tense. The skin is also cold, very dry, and covered with a kind of scales,

similar to bran—a branny desquamation, not unlike that in xeroderma,—and, owing to its dryness, there is an increase of electrical conduction. These changes are evidently trophic in character, for in the same way the appendages of the skin are affected, especially the sebaceous and sweat glands, which cease to act. The absence of perspiration is also a remarkable characteristic.

The hair of the head is dry, fine and brittle, in women, as if it had been frizzed, or it is almost totally lost; the eyebrows and eyelashes are thin, and also the pubic and axillary hair. The nails often become cracked and brittle.

Physiognomy.—The physiognomy of myxœdema is characteristic, the sufferers presenting a family likeness to one another which at different times has been described as cretinoid, expressionless, apathetic, stupid, dull, mask-like, &c.

The first aspect of the face is one of anæmia, the general expression indicating monotonous immobility, for the patient is not excited by a question, statement, or sudden movement, but is placid, his expression being, according to Sir William Gull, "like a full moon."

The aspect is sad and dejected, although often kindly, for facial reaction not being entirely lost, the patient may yet smile. The face is nearly always pale, often sallow, with a permanent patch of dusky

redness or a brilliant circumscribed blush over each malar bone, the colour not being fresh or healthy-looking, but due to the distension of the arterioles and capillaries from weakness. The expression of sadness may be conveyed by the pallor and the more or less ruffling of the forehead, accompanied by a drooping of the eyelids and elevation of the eyebrows, which is a typical feature. From this we see that the physiognomy of the disease approaches that of the depressive form of mental disease; and, like melancholia, myxœdema appears to be much more frequent in dark than in fair persons. But we cannot say that the corrugator supercilii, pyramidalis nasi, and central fibres of the frontalis, *i.e.* the "grief muscles," are acting in combination, for in myxœdema the lines of expression become either coarse or are obliterated.

Friends often remark the alteration of physiognomy, but cannot always accurately describe it. They may state that the patient looks older than he is, and that any good looks which he may have had are lost.

The face is larger than it was in health, being increased in all directions, more especially in the transverse diameter; but the features are symmetrical, and swollen without regard to the law of gravity: for example, the upper and lower eyelids and both lips are equally enlarged, and the "alæ nasi" are

thickened and dilated. In advanced cases the swelling of the nose may be so great as to render the respiration difficult. The whole nose is swollen and the bridge flattened.

The upper eyelids, like alabaster in their transparency, droop; and thus, swollen as they are, may sometimes narrow the apertures of the eyes and intercept the vision, it being necessary to support them in order to allow the patient to see. The lower eyelids are often "baggy," and a puffiness of the tissues immediately below them forms a characteristic of the blob-cheeked face. The mouth is widened transversely, the lips large, thick and pouting, and often of a livid colour. The skin of the face is said at times to be affected with chloasma.

A typical case is thus easily recognised, in a woman of or beyond middle age, by her appearance alone; the characteristics of which are that the features lose their general form, the alæ nasi are broadened, the mouth is changed in shape, the skin is opaque in texture, and there is a tendency to pigmentation and wrinkling. At this age, too, the symptoms develop gradually, and the access of serious symptoms is slow.

In a person affected with myxœdema at a younger age anæmia is more marked, the skin is generally translucent and free from pigmentation; there may be much œdema of the eyelids, and the progress of the case tends to be a rapid one.

The difference, as Dr Ord remarks ('St Thomas's Hospital Reports,' vol. xix), is probably in part connected with the progressive changes in general nutrition proper to each period of life, in part determined by the diminishing importance of the thyroid gland as life advances.

The hands.—The œdema of the skin shows itself in the hands, which, like the face, become distinctive of myxœdema. Sometimes the first sign of the disease is an inability to wear the ordinary gloves, because the hands become larger on account of the very thick, dry, and coarse state of the skin, and broaden themselves out transversely. Each finger is uniformly thickened, giving to the whole hand a singular aspect, which has been expressed by the phrase "spade-like." This name was given by Sir William Gull, because the fingers, upon being pressed one against the other, lose their natural conformation. With regard to this, however, it ought to be noted that, although the hand takes a peculiar form, it is not always like that of the English spade. It has even been compared to a battledore. The skin of the palm is moderately dry and often cracked, the patients complaining that they cannot keep their hands clean. In some advanced cases the swelling of the hands is so great that the fingers cannot be interlocked, the pulse at the wrist cannot be taken, and a ring becomes so embedded in the flesh that,

in order to take it off, it may be necessary to break it.

The lower extremities.—Changes, similar to those in the hands, take place in the lower extremities. The members in almost every case are very large and deformed, they lose the delicacy of their form, and the patient often acquires "the look of an individual hewn from a block by the blows of an axe" (Ridel-Saillard, 'Thèse de Paris,' 1881). The legs swell, and sometimes, under the pressure of the finger, the ankles "pit on pressure;" but this sign is little pronounced.

The skin of the sole of the foot becomes so rough that it has been compared to sand-paper, and at times it is so dry and thick that it acquires almost a horny consistency.

Beyond the general distribution of the swelling, there is an elastic fulness in each supra-clavicular region, a soft tumour, ill-defined and apparently painless, occupying the posterior inferior triangle of the neck.

These swellings are very frequently present, and were noticed long ago by Curling in 1849. They are said to be more common in children than in adults. According to Bourneville and Bricon they are almost constant in cretins, and occur also in the axillary region ('Archives de Névrologie,' 1886). Although they are generally considered as being

pseudo-lipomata, their nature and the reason of their being in that situation are still subjects which require further investigation.

The mucous membranes.—Like the skin, the mucous membranes are altered, as is well seen in the mouth,—the soft palate, uvula, pharynx, gums, and tongue swelling and becoming pale and characteristic. A thick mucous discharge from the mouth at night has been noticed. The œdema of the mouth may interfere with respiration, and also with the action of swallowing, since slight difficulty in deglutition is not at all uncommon in myxœdema. The aspect of the tongue is especially noteworthy. It is pale, smooth, swollen, and marked by the teeth. In some cases it arrives at such dimensions, especially in children, that it can with difficulty be kept in the mouth. The teeth become carious and loose, because the gums, although swollen, recede from them. They are subject to bleeding, and losses of blood from the nose and throat are common, as well as other hæmorrhages occasionally.

The implication of the nervous system.—The whole nervous system of the patient being defective, there is apathy, stolidity, inertia in mind and body, want of thought and movement. Sensation, the motor functions, speech, and the special senses (vision, hearing, smell, taste, and touch) are all affected.

The sensation.—The general tactile sensation be-

comes less delicate, and the transmission of impulses from the skin to the cerebrum is very much delayed. Abnormal subjective sensations are frequent. The patients very often complain of a sensation of cold equal to that which happens when cold water falls drop by drop on the skin.

The temperature.—The temperature of the body is always subnormal, generally about 97° F.; but it has been observed as low as 94·2° F.; and in the 'Lancet,' i, 1886, p. 618, there is a case recorded in which it is said to have fallen as low as 66—70° F.

The daily variations of body heat are not such as in a state of perfect health. There may be some blushing, but the temperature is not easily raised. This loss of temperature is so constant that a thermogenic function has been attributed to the thyroid gland, but whether it is so, or whether this function is held by the pituitary gland (? a complementary organ to the thyroid) remains yet to be proved.

The motor functions.—The movements of the body are slow and languid, and, in order to sustain a fixed position, the patient has to employ a certain amount of effort, and soon becomes tired. The hand-grasp is weakened. He cares not to, and indeed cannot, execute delicate work which requires any special precision: for example, women are obliged to give up their embroidery and crochet work, because it becomes difficult for them to manipulate objects so

small as the needles ; and, again, they often fumble in dressing themselves, and cannot button their clothes.

The muscles contract weakly under the action of electricity, and the reflexes are generally diminished. It seems as if the muscles were without tone, and they remain very relaxed during rest. A considerable initial contraction is necessary in order that they may begin their regular action. Fracture of the patella has happened in certain cases on account of this, and hence originates the stooping attitude which the patient affects during the course of the disease.

In myxœdema the head, at length, may incline forward, as though too heavy for the muscles of the neck, in such a way that the chin may touch the sternum, and the individual presents exactly the attitude commonly observed in cretinism and melancholia. Muscular sense also seems to be torpid ; but, even should there be a loss of strength, there is no loss of muscular substance. According to the French school, the muscles preserve their normal strength in spite of the habitual torpor, but there is a want of energy in the stimulus transmitted from the brain. There is no actual loss of muscular power, but rather an awkwardness or want of co-ordination in the ordinary actions of flexion and extension.

According to others, on the contrary, the loss of strength, the embarrassment of speech, the immobility of face, and the alteration of voice are due to a true

paralysis; but it is more probable that they are due to an infiltration of mucoid material between the fibres of the muscles concerned.

Although paresis of muscles, *e.g.* of the limbs, chest, &c., is so common in myxœdema, yet true paralysis, unless as an accident or a complication, certainly does not exist. The gait is remarkable, nearly all the movements are executed with precision and deliberately. It is at the beginning of the disease rather ponderous, but gradually becomes more or less vacillating, and then there is a difficulty in maintaining the equilibrium, the result being that the patient is afraid to go about alone, and feeling himself about to fall from his knees giving way, likes to pass his days undisturbed, ruminating by the fireside.

The speech.—In myxœdema the speech is characteristic, and there have actually been diagnoses made by this means alone. It is slow, deliberate, and persistently continuous, and the voice is monotonous and muffled, sometimes nasal in character. There may be short pauses between each word, or a habit of swallowing before speaking. Ideas are expressed correctly and with precision, but the articulation is painfully slow. The faculty of speech is disorganised, and, if I may be allowed the expression, it is "cretinoid." The patient wishes to speak more fluently than he can, there being what may be almost called a kind of "strike" on the part of the functions of

speech. Beside the muscular inability, the articulation is, without doubt, affected mechanically by the volume of the tongue.

The speech is so characteristic that, in cases of paralysis agitans, where it is affected, its difficult and hesitating character has been well defined as myxœdematous; but in some cases the speech of myxœdema may be almost normal, and the patient even garrulous.

The sight.—Often the patients have some defect of vision, but no characteristic affection is recognised, unless it be lachrymation and a general diminution in the field of vision. Exophthalmos has been noted at the commencement of a few cases.

The hearing.—Deafness caused by non-purulent catarrh of the internal ear is very common, and in some cases the deafness may be complete, evidently being due in these instances to nervous influence.

The smell and taste.—Smell and taste become affected; generally they are defective,—by reason, perhaps, of the constitutional affection, for we have already seen that the extremities of the nerves of cutaneous sensation are affected by myxœdematous material. It is therefore very natural that, in the mucous membrane of the nose, tongue, and palate, the extremities of the nerves of special sense may be affected in a like manner. At times there are subjective sensations; but often, when the patient fancies

he perceives a disagreeable smell, this may in reality come from his carious teeth.

Pains.—As a rule, the patients suffer from pain in different parts of the body, similar to those of muscular rheumatism, the most constant of them being in the occipital region, where, according to the opinion of some, it is due to an affection of the torcular Herophili. Cramps in the legs are not uncommon.

Body weight.—There is a gradual increase in weight, the whole body becoming larger. The patients complain of the usual dress being too tight. A case has been noted in which the body weight reached 22 stone. Increase and loss of bulk, however, may be variable in myxœdema.

The mental symptoms.—Mental symptoms form an important characteristic of myxœdema. At the beginning the patient feels tired, worn out, enfeebled, and sad; a little later he becomes pensive, half stupid, taking his time to comprehend and respond to a question, and requiring much time to think. The cerebrum is slow to create, arrange, and exhibit its ideas, although the mental process is finally correctly performed. He forgets with extreme facility even the most recent facts. This deterioration of the memory is a strange symptom, also seen in the spelling, which becomes at times very bad. The handwriting also may be changed, but this is evidently

due to the alteration in the shape of the hands. It is possible that, with the advance of the disease, the patient may even lose his memory completely; but although convinced of his state he does not seem to feel it much, simply thinking that he is growing old. Yet sometimes he may be quite irritable and very suspicious, with hallucinations and illusions. Spasmodic convulsions may also show themselves. In one of the cases of which I give the notes, the patient suffered remarkably from these mental symptoms. This case was complicated with insanity.

As a conclusion to the symptomatology of myxœdema, let us suppose an extreme case. A young woman of nervous temperament, full of grace and elegance and of perfect form, becomes affected with myxœdema. Her condition is pitiable. Ingenuity and intelligence, with talent and nervous energy predominating, are replaced, as it were, by a "chronic cold debility." She becomes dejected and stout, walking heavily after the manner of an elephant.

The sensibility of heart, the many and rapid sensations, the quick and brilliant imagination, are all changed to sloth, hebetude, and indolence. The woman formerly so sympathetic and lovable has now a mournful, uninteresting look upon her face; her life is a burden, and she must live in retirement, for it is almost impossible for her to take her place in society or to conduct herself with courteous polite-

ness, for she can neither express her thoughts with facility nor make any graceful movement.

This condition progresses, and sooner or later she arrives at a state of almost vegetable existence. Then the question is, what is to follow? Either she succumbs in spite of all palliatives, or, by means of modern treatment, her mind and body gradually but surely become reanimated, as if there were a resuscitation of the vital forces.

Physical signs.—Generally, physical examination of the chest and abdomen discovers nothing abnormal.

The heart preserves its natural size more or less, and is apparently sound, although in many cases the pulse may be quite slow. Arterial tension and atheromatous degeneration have been noticed, but as a rule the pulse indicates weakness.

The lungs preserve their normal state, and respiration is unaffected.

The liver and spleen are probably also healthy, but the functions of digestion are altered.

Dyspepsia is common, and constipation the rule, although a case has been reported in which there was incontinence of fæces ('Medical Record,' October 7th, 1893).

There are very often hæmorrhoids, which are apt to bleed.

The kidneys show no physical sign of hypertrophy,

but the sensation of pain in the lumbar region has led to a careful examination of the urine, and attention has been frequently called to the diminution of urea in it.

The urine with this exception may be normal, perhaps increased in quantity and of a low specific gravity, but without albumen, casts, or sugar. However, at the end of the disease albuminuria appears, tending to cause kidney disease, and so death.

The uterine functions suffer no pathognomonic alteration. There may be absence of menstruation, yet in other cases it may be excessive.

Post-partum hæmorrhage, due in part to an altered condition of the blood, and in part to uterine inertia, is not uncommon. The blood on microscopical examination shows a diminution not only in the number of red corpuscles, but also in the amount of hæmoglobin.

CHAPTER IV

THE COMPLICATIONS AND VARIETIES OF MYXŒDEMA

One of the most noteworthy complications of myxœdema is albuminuria, and, with the progress of the disease, comparatively sudden death may be caused by uræmia and coma. There may be weakness of the circulation, and ordinary œdema or perhaps anasarca may complicate the swelling of myxœdema. Sometimes there are chilblains and also warts on the hands and feet, sometimes moles on the body. There is a tendency to the production of subcutaneous ecchymoses from slight causes, and a delay in the process of cicatrisation of wounds.

Intercurrent diseases are very often the cause of death, especially pulmonary diseases such as pneumonia, fibroid degeneration of the lungs, and above all tuberculosis. In spite, however, of tubercular affections being so common, tubercular degeneration of the thyroid itself is very rare, and, indeed, is almost unknown.

True insanity ought to be considered as a complication. In confirmed myxœdema it corresponds to

those forms of dementia which we meet with in malnutrition, similar to those which sometimes happen in cardiac cases, cases of depression, &c. But it is also true that, in some cases of myxœdema, there may be periodic attacks of homicidal and suicidal mania. Suspicion, hallucinations, and "self-accusation" are very common, and if intensified, *e.g.* by change of surroundings, may lead to violence. Delirium is recognised as a not unfrequent occurrence, and melancholia with epilepsy has been reported (Claye Shaw, 'British Medical Journal,' August 27th, 1892).

Delirium would be "chronic," characterised by prolixity, very prone to run into insanity. One of the chief predisposing causes to the mental aberration would be a "neurotic predisposition." At the commencement, symptoms such as these—peevishness, want of confidence, inconclusive conception, and misanthropic distrust of the kind offices of friends—may be noted, and, being similar to those met with in elderly widows of a nervous type, may not attract much attention until the dulness of perception is noticed and myxœdema is diagnosed, when the supervention of a paroxysm of mania ought to be provided for.

If false perceptions and delusions continue after the abatement of physical violence, the prognosis is bad, as the patient may pass into dementia.

Sometimes it seems as if death is caused directly by the disease, the patient succumbing to nervous and general weakness, a true cachexia due to the intense anæmia so common in myxœdema.

In these cases it is very remarkable that, at the approach of death, the œdema diminishes, though the skin never regains its natural flexibility.

Loss of bulk, however, is not necessarily a sign of downward progress.

Some writers have endeavoured to divide cases of myxœdema into primary and secondary classes, but as regards varieties we shall only mention here the true myxœdema of adults and the myxœdema of children.

The identity of the latter with cretinism is a debated question. The sporadic form of cretinism is far more like myxœdema than the endemic form. In endemic cretinism there are anatomical differences in the atrophic process, for, with few exceptions, all these cretins are goitrous, and the dissections of Virchow show that the parts at the base of the cranium are early ossified in the form of a rectangle, and in reality very many varieties of cranial deformity may be met with in cretinism, *e. g.* synostosis may be deferred instead of being premature.

Again, the geographical distribution of endemic cretinism points to a difference in their causation, for in continental countries, at least, where it is found, goitre is always met with as well, and here atmo-

spheric, telluric, and possibly geological conditions may exercise an influence in the causation of both.

Between myxœdema and sporadic cretinism there certainly exists a great similarity. Atrophy of the thyroid is more or less constant in sporadic cretinism.

There are, however, some differences between them, *e. g.* in myxœdema, the absence of the thyroid is, as a rule, permanent, women are commonly affected; and the sensible diminution of temperature, the very gradual weakening of the faculties, and the flush on the cheek with the drooping eyelids are distinctive.

In sporadic cretinism the patients are males, as a rule, and these signs are less pronounced; indeed, the flush on the face is generally absent, the skin presenting a dirty chalky appearance, a fact which may perhaps account for the derivation of the name from *creta*, chalk, although others ascribe its derivation to the fact that these cases so frequently occur in districts where the soil is chalky or cretaceous.

In the cretin there is a distinct arrest in his physical and intellectual development, and fatty tumours in the posterior triangle of the neck—the supra-clavicular swellings—are said to be pathognomonic (Hilton Fagge). The stunted cretin, rarely above four feet and a half in height, with his many infirmities (hernia, deaf mutism, &c.), will stay warming himself on his haunches in the sun like a lower animal, taking notice of no one, turning with indifference from all

that is not eatable. The well-proportioned patient with myxœdema may do the same, but, as rarely happens to the cretin, there may be in him homicidal tendencies; it is then necessary to shut him up in a lunatic asylum for the time being.

The debased cretin, on the contrary, although subject to tremors and to epileptiform seizures, is not dangerous, and very often becomes an inmate of an idiot asylum, living a miserable, automatic existence for a number of years, rarely exceeding forty or forty-five, each sufferer resembling his fellow in every way, always a poor creature who, even at an adult age, does not develop beyond a strange uncouth child.

CHAPTER V

THE DIAGNOSIS OF MYXŒDEMA

Myxœdema certainly presents a pathological entity which it is impossible to confound with other affections. The diagnosis is chiefly based on the combination of œdema and paresis, on the peculiar hardness of the subcutaneous infiltration, on the special aspect of the face, and on the absence of albumen in the urine. The similarity between myxœdema and Bright's disease is very remarkable, so much so that it has been suggested that the two conditions are identical (Mahomed). Doubtless in past times, when the nature of myxœdema was not well understood, many cases of it were classified as chronic disease of the kidney, because at first sight there seems to be many points of resemblance. Both come on insidiously and run their course slowly with increasing debility and anæmia. In each the urine may be pale, of low density, with a small amount of albumen, perhaps casts, and diminution of urea. Hæmorrhages from mucous membranes, dyspnœa, general œdema,

and headaches occur in both. Uræmic coma with low temperature or pneumonia may close the scene in either.

But the hard skin of myxœdema with all its special characters, dryness, non-pitting œdema, &c.; the customary low temperature, the mental state and the speech are by themselves distinctive, not to mention the most important of all differences, *i. e.* the absence of albuminuria (unless as a complication) in myxœdema, and the extreme rarity of retinitis and renal asthma. Dr. Bazile Féris insists upon the similarity between myxœdema and beri-beri, and, in a memoir published in 1883 ("Myxœdème et béri-béri, ou Hydroparésie nevrovasculaire," in 'Gaz. Hebd. de Méd. et de Chir.,' juin, 1883), he holds that the two are identical. But, indeed, until the last two years, there has existed considerable confusion as to the true conception and definition of the disease known as beri-beri. Even systematic writers upon tropical diseases have been so far influenced by too hastily formed theories as to its nature and origin that, in their desire to fit the facts to some favourite theory, they have dealt too loosely with original descriptions, dwelling with undue emphasis upon some points which accorded with their theory, and passing lightly over others equally, if not more important, which were opposed to it.

These facts appear to indicate that in reality the

points of resemblance between the two diseases are not many.

A very brief contrast of the two diseases will show this. Now the chronic, dry, or relapsing beri-beri of Ceylon, termed "false beri-beri" (though there is no line of demarcation between it and the "sub-acute" beri-beri), is probably identical with the barbiers of older writers (Bontius, Marshall, &c.), and is apparently related to anchylostomiasis. It certainly, therefore, presents no similarity to myxœdema, and may therefore be eliminated from the terms of the contrast.

Let us take, then, the commonest type of "sub-acute" beri-beri, *i. e.* the mixed form, met with in Japan, the Malay Peninsula, China, India, Africa, and Brazil. Now true beri-beri, as distinguished from myxœdema, is an acute disease of the nervous system, characterised by oppressed breathing, paralytic weakness, numbness and stiffness of the lower extremities, a fair amount of œdema, and great prostration of mind and body. The keynote to all its complex symptoms is, as Dr. Manson points out (Davidson's 'Diseases of Warm Climates'), the fact that it is a peripheral neuritis. In beri-beri the appearance is leucophlegmatic; there is not the special kind of swelling found in myxœdema; the patient looks ill, which he may not do in myxœdema, and he may be carried off unexpectedly during con-

valescence by sudden suffocation from œdema and congestion of the lungs, or by heart paresis, by hydropericardium, or by paralysis of the diaphragm. In myxœdema, if death happens suddenly, it depends only on uræmia. It is said that a feeling of habitual constriction round the waist, sometimes met with in myxœdema, resembles the symptom of beri-beri called by the Brazilians the "cinta beriberica," or "beriberic girdle;" that warm countries, in which the air is charged with watery vapour are those in which the two diseases develop in their greatest intensity; and that in myxœdema there is paralysis, and that the extensor muscles are especially affected in both; and, again, that the gait is similar in the two cases. The gait of myxœdema, however, is not like that of beri-beri; for as the Malay name "berhii," or sheep, indicates, it is at first more like that in the commencement of locomotor ataxy, and comparable to that of a man who walks with his trousers drenched, the heel being raised very high to fall with a flop as he advances. Later it becomes sheep-like, and the patient, gradually coming to have no control over his legs, shuffles along and clings to any available support, until he eventually loses the use of his legs and lies "water-logged."

We may note here that although some patients with myxœdema are unable to walk in the dark and cannot hold themselves upright with their feet to-

gether, their gait is quite different from the vague staggerings and violent jerks of advanced locomotor ataxy and from the rhythmical tremors of disseminated sclerosis. In other times, while some cases of myxœdema were probably classified as cases of chronic Bright's disease, others may have been classed as "dropsy." At first sight the flushed face and lividity of the lips might suggest the idea of endocarditis, more especially if there were dyspnœa from the swollen ace-of-spades-like nose, with more or less cyanosis, which has been described as occurring in myxœdema. But it is easily seen that in myxœdema the swelling of the face is greater than it would be in a case of endocarditis; the face is not "puffed," and the watery, bleary eyes and the orthopnœa of endocarditis are absent. The great sensibility to cold, the greater impressibility to its effects, the difficulty in perspiring, and the dislike to any mental effort, which clearly show themselves in myxœdema are not found in cardiac disease. There is no danger of confounding myxœdema with acromegaly, because in myxœdema the increase in the weight of the body is due to a general swelling, the limbs becoming cylindrical, like posts, as it were, while in acromegaly there is an increase in weight through the growth of the bones at the extremities. In myxœdema the hair of the head, of the body, eyebrows, is generally ragged and scanty; in acromegaly, on the contrary, it

grows abundantly. In myxœdema the skin is dry, with an increase of electrical conductibility, in acromegaly there is the opposite; and if warts exist in myxœdema they are flat, whilst in acromegaly they are pedunculated.

For similar reasons myxœdema is recognised as quite distinct from "hypertrophic-osteo-pulmonary-arthropathy," in which the bones are larger and the chest affected.

The general and special symptoms of myxœdema would be sufficient to make a diagnosis between it and the diffused form of scleroderma. With regard to Graves' disease, we need not stay to dwell upon any points of contrast, because the subject, instead of being one for differential diagnosis, exhibits a complete antithesis between the two. We will only note rapidly that Graves' disease—"the goitre of anæmia"—occurs chiefly in excitable girls at an age of full sexual activity. With it there is the "rapid heart," the nervous tremors, the neurotic temperament, the tendency to the exaggeration of perspiration, and of temperature from slight causes, the trophic changes in the skin, and the emotional condition of mind, with an enlarged thyroid gland and protrusion of the eyeballs. Myxœdema occurs chiefly in stolid women at the change of life. With it there is a slow, weak heart, absence of all tremor, want of perspiration, loss of temperature, special structural

changes in the skin, a passive condition of mind, and a diminished thyroid gland.

Mania occurring in Graves's disease generally takes an active character; in myxœdema the tendency is to an opposite one.

It is very remarkable that these two diseases, so opposite in character, may perhaps depend upon different disorganisations of the same gland.

CHAPTER VI

TWO CLINICAL CASES OF MYXŒDEMA

Many clinical cases of this disease have been published, but two simple ones are only here recorded as being typical examples of myxœdema in either sex.

Sophia S—, forty-nine years of age, native of England, was admitted on January 14th, 1887, to St Thomas's Hospital, London, under the care of Dr Ord.

Family history.—The patient, a married woman, has two children, twelve and fourteen years of age respectively. She says, but it is not certain, that one of her sisters died of consumption, otherwise the family history is good. Her father died of gastric fever; there is no evidence of the existence of myxœdema either in direct or collateral lines; her grandfather and grandmother died of old age.

Previous history.—The patient's life had been a quiet and happy one; she had never been ill before with the exception of the ordinary diseases of childhood. She had, however, a bad attack of measles, and is said to have been blind for three days, evidently from phlyctenular ulceration of the cornea.

Menstruation had always been regular; and there had been no miscarriages.

Present illness.—About twelve months ago the patient noticed for the first time that her hands were swollen and that she could not do her household work, sewing, &c., with the same facility as formerly, this being due in part to the want of inclination to do anything. She afterwards observed that her hands and feet were always cold, that her feet and ankles were swollen, and that she could not walk any distance without swaying, falling, and feeling tired.

She has lately complained of pains throughout the body. At times the pain has been severe, especially in the left hand, with a sensation of burning. She has a difficulty in speaking, and cannot swallow well. The sense of smell is good and also that of hearing, but the eyesight is defective, and she complains of a disagreeable taste in the mouth.

State of patient on admission.—She is a well-nourished woman with a swollen face, with the skin like wax, and the lines of the face quite obliterated. The general aspect is anæmic, except for a bright circumscribed blush on each malar bone. The skin does not pit on pressure; it is dry and rough, especially on the face, hands, and dorsum of the feet. The patient says that she rarely sweats except in the summer. The hair is dry and falls out. The teeth

are carious and the gums shrunken. The hands are swollen and deformed and the fingers clubbed.

The left lobe only of the thyroid can be made out, and that with difficulty. There is a good deal of subcutaneous swelling over the clavicles. The speech is slow and hoarse and the voice monotonous. She is not fond of writing, and takes a long time over her letters. She says that she has fits of irritability, and her memory is not so good as it used to be. She does not respond readily to what she is asked, but often hesitates before answering; she has occasional falls because her legs give way. She complains much of the cold; her temperature is subnormal.

The chest is well developed and the heart and lungs are normal. The urine is pale, acid, sp. gr. 1009, without albumen and without increase of indigo; the daily quantity is normal. Bowels regular. The knee-jerks are exaggerated; there is no ankle-clonus. There is some diminution but no loss of sensation. In both cornea there are nebulæ, that in the right eye is the most marked.

Observations.—This case is almost typical of an early stage of myxœdema, and it is during the winter that the patient, as one might expect, asks for treatment. It is remarkable that she is not deaf and there is no inherited predisposition, no catamenial disturbance, no excessive child-bearing or lactation, nor rapidly succeeding pregnancies, and no history of

mental worry nor of any specific or exhausting illnesses.

Her gait is very characteristic; when asked to walk down the ward she will begin to waddle from her bedside in a slow and deliberate manner, proceeding cautiously and leisurely, until a tremor seems to attack her legs, then she reels and almost falls.

There does not seem to be any loss of muscular strength, and she is well nourished and strong. Shortly after admission to the hospital she began to have hallucinations at night, but when she went out these had left her and her sleep was perfectly natural.

During this time she never had albuminuria nor epistaxis. She certainly improved with the treatment which she received in the hospital. She was given the hypophosphite of soda, gr. xv in water, three times a day, and having some appetite, was allowed the full diet. At this time, myxœdema was considered a disease more or less incurable, but in order to alleviate the pains which she suffered from, Dr Ord recommended the continuous galvanic current to be applied daily to the hands. This was done; at first she seemed to derive some benefit from it, but the improvement did not continue.

It is to be regretted that the ultimate history of this patient cannot be followed, and the account of her case may seem to be incomplete, but in order to

avoid repetition it is advisable to shorten it. I have not seen her since her discharge from the hospital in March, 1887.

The second case is extremely interesting for many reasons.

George E—, forty-four years of age, native of England, barber, living in High Street, Uxbridge, during the last few years has been engaged in copying manuscripts, illuminating texts, &c., and came under my observation on April 28th, 1890.

Family history.—There is no case of phthisis in the family as far as is known. The grandfather was "scrofulous." A sister is said to suffer from evident myxœdema. The patient has been married for twenty years, and has one daughter, aged seventeen years, who is at present under treatment for tubercular disease of the hip-joint.

Previous history.—He was never given to alcoholic excesses, has never had syphilis, but had gonorrhœa when a youth. He had lived a sedentary life. About seven or eight years ago he was under the care of Dr Savage on account of religious mania, and remained in Bethlem Royal Hospital for nearly six months, leaving as cured. At the time of his admission to the asylum he was suffering from myxœdema. He said that his attack of insanity began one day at Windsor, with a sudden loss of words, when he was speaking on religious matters. This account was a

delusion, as will afterwards be seen from Dr Savage's remarks.

Present illness.—It seems that dryness of the skin of the hands was the first symptom which he perceived, about six or seven years ago. This was especially noticed by him when he was engaged in his office of barber. He has suffered from deafness in the right ear for about ten years, and in the left ear for about eight years, and has complained from time to time of giddiness. This sensation is now constant, and, to use his own expression, he frequently desires to "lay the head down." Locomotion has gradually become uncertain, and now his gait is frequently very tremulous. His speech has gradually become slow and hoarse and the voice uniform in tone. He is very garrulous, and if allowed to do so, will spend hours talking about his illness. He is intelligent and says "my mind travels faster than my tongue." He says that his memory is excellent, but that he cannot write and draw so well as he used; he can, however, still do both well, but there is evidently some failure of memory. He sleeps much but does not dream. Lately he has had hallucinations, imagining that persons whom he knows appear before him in order to converse with him and prompt him to use bad language. He says that it is when he feels very weak that these hallucinations occur. At times he has fits of irritability. He never

sweats, and complains much of the cold, saying that the winter is much worse for him than the summer. He has suffered for a long time from pains in the occipital region, and from a pain in the head which shoots towards the eyes. He has not complained of pains in the hands or feet. The eyesight is not bad, but he complains of a dimness of vision in the left eye; and with both of them he sometimes sees confusedly, not being always able to judge the distance of objects. He has no colour-blindness.

The sense of smell is generally very keen; but lately he fancies that he has perceived a disagreeable smell, like that from carious teeth. The sense of taste is good, and does not correspond to that of smell. He has never had bleeding from the nose, but has had it from the gums.

The appetite is small, but muscular force has not diminished. Constipation is the rule, and he has suffered from hæmorrhoids for some time.

Physical examination.—The patient is a heavy man and distinctly anæmic. He has a swollen face, with the features coarse, the nostrils tumid and dilated, the lips thick, purple, and everted, contrasting with the pallor and yellowness of the skin. There is no blush on the face. The œdema is especially noteworthy under the lower eyelids. His expression is tranquil, a little sad, although he often smiles. The hair of the head was for a time quite lost, but

now, after the diligent application of a stimulating embrocation, it has reappeared, but is scanty and very dry.

Dryness of the skin is noted on the backs of the hands. The fingers are a little clubbed (doigts Hippocratiques), but the hands are not markedly spade-like. The nails are very dry and bitten close. No trace of a thyroid body can be made out on palpation, nor do there seem to be any supra-clavicular swellings. The temperature is subnormal (97° F.) The urine is pale, acid, sp. gr. 1015, containing phosphates but neither albumen nor sugar. The microscope shows nothing of importance, nor is there any diminution in the amount of urea. The pulse is weak (60). The tongue is coated; it is remarkably thick and swollen; many teeth are loose and carious; the gums are spongy and the breath foul. The knee-jerks are brisk, but there is no ankle-clonus. Loss of cutaneous sensation is not noticeable. The heart, lungs, and liver are in a normal state. The abdominal walls are thick and the pubic hair is scanty.

April 25th.—During an examination of the abdomen the patient had a great nervous tremor (? "nerve-storm") which lasted for three minutes. His teeth chattered, and respiration appeared difficult; his eyes were watery, and his face was drawn up into a curious expression, half painful, half comical, due to the rapid convulsive contractions of the facial

muscles. He moved neither arms nor hands. During the attack the pulse became very weak and the surface of the body very cold, and he complained of pain in the head.

The knee-jerks were very brisk, but there was no ankle-clonus. He says that during the last two months these convulsions have been very frequent, occurring after exposure to cold or even to slight draughts, and also after any prolonged mental effort. During a strong attack he used to take a little cognac and water, and wrap himself up in a blanket until it passed off.

April 26th.—The patient had rather considerable hæmorrhage from the gums. The blood came from the site of a recently extracted tooth; it was stopped with cotton wool and tannic acid, in default of the extracted tooth. He was given 15 grains of hypophosphite of soda in camphor water three times a day.

Observations.—The case is noteworthy, for the patient is a man who has suffered from insanity, and has had frequent occurrence of hallucinations and delusions. It seems unique, and is mentioned by Dr Savage in his book on insanity, page 416. On consulting the work, it is evident that the description which the patient gave me of the commencement of his illness was a delusion. Dr Savage says that the insanity began with the suspicion that a young man wished to assassinate his wife, and that his food was poisoned; he was restless, sleepless, and very de-

pressed. At this time he also had hallucinations of hearing, thinking that bad language appealed to him. Dr Savage sums up the account of this man in these words:—"Slowly but surely he will pass into dementia, and no treatment will be of any use." The facial expression of this patient shows well the relation which exists between dementia and myxœdema, and it is remarkable that he is so intelligent.

In 1890 he was still fit for his work, but his cold, rough hands gave an unpleasant sensation to his customers, and his work was not easy on account of the shivering-fits which used to attack him suddenly from time to time.

Chrétien also quotes the case of a haircutter who often used to let his scissors fall.

His mode of speech was like that of one suffering from tonsillitis, except that he was very fond of talking. A good sign in his case was that he had no albuminuria.

During the last few years his condition has not undergone any alteration, no special treatment being employed. His chief trouble is constipation. Perhaps there is at present a period of interruption in the march of the disease, for it is known that, myxœdema being very chronic, these periods of interruption are wont to occur, although patients who are subject to no special treatment will never completely lose their characteristic facial aspect.

PART II

CHAPTER I

THE ANATOMY OF THE THYROID GLAND

As the names of myxœdema and the thyroid gland are now becoming more than ever inseparable, an account of the anatomy of this gland may be of some service in recalling the attention to the arterial and nervous supply, &c., and thus, perhaps, rendering its physiology clearer.

The thyroid gland is situated in front of the trachea: it consists of two lobes, right and left, which cover and overlap it on the two sides; hence the name *θυρέος*, a shield, the lobes being joined together by a flat transverse band called the "isthmus." The gland has thus four surfaces,—anterior, posterior, and two lateral. The anterior surface is convex, and a little hidden by the muscles sterno-hyoid, sterno-thyroid, and omo-hyoid. The lateral surfaces are also convex, and are in intimate relation with the common carotid artery; the gland therefore is near the internal jugular vein. Seeing that many branches of the vessels which

circulate blood in the gland enter into this great vein, this relation is a very important one, more especially as regards surgical anatomy. The posterior surface is concave, and in health embraces the trachea. Its borders are in relation with the pharynx. Each lobe is more or less conical, about two inches in length and three quarters of an inch in breadth.

The isthmus is sometimes wanting; when it exists it is a narrow transverse band, whose breadth varies from a quarter of an inch to three quarters of an inch, and which covers the second and third rings of the trachea.

There is also a third lobe, which is only met with in some cases, and which has been called the "pyramid." This may have its origin in the left lobe, but is generally a tubular prolongation from the median portion, reaching perhaps as high as the hyoid bone. It may be separate from the gland or divided into two parts. Although in many cases it does not exist in the human being, it is well to bear its occasional presence in mind, because it may serve as an accessory thyroid gland, and may have its importance in the diagnosis of obscure tumours, doubtful cysts, and fistulæ occurring in the neck. It is said that autopsies have demonstrated the presence of this lobe in eight per cent. of the bodies examined. Reliable statistics, however, are wanting on this point, but the post-mortem examinations seem to show that the thyroid gland

participates to a certain degree in the general changes of nutrition which are met with in the other organs.

Besides the "pyramid," other lobes have been described and classified in the following way:—(i) præ-hyoideal, (ii) supra-hyoideal, (iii) epi-hyoideal, and (iv) infra-hyoideal; or, according to Wenzel Grüber, into superior, inferior, and posterior, the first two groups being further subdivided into median and lateral.

The existence of these glands was recognised as early as 1779, by Albert of Halle, and the proportion in which they are found is differently given as 1 to 13 of the total number of cases by Grüber, or as 1 to 6 by Streckeizen.

Reference to the literature of these accessory thyroids may be found in the 'Anatomie menschlicher Embryonen,' iii, p. 101, by His.

Besides these there are little pieces of glandular tissue—glandules—to be met with near, and often adherent to, the hyoid bone, and in other places where their existence would not readily be suspected, which, however, is more constant than might be thought. Nevertheless, probably from this variability in position and small size, these vestiges have not often been met with during the operation of thyroidectomy.

In dogs, accessory thyroid tissue is to be found in the region of the aorta and great vessels. In these

and other animals—for example, in the sheep,—there may be in the thyroid gland itself a difference in weight from 2 to 8 grammes in the different individual animals.

It is said that the gland is heavier, although perhaps smaller, in men than in women; the average weight in men being 18 grammes, and in women 13·50 grammes.

In some persons, during health this gland is not apparent, and it is necessary to palpate the neck with some care in order to appreciate it. In myxœdema, on account of the swelling of the skin, the examination becomes even more difficult.

It is certainly greater, in proportion, in infancy than in old age. The proportion is, in a new-born child, 1 to 240 up to 400; at the end of the third week 1 to 1166; in adults 1 to 1800 up to 1900 (Huschke).

The development of the thyroid gland is important, and its interest centres round a fœtal structure called the ductus thyreoglossus, about which the gland is developed. In the human embryo, a median diverticulum takes place from the anterior wall of the pharynx, opposite to the ventral ends of the second visceral arches. This is the thyreoglossal duct, which, passing downwards, is found as a hollow bifid vesicle (His), each of the branches subsequently coalescing with the embryonic tissue, which forms the

lobes of the thyroid gland, and which is derived by two lateral diverticula from the posterior wall of the fourth visceral cleft. As development goes on the median diverticulum is connected with the upper surface of the tongue by the formation of the foramen cæcum, and, on account of the development of the hyoid bone, the duct becomes divided into two parts, an upper or lingual and a lower or thyroid, although the vesicle may keep its original form for some time.

When development is complete, however, the duct is obliterated and the vesicle becomes solid, forming the isthmus of the thyroid gland; while, with the exception of a small portion near its origin at the base of the tongue (the foramen cæcum of Morgagni) the thyreoglossal duct disappears. In the newly born child, and even in the adult, the lingual part of the duct termed the "ductus lingualis" remains, in some cases, patent, and allows the passage of a bristle downwards and backwards from the foramen cæcum of the tongue as far as the body of the hyoid bone. In other cases it may be well developed and remain as an accessory thyroid gland, projecting into the mouth and forming a tumour of the tongue. In other cases, again, the thyroid part of the duct may be well developed, and so form the pyramid; or it may be recognised as a fibrous cord passing from the hyoid bone over the thyro-hyoid membrane to the thyroid

gland, or, being closed at each end, it may persist and form a dermoid cyst.

The other accessory thyroid lobes are also referable to the thyro-lingual duct.

The vascularity of the thyroid is very perfect, especially as regards the lobes, which contrasts with the poor supply of the isthmus; the vessels come from the superior and inferior thyroid arteries, branches of the external carotid and subclavian. They are very large, and frequently joined by anastomosis. In some cases a special artery, the "thyroidea ima," is met with, derived from the trunk of the innominate or from the aorta. The veins are very numerous; they form themselves into a plexus on the surface of the gland, and from this plexus are derived the superior, middle, and inferior thyroid veins. The lymphatic vessels are also numerous and very large, ending on the right side in the right lymphatic duct, and on the left side in the thoracic duct. This rich supply of vessels, as well as the great development of the gland during intra-uterine life and at infancy, shows how great is the importance which the gland has in the general nutrition of the body. The nerves are derived from the pneumogastric and from the middle and inferior ganglia of the sympathetic. The left recurrent laryngeal nerve is in close relation to the gland, and Hale White has suggested that it is the trophic nerve of the thyroid gland.

With regard to comparative anatomy, Dr Lloyd Andrizen finds that the first evidence of a thyroid organ, obtained by his investigations, is the presence of a hypobronchial organ in the Amphioxus, and a mass of glandular tissue—an endostylar organ—in the Ascidians. In the higher classes, such as the fishes, a lobe, covered by and sinking into the subjacent tissues, is formed at the entrance of the pharynx. Here its functions are those of a secretory organ, and it has a duct which opens into the pharynx and discharges secretion into it, mixing with the current of aërating water, either fresh or salt, which passes over the pharynx and vascular arches of the gills. This lobe seems to be formed in order to secrete a fluid, which is absorbed by the vascular arches together with the current of water, and which consequently operates on the respiratory organs so as to facilitate oxygenation. For these reasons the thyroid gland may be considered as being joined—anatomically with a primitive respiratory system, and physiologically with the changes of gases in respiration.

But, although it is difficult to understand the manner in which the gland, not having an excretory duct, can in the highest class of Vertebrata act in the same way, yet the fundamental action may be the same in all.

CHAPTER II

THE HISTOLOGY OF THE THYROID GLAND

The gland has no excretory duct; its structure consists, like that of other glands, of a capsule and glandular tissue proper, divided into lobes and lobules, united among themselves by a stroma which is derived from the capsule.

This is a sheath of areolar tissue, strong, fibrous, and containing some elastic fibres and many vessels. It sends a stroma of fibres into the gland, forming a kind of network which pervades the gland-tissue proper, the arteries, veins, and lymphatic vessels, running in its trabeculæ. The gland-tissue proper consists of vesicles, little depressions or cul-de-sacs, similar to the secreting glands of the stomach, and having a diameter of 0·004 m. to 0·001 m. They are lined with a hyaline membrane, which supports only one layer of cubical cells, the vesicles containing an alkaline, viscid, transparent fluid.

This secretion is not mucin, for it cannot be represented approximately by the formula $C_{52}H_7N_{12}O_{28}$, and does not yield a flocculent precipitate with alcohol

or acetic acid. It yields neither peptone nor proteose, and is not an alkali-albumin, nor does it contain an appreciable amount of globulin, but the proteid part of the colloid matter is a nucleo-albumin. That the thyroid secretion is largely an albuminous fluid has been demonstrated by Sir A. Cooper, whose notes ('Guy's Hospital Reports,' Series 1, vol. i, 1835) contain a chemical analysis by Babington. Recent investigation by Langendorff confirms this, and Virchow suggests it to be alkali-albumin modified by a large percentage of sodium chloride.

There is also in the thyroid, as in other glands, a certain amount of lymphoid tissue, which seems to exist as irregular nodules scattered about in the fibrous stroma. We may find also, and very often in groups, some glandular spaces as yet undeveloped, indicating that normally there exists, as in other glands, a reserve of secreting tissue, capable of development according to the physiological need, and probably always in use during life. The contents of the lymph spaces are identical with the colloid substance of the follicles. The lymphoid tissue has the same structure as is in the spleen, tonsils, and pituitary body ; but in the thyroid it is very vascular, and consequently, for this reason, very active in its functions. Besides the colloid matter which fills the vesicles or acini of the gland, observers have seen that there are bodies which are very like " blood-

plates." They have been observed by Kohlrausch, Horsley, also by Gibson, who calls them coloured microcytes.

On chemical analysis the thyroid gland is found to consist of albumen with olein, stearin, extractive material in small amount, leucin, and water; there are also salts, both alkaline and earthy, principally the chloride of sodium, the sulphate and phosphate of lime, the phosphate of magnesium, and a trace of the oxide of iron, and also of para- or sarco-lactic acid.

CHAPTER III

THE PHYSIOLOGY OF THE THYROID GLAND

The thyroid is one of the old so-called "blood-glands." Its physiological function, like that of other members of the same group (thymus, supra-renal capsule, &c.), is obscure, although they must all exercise some function of a nature very important to the vital economy. Yet it was once said that it was doubtful whether the gland had any function at all! No further evidence than that which follows, however, is necessary to show that its functional activity is practically essential.

(i) Professor Horsley has shown ('Brit. Med. Journ.,' January 30th, 1892) that the thyroid is so well developed in intra-uterine life, that at the sixth to the eighth month the epithelial cylinders of the gland are secreting.

(ii) The child with congenital absence of the thyroid is in an advanced state of the worst form of cretinism, and this myxœdematous cachexia, which is probably identical with "fœtal rickets," must have developed *in utero*.

(iii) The healthy infant at birth, a time when

metabolism is so active, has the thyroid very well developed and very large in proportion to its age.

(iv) All clinical and pathological observations positively demonstrate that atrophy and the loss of the function of this gland cause the disease known as myxœdema; for—

a. In children with atrophy of the thyroid, statistics show that 75 per cent. are semi-cretins. *β*. In adults the myxœdema of Ord supervenes. *γ*. In persons with goitrous degeneration of the thyroid, there is a degree of myxœdema in proportion to the amount of thyroid tissue absent.

(v) Extirpation of the thyroid, either actual or virtual, alters the health to a considerable degree, and in some animals its total destruction is fatal, and in all of them it causes some hitherto unforeseen alteration—a cachexia strumipriva—which is identical with myxœdema. Dr Occhini even quotes the fact that partial destruction of a goitre by electrolysis has been followed by cachexia strumipriva ('Sobre o Myxedema,' p. 35; 'Thése de Lisboa,' 1890).

(vi) In cases in which complete thyroidectomy has been performed experimentally in animals, hypertrophy of the accessory glands or thyroid tissue has occurred, as shown by Hofmeister; ('Fortschr. der Med.,' 1892, Nos. 3 and 4) and, although not sufficient to fully compensate for the loss of the gland, it is enough to avert a fatal issue.

(vii) A partial excision of the thyroid is followed by an hypertrophy of the remaining portion, and Halsted has even demonstrated, that this hypertrophy is so rapid and complete, that many times the weight of the normal gland can be removed by performing partial thyroidectomies at intervals of several months. From this it may be seen that the thyroid is a structure essentially connected with the metabolism of the blood and tissues; and, as early as 1836, King, in his paper "On the Structure and Adaptations of the Thyroid Gland," showed that the thyroid secreted a peculiar fluid, which found entrance into the general system through the lymphatics. The presence of this secretion was confirmed by Kohlrausch ('Müller's Archiv,' 1853, page 142), and later by Langendorff, Horsley, and others. King supposed that the secretion entered the blood-stream; and that this was brought about by means of gentle and continuous pressure exerted not only by the muscles which invest the gland, but also by the movements of the larynx and by the distension of the œsophagus in the descent of food. It may be that the secretion enters the circulation through the lymphatics in this way, either to directly neutralise certain toxic products in the blood, or to prevent an auto-intoxication by very slowly altering these products into bodies which are more easily eliminated. The process appears analogous to the glycogenic func-

tion of the liver, for there sugar leaves the organ through the blood in the hepatic vein without the aid of any special duct. Putting on one side the fact that the thyroid has no duct, it seems to be similar, more or less, to a secreting gland, and to exercise some form of modified secretion,—that is to say, an "internal secretion." As regards the functions of the thyroid, many other theories have been brought forward, some of which may be recounted as follows:

i. It helps to preserve the contour of the neck.

ii. It acts as a mechanical cushion in order to protect important vessels and nerves from muscular compression.

iii. It acts mechanically in supporting the larynx, and so improves the voice in singing and phonation.

iv. It plays an important part in the production of sleep.

v. It is a kind of reservoir, in which the blood accumulates, to be transmitted to the brain in sufficient quantity at the proper moment.

vi. It is a kind of regulator of the cerebral circulation.

vii. It elaborates some substance especially necessary for the central nervous system.

viii. It communicates to the hæmoglobin the faculty of fixing oxygen.

ix. It is directly a blood-forming organ.

x. It is indirectly a blood-forming organ.

xi. It plays a special part in the metabolism of the sexual organs.

xii. It modifies or destroys substances which, circulating in the blood, are prejudicial to the general economy.

xiii. It secretes some substance useful to the general economy.

The first five of these hypotheses may be passed over with but little comment, because they are advocated without the aid of the true method of inquiry, viz. the experimental.

Formeris, who noticed a diminution in volume in the gland during sleep, thought that it had to do with the production of sleep. The small amount of sleep required by the aged may perhaps be accounted for by the gradual atrophy of the gland as life advances.

Meuli, who ascertained by precise measurements that there is an increase in the volume of the gland when the individual is lying down, considered that it acts mechanically as a kind of reservoir.

Schraeger, arguing from the position of the gland midway between the brain and great vessels, thought that it served as a kind of regulator of the cerebral circulation. This view was also held by Schiff, who endeavoured to prove it by experiments upon animals,

and found that, in his post-mortem examinations, there was, after thyroidectomy, an hypertrophy of the spleen and mesenteric glands as well as anæmia of the brain. But Lannois well remarks, that if the theory were true, after thyroidectomy, congestion and not anæmia of the brain should be met with. The theory that the gland elaborates some substance especially necessary for the central nervous system is worthy of much attention, seeing that the nervous system may suffer so prominently in myxœdema.

Professor Schiff was the first to maintain this view, by noticing how great were the nervous symptoms which followed his extirpation of the thyroid in dogs.

Morbid phenomena, such as the following, occurred either some hours, or within three or four days, after total extirpation of the gland:—Somnolence, apathy, uncertainty in movement, fibrillar contractions in certain groups of muscles, convulsions, clonic and tonic, loss of feeling, and cardiac respiration, *i. e.* a respiratory movement with each beat of the heart. Many theorists, who are always ready to criticise rather than to experiment for themselves, were not wanting, to attack these new views and strange assertions brought forward by Schiff, and the accidents which follow thyroidectomy were successively attributed to reflex action, to lesions of neighbouring tissues during the operation, and to septic infection.

The operations were, however, repeated, and the

results confirmed by a great number of physiologists.

Professor Rogowitsch especially records some extremely interesting experiments made by him upon various animals, cats, dogs, rabbits, &c. Complete extirpation of the gland provoked, in some cases, symptoms of irritation; in others, of depression. In some the convulsions were localised, but in others a general tetanus occurred. The nervous system, examined histologically by him, showed that in the brain, medulla, and about the anterior roots of the spinal nerves there is a subacute inflammation—a parenchymatous encephalo-myelitis (Rogowitch, 'Arch. de Physiologie,' 1888). This author also thinks that the pituitary gland is a complementary organ to the thyroid, because dogs and rabbits which have succumbed to thyroidectomy have shown an exaggerated formation of colloid matter in the pituitary gland. This swelling, after thyroidectomy (? compensatory), has also been observed by Steida, Hofmeister of Halle, and Gley, who have shown that removal of the pituitary body in rabbits produces symptoms similar to those which follow thyroidectomy. Dr Lloyd Andrizen also remarks, that there seems to be a physiological relation between the thyroid and the pituitary gland; and, putting aside the fact that one is related to the respiratory function of the blood-vascular system and the other to the

central nervous system, there are indications of parallelism in their early evolution and functions. Clinically we may note that loss of temperature is common in cases of cerebral tumour of the pituitary gland and in myxœdema; so also is loss of knee-jerk, although this is not constant in myxœdema. That the thyroid gland gives the power of fixing the oxygen to hæmoglobin—the "anoxyhæmic function" of Herzen—was held by Albertoni and Tizzoni, who thought that all the symptoms of the acute cachexia strumipriva in the dog were due to an enormous deficiency of oxygen, the arterial blood of the sick animals containing 50 per cent. less oxygen than the venous blood of healthy animals. They also claimed to have proved, that the deficient oxygenation was not due to mechanical interference with the respiration, because they obtained the same results in dogs in which tracheotomy was performed after thyroidectomy. This theory and the two following, concerning the action of the thyroid in the formation of the blood, are so intimately connected with thyroidectomy in animals, that it may be well to give a short account of the effects of the operation.

The objections to the theory held by Albertoni and Tizzoni are shown in an elaborate article by Herzen in the 'Semaine Méd.,' Sept., 1886.

The effects of total excision of the gland have been bad in every case, varying, however, in intensity

according to the importance of the gland to the particular animal selected. Although the occurrence of idiopathic myxœdema in the lower animals is doubtful, it would seem that the function of the gland is essentially the same in all mammals, in whom alone the lateral and median parts become united into one organ as in man. The cachexia, however, which follows excision is observed less frequently in the rabbit and dog, than in the monkey and man. Rabbits bear the operation well, as do sheep, calves, and horses (all herbivorous), in comparison with dogs, cats, and foxes, which live upon an animal or mixed diet. These seldom survive it; and in young animals, chiefly guinea-pigs, the effects are almost always fatal, although the older ones may only exhibit indolence and incapacity. From this it appears, that the gland exerts its functions in the highest degree, when the metabolism of the tissues exists in the greatest activity; and that it must be particularly related to the general nutrition of the body is shown by the fact, demonstrated by Wagner and others, that hypertrophy of one lobe will follow extirpation of the other.

Now with regard to the supposed blood-forming properties of this gland. Professors Schiff, Credé, Zesas, and others were led at first to think that the thyroid might be supplemental to some other organ, such as the spleen, the thymus, or the supra-renal

capsules, and that it had the power of directly transforming leucocytes into hæmocytes. This, however, has not been proved; for although Credé and Zesas claimed that experimental extirpation of the spleen in animals was followed by hypertrophy of the thyroid there was a diminution in the number of red corpuscles ('Archiv f. klin. Chir.,' vol. xxviii, 1883, pp. 401 and 815).

Gley found that extirpation of the spleen added neither to the rapidity of death nor to the severity of the symptoms. And Albertoni and Tizzoni, after a careful study of the blood of animals after thyroidectomy, concluded that there was no modification in the number or in the structure of its corpuscular elements, and that the gland did not directly contribute to the production of red blood-corpuscles.

Professor Horsley noted clinically, and verified by post-mortem examination, that hypertrophy of the spleen, and also a continued diminution in the red blood-cells, with a temporary increase of leucocytes, followed experimental thyroidectomy. In order to settle this point—the direct hæmatopoietic function of the thyroid—Dr J. L. Gibson, of Brisbane, made experiments on dogs in 1885 and 1886, these animals being chosen because they suffer very acutely from the effects of interference with the thyroid gland. He seems to have been convinced by his experiments, that the thyroid really has no action in the produc-

tion or formation of the red blood-corpuscles. In the case of three dogs, from which he removed the thyroid, he found, after the operation and before death, that there was no reduction in the number of hæmocytes as compared with the number which existed before the operation—a time when one may suppose that the dogs were in good health. This is a matter for surprise, for, as always happens sooner or later after thyroidectomy, the dogs died. Dr Gibson writes :—" It is clear that we cannot attribute blood-forming properties to a gland whose extirpation is not followed by any reduction in the number of red blood-cells, nor any important alteration in the white corpuscles." In recording the effects which followed his experiments of thyroidectomy, he gives the following proof of his statements. In every case, the dog being deprived of its whole thyroid, death occurred, preceded by acute nervous symptoms. In one case only was there a slight reduction in the number of the hæmocytes. This may have been caused by the shock of the operation and aggravated by the voluntary starvation of the animal. In another case the spleen was extirpated with a resulting diminution in the number of the red cells. Afterwards and from the same dog a lobe of the thyroid was excised without causing any bad effects on the animal, or altering in any way the number of the red cells. Later on, the other lobe was excised with such

a slight effect on the hæmocytes that, two days before the death of the dog, their number was equal to that which had been recorded after the excision of the first lobe. And Dr Gibson concludes that, whatever may be the blood-forming action which the thyroid may have in some animals, this ought to be attributed solely to the presence of its follicular lymphoid tissue. He remarks that, there being a general distribution of this tissue in the liver, spleen, glands, &c., it is not permissible for this reason alone to state that the thyroid is a blood-forming organ. The theory of an indirect hæmatopoietic function is based chiefly upon the observations of the condition of the blood following thyroidectomy. Anæmia always occurs when the gland is entirely removed; and Professor Horsley remarks, that if the gland is really hæmatopoietic, then this is easily explained by its removal, but that it may well be that the alteration produced in the metabolism of albumins by the operation reflects injuriously on the corpuscular part of the blood as a tissue.

With regard to experimental observations on animals, the works of Professor Horsley have cast a shining light on the physiology of the thyroid gland, and have powerfully contributed towards explaining the pathology of myxœdema. He used, among other animals, the monkey, and was able, by excising its thyroid, to reduce it to a veritable state

of idiocy or cretinism. According to the animal's age, species, and after-treatment, either acute or chronic experimental myxœdema may be induced, the fatal symptoms in the former following each other rapidly and continuously. Cold greatly influences the mortality, but heat on the contrary delays the onset of myxœdematous symptoms.

In the acute form of experimental myxœdema, Professor Horsley proved that a mucoid degeneration, clearly demonstrable by chemical analysis, and also by the naked eye, was present in the connective tissue of the body, and that in many cases there is a manifest increase of mucus, excreted by various organs, *e. g.* the intestinal canal and bladder, and a remarkable secretion of mucus by the parotid gland. These effects take place after a time, and are better seen in monkeys than in dogs, the latter dying before the changes are developed. In the chronic form of experimental myxœdema, determined by keeping the animals warm after the operation, mucoid degeneration of the tissues is not observed after death, but on the contrary the tissues become fibroid or cirrhotic.

The animals seem to pass through three stages—a neurotic, a myxœdematous, and a marasmic or cretinic one. In the first, or neurotic, the animals have great tremors, and the young ones die. In the second or mucoid stage, mucin is deposited in the tissues and in the blood, this being most marked

in monkeys. In the third, or atrophic, the animals lose their excess of mucin and die of marasmus.

That the thyroid exercises some special action on the sexual organs is an idea which is very old, as was demonstrated by Freund. It is said that the gland increases in size during menstruation, coition, sexual excitement, and pregnancy, and is, like the breast, considered by many a mark of beauty in women. In confirmed myxœdema impregnation seldom occurs, and in men sexual desire is often lost. That the thyroid modifies or destroys substances which, circulating in the blood, are prejudicial to the general economy, is a very important view, for evidence seems to point to the fact, that it may have much more to do with blood-purification than with blood-formation. Horsley concluded from his experiments that the function of the thyroid consists in determining the metamorphosis of the albumins into their final products. After thyroidectomy the albumins do not undergo this transformation, but remain in a mucoid state. In this form the blood cannot sufficiently nourish the brain and other organised tissues, and hence the occurrence of myxœdema. Professor Horsley also says that the thyroid gland seems to consist of two distinct parts, viz. (α) a glandular part which has the function of excreting mucin (?), and (β) a more vascular part composed of lymphoid nodules, which has a hæmatogenic function (?).

The most important of all the views is that it secretes some substance useful, if not necessary, to the general economy. Recent opinion points to the secretion of the thyroid as preventing the development in the blood of some toxic product, which poisons the system if the gland is removed. But what the essential part of this secretion is, whether it is a ferment capable of dissolving mucin and associated with the paralactic acid of the gland, or whether it is a nucleo-albumin peculiarly rich in phosphorus, and how it exactly acts, are points yet to be determined.

Seeing that the extraordinary condition of myxœdema follows, in man, monkey, and dog, on the removal of the gland, an operation which entails an altered chemical composition of the blood, a mucoid condition of the subcutaneous tissues and salivary glands, and a profound effect on the nervous system, then the only possible practical conclusion is that total extirpation of the gland is unjustifiable except in malignant disease of both lobes, in which case the surgeon ought to remember the possibility of there being an accessory thyroid gland, and the physician the chance of supplying the function of the thyroid by means of subsequent treatment.

PART III

CHAPTER I

THE PATHOLOGY OF MYXŒDEMA

The end of modern pathology being the examination of lesions in the normal elements and tissues, it is necessary, for the full understanding of any disease, to follow a course parallel to that taken in the study of health. So, in the case before us, it will be well to note first the most salient differences from normal anatomy as seen in autopsies, then the finer changes which the microscope reveals, and lastly, by study, to find, if possible, the cause of these differences. We have seen, from the more or less constant grouping and sequence of symptoms, that myxœdema is a distinct disease, and consequently it ought to depend on the abnormal condition of one or more organs. There can be no doubt that the thyroid is affected, but it is difficult to say whether this is the sole cause of the disease.

Dr Ord demonstrated that the thyroid gland, in cases of myxœdema, was remarkably small, of a pale

or yellowish instead of the normal dull red colour, firm in consistency and symmetrically atrophied. On microscopical examination it has been shown that at first there is a small cell-infiltration into the walls of the vesicles, with proliferation of their epithelium; next, an atrophy of this epithelium with conversion of the small cell-infiltration into delicate connective tissue, and lastly a contraction of this tissue, so that the gland becomes composed of only fibrous tissue with some remnants of the gland tissue proper, occurring as widely separated islets; or else the gland tissue is completely destroyed. This is a pathological fact of far more importance than the simple alteration in the size of the gland. At the same time Dr Ord demonstrated that all the connective tissue of the body swells, becoming gelatinous and œdematous. His analyses, with those of Dr Cranstoun Charles, revealed the existence of remarkable proportions of mucin in the skin; and by their microscopical examinations it was found that the arteries were obstructed by it, and that the central ganglia of the nervous system, the tongue, palate, and intestines, were full of it. This swelling seemed sufficient to explain all the symptoms, it being alleged that the heart was obstructed by it, and that from this resulted the loss of temperature, the deficient aëration and weak circulation of the blood, as seen by the lividity of the lips, &c., while the constipation was regarded as due

to obstruction, through swelling, at or near the anus. The experiments of Professor Horsley on monkeys, showing also an excess of mucin after thyroidectomy, supported these observations. But it was afterwards observed (Halliburton) that in man such an excess of mucin was not constant in the skin and tissues generally. This, however, may be in part explained by the fact of the experiments having been made on the skin of patients who had not died during the typical period of the swelling.

As in the thyroid gland, so there is also in the skin a development of connective tissue, especially about the sudoriferous and sebaceous glands, the lumen of whose tubes becomes obliterated by the swollen epithelium and the development of a nuclear tissue around them and about the roots of the hair-follicles. The organs of the body, such as the kidney, &c., beyond interstitial changes, show no pathognomonic alteration. And beyond the deposition of fat in the tissues, which is sometimes very great, it may be said that the thyroid gland is the only seat of any constant pathological change.

This may be seen by a perusal of the post-mortem notes of a fatal case of myxœdema under the care of Dr W. M. Ord, written by Dr Sharkey and published in 'St. Thomas's Hospital Reports,' vol. xix. This patient had also suffered from gout, and died of cerebral hæmorrhage.

Notes of the post-mortem examination by Dr Sharkey :—Weights of organs: right lung, 1 lb. $6\frac{3}{4}$ oz.; left lung, 1 lb. $6\frac{3}{4}$ oz.; liver, 3 lbs. $10\frac{1}{2}$ oz.; heart, $15\frac{3}{4}$ oz.; kidneys, $9\frac{1}{2}$ oz.; spleen, $3\frac{3}{4}$ oz. Body of a pale man, with thickish lips and rather puffy face, scarcely noticeable œdema under eyelids. Face suggestive of myxœdema, no œdema of legs or elsewhere. Nothing remarkable about the skin, not particularly dry. Fat throughout the body plentiful, and of healthy, semi-transparent, yellowish colour. Blood abundant and rich in colour.

Hands not characteristic of myxœdema.

The tongue was large but normal; the tonsils small.

The pharynx, soft palate, and uvula were very remarkable in appearance; they were in no way inflamed, but they were swollen, and the swelling looked like œdema, but on incision, fluid did not exude. This kind of solid œdema was most marked in the posterior pillar of the fauces on the right side and on right side of pharynx, but it extended though in less marked degree to the left side. The epiglottis was remarkably large both in length and in breadth; it was healthy, as was the larynx.

The thyroid gland was very small, but not reduced to the insignificant proportions often seen in myxœdema; it was pale in colour and firm on section, and presented none of the appearances of healthy

thyroid; the section was uniformly pale, and was broken up into little islands by fibrous tissue. Heart was large, especially the left ventricle, but both muscle and valves appeared healthy. Lungs somewhat emphysematous, otherwise healthy. Some few adhesions here and there on both sides. Liver healthy. Spleen small but normal. Supra-renals normal, colour deep yellow and opaque. Kidneys did not appear before section to be particularly small, but when cut it was clear that the cortex was pale and greatly reduced in size. The capsule was rather adherent, and left a finely granular surface on removal. Very slight deposit of urates in both great toe-joints. Cervical sympathetic chain seemed to be healthy. Brain.—Dura mater rather thick. Sinuses normal. Both hemispheres of brain covered over large extent, the right more extensively, with a thin layer of blood effused in pia arachnoid. Under surface of brain and whole surface of cerebellum similarly covered. A very large hæmorrhage had occurred between the nucleus caudatus and nucleus lenticularis on left, and ploughed up the centrum ovale and basal ganglia, except the optic thalamus, which it had pushed backwards and towards the ventricles, which were filled with blood. The fourth ventricle also was filled by a clot. The blood had passed down the cord, too, in the pia arachnoid, but only a very thin layer. The vessels at the base were very atheromatous. The

pituitary body presented nothing remarkable. Cord healthy.

In a few cases the pituitary body has been found enlarged. The question then was, how could the mental symptoms be explained? and was the disease central or peripheral? Dr Ord held that the intellectual and the physical torpor originated from the mucoid material invading the connective tissue of the body, because the nerve endings, being involved in mucin, received imperfectly impressions from without, and transmitted them abnormally to the brain. That is to say, mental deterioration can result from the loss of peripheral stimulus. This theory was keenly contested, because nothing proves the chronological subordination of cerebral to cutaneous lesions (Lannois), and diseases such as hysteria and leprosy with cutaneous anæsthesia are not analogous. Goodhart held that the mental symptoms depended upon a mucoid infiltration; and opinion inclined towards considering them as caused not only by a peripheral but also by a central affection—a pathological process in the cerebrum equal to that taking place in the skin.

Morvan, considering the muscular paresis to be a paralysis, thought it extended to the vaso-motor system, and that the origin of the œdema was due to a nerve paralysis; but this did not explain the mucoid nature of the œdema. For many years in England

it was thought that the disease was caused by a morbid condition of the sympathetic system; and Dr Hadden, like Morvan, thought that there was a general spasm of the vessels due to alteration in the sympathetic, and originating in an incomplete nutrition, so that there was an extreme delay in the interstitial changes caused by contraction of the lymphatics which rendered them unable to absorb the interstitial exudation. But it has been proved by a great number of experiments, by Ewald, Führ, Weill, &c., that mechanical stimulation of the glandular branches of the sympathetic produces absolutely no similar result.

According to White, there is a paresis of the sympathetic system which is brought about by the diminution of arterial pulsation, so that, from an extremely slow circulation, a decomposition of the albumins results, with the formation and transudation of mucin.

Fournier thought that myxœdema, like scleroderma, leprosy, and cases of neuro-arthropathy, was due to a trophic neurosis. Later it was again demonstrated (Horsley, Virchow) that near the "acini" of the gland there is an infiltration of cells, which form an organised fibrous tissue, and that there is a proliferation of the cells of the "acini," which also form the same tissue; while the morbid process in the skin was considered as not being passive or

atrophic, but as having an irritative character resembling the inflammatory process ('Berliner klin. Woch.,' Feb. 2, 1887).

Accordingly it appears that there may be, in myxœdema, a rapidly progressive form of the atrophic cirrhosis, which, as age advances, gradually obliterates this gland even in healthy persons. Dr Hughlings Jackson surmises that the cause of this cirrhosis in myxœdema may be due to an abnormal state of the nuclei in the base of the fourth ventricle; and, indeed, persistent changes in the nutrition and structure of these nervous centres might cause a premature increase followed by a cessation of the activity of the gland.

It has been alleged that the reason why some men live to a hale old age, while others, apparently as robust, die younger, is because in the former the thyroid gland continues to exert its functions without undergoing the ordinary atrophy of old age.

Nevertheless, if the case is merely a question of the loss of nutrition, ought not cold, starvation, and overwork to have a great influence in the causation of this disease. As regards myxœdema we can only say that it is common at middle age,—a period, it is true, in which the greatest working activity is reached, and in which the fatigues of life begin to be most felt.

Granting the doctrine held by Liebermeister, that

the loss of thyroid function may, by means of alterations in the blood-circulation, even affect the cerebral functions, it is not too much to affirm that it exerts its influence over the connective tissue of the body, causing a regression to the embryonic state, or that it controls in some way, by means of the blood-circulation, the production of mucoid tissue; causing under these circumstances the formation, in excessive quantities, of a tissue little organised and somewhat similar to the mucoid tissue of the fœtus.

Why, however, should the gland become so gradually changed that its condition becomes little better than a piece of fibroid tissue, when, from its normal structure and the previous existence of colloid matter, we might at first, at least, expect either its hypertrophy in consequence of exaggerated activity, or, perhaps, Graves' disease? for Möbius has recently revived the idea that this is caused by over-secretion on the part of the thyroid itself, due to a morbidly increased activity of the gland. Perhaps, in myxœdema, the mucoid matter may be produced so quickly and absorbed so greedily by the lymphatics that at first it is impossible to keep a store of it in the thyroid vesicles, and later comes the atrophy from over-secretion and loss of reaction.

Professor Kocher adopted the opinion that myxœdema was an anæmia due to deficiency of hæmoglobin, and caused by an insufficient respiratory

process; Baumgärtner espoused a nearly similar opinion, and König of Göttingen was a strenuous defender of this theory. Tracheotomy before and after thyroidectomy has actually been performed in support of it.

Supposing that the secretion of the thyroid, so necessary for the conservation of good health, has the character of a physiological ferment related in some way to the perfect oxygenation of the blood, we may conjecture that the atrophy of the gland, interfering with the exercise of this function, might cause the formation of a pathological ferment to take the place of the physiological one, and to remain in the remnants of the atrophied gland. What then would be the effect of removing this tissue by operation in myxœdema? We know that, in exophthalmic goitre, very pronounced good has followed removal of the thyroid. Lemke even considers exophthalmic goitre to belong to the surgical wards ('Medical Annual,' 1893). Certainly much disappointment attends the treatment of this disease by drugs.

With regard to the supra-clavicular swellings in myxœdema, they are generally considered as pseudo-lipomata; but may they not also be caused by an infiltration of myxœdematous material, either within or near to those lymphatic glands which are in intimate communication with the thyroid, and become for this reason more easily infected than glands in

situations more remote? It is known that the properties of the ferments and albumoses, which distinguish them strongly from the "ptomaines," or alkaloid poisons, are their tendency to remain in the body for a length of time, and their lasting influence over the protoplasm. Hence, perhaps, the necessity of a prolonged treatment in myxœdema is accounted for. The gradual absorption of such a ferment might produce a chronic poisoning, a true intoxication, so to speak, according to Schiff, of the organism which, besides the other ill effects which it causes, attacks the cerebrum and bulbar nuclei. Professor Rogowitsch, in support of this toxic theory, points out the analogy which the post-mortem changes in the nervous system in myxœdema bears to cases of phosphorus poisoning.

The theory of intoxication is undoubtedly a rational one, because by it the mental symptoms can be explained; also because, in myxœdema, there is a loss of temperature which predisposes the patient to succumb to any toxic influence, this predisposition being in part counteracted by the elevation of temperature as the result of treatment. Beyond this, bacteriology does not seem to serve as a help in explaining the nature of the disease. Dr Souza Martins, of Lisbon, has been led, from clinical observation, to conjecture whether myxœdema might not be contagious; yet it must be confessed that the

true pathology of myxœdema is yet to be determined, and the germ of the disease still to be discovered. There are few subjects which offer a more fruitful and worthy field for investigation. It is evident that such investigation should start from the thyroid gland, and probably it will end in it also.

CHAPTER II

THE TREATMENT OF MYXŒDEMA

Until a few years ago the treatment of this disease was unsatisfactory. Indeed, in many cases it had been scarcely palliative; although Sir Andrew Clark claimed to have cured some cases with the employment of iron and arsenic, combined with frictions, a careful diet, and hot baths.

The treatment recommended by Dr Ord always had these three aims before it:—to improve the patient's general health by regular and early hours, to promote the *mens sana in corpore sano* by means of a simple but good diet of easy digestion, and to try to make the patient's life happier by sheltering him from cold. At the same time, in order to increase the power of resistance of the tissues, and to meet the obvious debility, tonics were given, especially strychnine and the hypophosphites. Both movement and speech became more active under this treatment, but the physical appearance in no wise altered.

Iodide of potassium in small doses has been given

as an alterative, and galvanism to the spine with hot electric and Turkish baths has been employed, but with little permanent benefit. The absence of perspiration led to the use of pilocarpine and jaborandi. The latter has been given every four hours in doses of 30 to 60 drops of the tincture (B. P.) or 60 drops of the fluid extract, and the former in $\frac{1}{4}$-grain hypodermic injections. In accordance with the doctrine of Trousseau, "chronic diseases require chronic therapeutics," this treatment was continued for months, and, especially when followed during the summer months, it did much to alleviate the sufferings of the patient. Besides acting on the skin, these remedies stimulated the sympathetic system, and restored in some degree the rapidity of the circulation and respiration. In some cases in which arterial tension was noted the administration of nitro-glycerine seemed to be useful, and the improvement which followed favoured the opinion held by a few, that myxœdema was a form of chronic Bright's disease.

Massage and gymnastics have also been tried, but little if any real permanent benefit accrued, and the effects of a change of climate having been suggested, some patients were sent to the Cape of Good Hope, where they improved slightly,—becoming worse, however, on their return to England.

The therapeutics of myxœdema have been well discussed in a lecture by Charcot, published by Dr

de Ranse ('Gazette médicale,' 1880). In this lecture the late Professor of La Salpêtrière recommended as therapeutical agents a milk diet, sulphur baths, massage, and principally a long stay in a bland climate, such as the climates of the South.

In 1882, Dr Ord remarked that up to that time the march of the disease had not been affected by any remedy, and the treatment was still medical until 1890, when the idea of grafting the thyroid gland was suggested, and the surgical treatment of myxœdema was inaugurated.

In February, 1890, Professor Horsley, basing his arguments on the experiments upon animals by Schiff, Eisselsberg, and himself, proposed the idea of grafting the lobe of a sheep's thyroid or that of an anthropoid ape into myxœdematous patients, in order to supply that which is deficient in them, and so to arrest the progress of the disease.

This had already been done by Drs Bircher and Kocher in Switzerland in cases of cachexia strumipriva. In the adult suffering from myxœdema, the first case so treated was one at the Casa de Saude, Lisbon, by Drs Serrano and Bettencourt Rodrigues in June, 1890, but in a cretinoid idiot of fourteen years, Mons. Lannelongue, of Paris, was the first to carry out the operation in March, 1890. This trial operation by Lannelongue and Legroux—of such high scientific interest—resulted, as Chauveau pro-

phesied, in a complete failure. Two thirds of one lobe of the thyroid body of a sheep were introduced into a little space, previously arranged, in the subcutaneous tissue of the patient below the right nipple. This site was chosen in preference to the neck, on account of the considerable thickness of the tissues in the cervical region. The glandular fragment had been previously deprived of its capsule and slightly stimulated on the surface. The operation was a rigorously antiseptic one, and the wound healed completely by first intention, leaving the graft unaltered in size for eight days after the operation. At a discussion of this case at the Biological Society (séance du 7 Mars, 1890), Chauveau and Dastre, remembering the results of Paul Bert in the transplantation of organs, doubted the successful issue of this operation. Chauveau remarked, "Indeed, I have never made a trial of the transplantation of the thyroid gland of a sheep; but the transplantation of testicles which I have practised has never yielded a satisfactory result. Generally only a superficial grafting results, because sufficient vascular anastomoses are never obtained between the grafted part and the neighbouring parts to be a guarantee for the life of the graft; and the transplanted testicles, although actually embedded, always end by being absorbed." And he concludes in these words: "I believe the same thing will happen to the thyroid gland trans-

planted by Lannelongue under the skin of his patient"—which was what actually happened.

The case by Drs Serrano and Bettencourt Rodrigues was communicated by them at the Congress of Limoges, 1890. The patient was a married woman aged thirty-six, with myxœdema well marked, of eight years' standing, following her last confinement, and aggravated by subsequent fatigue and worry caused by nursing her husband. Menstruation was irregular and occurred before its time. The swelling was so great that she could neither stoop to pick up an object nor sit down on a low chair. Her husband was obliged to turn her in bed.

The thyroid could not be made out. All the circumferential measurements of neck, thorax, abdomen, arms, wrists, hands, thighs, legs, and ankles were much exaggerated on each side. Her body weight was 119·550 k., or over 395 lbs.! The number of the blood-corpuscles taken by the hæmocytometer the evening before the operation was 2,449,000 per c.mm.

The operation was performed on June 29th; an adult sheep furnished the grafts. The left lobe of the sheep's gland was introduced into the left infra-mammary region of the patient, and a third part of the right lobe into the right infra-mammary region. The lobes were neither dissected nor cut in sections, but simply disengaged from their surroundings and

introduced directly. The whole operation was done under perfectly antiseptic conditions. The right lobe was divided into three equal parts by two perpendicular cuts in the long axis of the lobe. This was done in order to compare the subsequent action of the two grafts—the one remaining in direct contact with the tissues of the patient by its fibro-connective tissue, the other in direct contact by its glandular tissue at the two lines of section. The dressings were removed, for the first time, seven days after the operation without a trace of pus being present. As seen from the *résumé* below, which is excellently given by Dr Bettencourt Goulart in his inaugural thesis, "Sobre o Myxedema" ('Escola Med. Cir. de Lisboa,' 5a Série, No. 16, 1891), the primary results were very good, and the patient left the institution on August 1st; but unhappily the effects were only transitory, and soon only a little nodule of cicatrical tissue on the right side remained to mark this brilliant operation. These surgeons, recapitulating all the details, were able to say—

(1) That after the operation the amelioration was manifest by the elevation of the patient's temperature, an elevation of more than a degree (Cent.); also that the increase in temperature could not be due to a febrile reaction after the operation, for the general state of the patient was excellent, there being

neither malaise nor shivering, and above all the rise of temperature was regular.

(2) That the number of red cells rapidly and progressively increased in the space of a month from 2,449,000 to 4,247,000 per c.mm., nearly the normal.

(3) That movements became quicker and easier, and the speech was not so slow nor so thick (*moins pâteuse*).

(4) That the perspiration, which had completely disappeared, was re-established after the operation, and that the sensations of cold, especially in the back, of which she had always complained, had ceased.

(5) That the swelling of the body appeared to be less, inasmuch as the patient could wear clothes and shoes which formerly she had been unable to put on.

(6) That the menstruation, which before the operation never lasted less than fifteen days (sometimes three weeks), after the operation scarcely lasted four days.

(7) That the body weight notably diminished, descending from 119·500 k. (395 lbs.) to 113·800 k. (380 lbs.). With great acumen they conclude that the fact that improvement occurred so soon seemed to indicate that the thyroid tissue was absorbed ('La Semaine médicale,' août, 1890), and that the improvement was caused by the absorption of the thyroid juice; for it was of course impossible that the graft, one, moreover, not even taken from a member of the

same species, should have formed an integral part of the patient's body in the short space of twenty-four hours. The third operation was done by Mons. Walther, in Paris, on a patient of Merklen's, and reported at a session held on November 14th, 1890. Like the preceding case, the improvement at first, especially as regards menorrhagia, was great, but not permanent. During 1890–92 there are, apparently, on record only four other cases in which grafting was done in the adult for the cure of myxœdema. These were in England under the care of Drs Hurry Fenwick, W. J. Collins, Thomas Harris and Wright, and John Macpherson. The results seem to have been disappointing, for a radical cure did not ensue. Although it was evident that a positive cure would result if vascularisation of the gland could be obtained, yet it was doubtful whether this would ever happen with a zooplastic graft. Professor Horsley suggested that, considering the gravity of the disease, and the guarantee afforded by the surgery of to-day, it would not be difficult to meet with individuals ready to allow a small part of their thyroids to be removed for transplantation into the patient. But the difficulty of maintaining rigid asepsis in this method, the possibility of failure of the growth or vitality of the gland in its new surroundings, and the inability of the surgeon to

determine how much gland should be used, did much towards rendering this line of treatment unpopular.

As regards cretinism, or myxœdema in the child, the operation seems to have been more successful, and such an interesting case is reported by Dr Gibson, of Brisbane, in the 'British Medical Journal,' January, 1893, that I give a short *résumé* of it. This patient was scarcely two and a half years of age, and was a sporadic cretin, or, more strictly, a myxœdematous child. The disease had its characteristic signs, and the child would lie quite still, taking no notice of anything or anybody. On July 20th, 1891, the first operation was done; the child and a lamb were anæsthetised in the same room; both the lobes of the lamb's thyroid were rapidly and antiseptically removed, and, after being longitudinally divided, were introduced directly into the sheath of the great pectoral muscle of the boy just below his right nipple. Nine days after the operation the child was lively, looking and laughing at his surroundings. The œdema was less, and both the hands and feet were warm. During the following months he improved rapidly. Subsequently he relapsed somewhat, and in May, 1892, another lamb was anæsthetised; its two lobes were extracted and introduced into the child's abdomen, one being sutured by silk to the anterior abdominal wall, and the other placed free in the abdominal cavity. The wound healed perfectly.

In September he was a well-nourished child with the skin soft and natural; in short, he was cured of his myxœdema, and his cretinism had diminished.

In March of 1892, at St. Thomas's Hospital, London, Mr Clutton and Mr Makins implanted a small piece of fresh human thyroid beneath the left pectoralis muscle of a female cretin aged six and a half years, under the care of Dr W. W. Ord. In this case the piece grafted, formed part of an hypertrophied human thyroid, which was operated upon at the same time by Mr Clutton. The child improved for a time after the operation, but it was found that, after the lapse of eight weeks, the implanted gland had practically disappeared, and the improvement in nutrition ceased. This child was subsequently perfectly cured by means of the method of treatment which is about to be described.

Dr George Murray, at a meeting of the British Medical Association in August, 1892, calling attention to the fact that myxœdema is due to the absence of some substance which is present in the thyroid during health, and concluding that the almost immediate improvement which had followed the operations was due to the absorption of thyroid juice, remarked that an attempt to supply the deficiency, as far as might be possible, by means of subcutaneous injections of an extract of the healthy gland would be only a rational treatment. This had already been

done in animals after thyroidectomy by Vassale and E. Gley by means of intra-venous injections, and had been proposed by Brown-Séquard and D'Arsonval ('Archiv. de Phys. norm. et path.,' 1891), but practically, in the human subject, the first case was that of a woman treated in April, 1891, by Dr Murray. The result was so astonishing that after three months she had lost all the essential features of her malady, and to him belongs the credit of having actually instituted this advance in medical science.

This system of treatment having given such excellent results, it is well to describe it as fully as possible.

Dr Murray employs the following method in the preparation of the extract for hypodermic injection. The lobe of a sheep's thyroid is excised as soon as possible after death, and the fat, as well as the connective tissue which surrounds it, is removed. All the instruments and glass vessels used in the preparation of the extract are either sterilised by heat or are perfectly cleansed with carbolic lotion, 1 in 20. The gland is cut into small pieces on a glass dish, and then placed in a test-tube with one cubic centimetre of a solution of carbolic acid of 0·5 per cent. in strength. The mouth of the test-tube is closed with cotton wool, and the mixture left for twenty-four hours in a cool place. The liquid is afterwards placed in a fine handkerchief, the handkerchief having been

previously placed for a few minutes in boiling water. It is then strongly squeezed in order to express as much of the fluid as is possible. By this means three cubic centimetres of a turbid pink liquid are obtained, ninety drops of which represent a lobe of the thyroid. This preparation, which will keep fresh for about a week, should be kept in a small bottle with a glass stopper and in a cool place. It is best to make the extract fresh each week, in order to avoid even the slightest risk of putrefaction, which gives it a peculiar and most repulsive smell. Glycerine is added with advantage, inasmuch as it is a solvent of the active portion of the gland, and prevents it from undergoing putrefaction. The fluid used for injection must be absolutely sterile; the curative agent contained in it and other preparations is probably contained in the nucleo-albumin of the gland, but the active principle of the gland in a fairly pure condition has not yet been isolated. In the greater part of the experiments the sterilised extract was obtained each week, ready made, from Messrs Brady and Martin, of Newcastle; the adult dose, injected three times a week, was from fifteen to twenty-five drops, according to the effect produced on the patient. The injections were given with an ordinary hypodermic syringe, which was carefully washed before and after use in a solution of carbolic acid.

In his first case Dr Murray gave the comparatively

large dose of two equal injections twice a week, each of 1·5 cubic centemetres, each representing more or less one eighth to half of a sheep's gland, in such a way that, during the first weeks, the patient received the extract of the thyroid lobe of a sheep each week.

After a time it was unnecessary for the injections to be made so frequently or in such large doses; in fact, Dr Murray divided his method of treatment into two stages,—the first in which the larger doses are given,—the second in which the improvement is maintained by means of smaller doses.

As regards dosage, however, in the reported cases there has been no uniformity in application, each observer giving the amount he thought best. The correct dose (*i. e.* the amount of extract capable of producing a curative effect without at the same time giving rise to toxic symptoms) and the frequency of administration have yet to be accurately determined.

A convenient place for subcutaneous injection is the loose skin of the back between the shoulder-blades, which at the time of injection should be carefully washed with carbolic lotion.

The injections ought always to be given slowly, when the patient is lying down in bed, and stopped at once if unforeseen symptoms, such as flushing, &c., should occur. It behoves us also to advise each patient to avoid any tiring work for some hours after each injection.

The thyroid gland of the sheep is used because of all animals it is the one which most resembles man in the duration and character of its symptoms after thyroidectomy, and of all animals it is the least affected by it. Besides that of the sheep, the gland of the lamb, pig, ox, and calf have been employed.

As the size of the gland varies considerably in the different classes of animals, and as therefore the fourth part of the gland of a certain animal may have a weight equal to that of half the gland of another of the same species, it will be very right to have an official table, fixing the strength which the extract should have, and establishing the proportion by weight which should exist between a certain quantity of thyroid and a given quantity of liquid employed in the preparation of the extract. In this way, although it is open to the objection that the glandular tissue from various animals may vary in activity, we should avoid the risk of injecting an excessive dose; hypodermic injections of the juice, obtained from the glands by expression only, are not to be recommended, as they are irritating, and the fluid is liable to decompose. Thyroid injections *per rectum* ought to be avoided, as they are said to be toxic.

No less than forty cases were soon published, in which this treatment had been put into practice, and in the large majority, which included some compli-

cated with insanity, the results were remarkably good. For on looking at the tabluated records by Dr Beadles ('Journal of Mental Science,' October, 1893) and Dr Kinnicutt ('Medical Record,' October, 1893) we see that the result is almost invariably reported as "marked improvement," "practically cured," "highly favorable," &c.; and in Dr Murray's original case, judging from the photographs alone, we can notice that, after seven months' treatment, the patient was transformed from a forlorn, dazed-looking old lady to a bright and intelligent woman.

Four clinical observations, which have now become established facts, are alone sufficient to demonstrate the power of this new remedy, either when given in this way or by a further evolution of the method to be presently described. These are its effects upon the temperature, the skin, the body, the weight, and the urine. As regards the temperature, in Dr Murray's first case, when the temperature had previously varied between 95° and 96°, on the administration of ℥xv of the extract it rose two degrees (F.) within twenty-four hours, and continued to register either 98·4° or 98° subsequently; each fall of temperature to 96° being combated by an injection of ℥xv of the extract. This rise of temperature by means of thyroid treatment is always constant, and it is preceded by an increase in the pulse-rate, which may be taken as a good guide for the administration

of more or less of the extract. The general sensation of warmth and comfort which is developed by this means must be most agreeable to the patient.

As regards the skin, a very remarkable desquamation has followed in almost all cases so treated, and these comprise cases not only of myxœdema, but also of chronic skin disease such as psoriasis, and also syphilis, in which extraordinary effects are claimed to have followed its use.

With regard to body-weight, this is remarkably diminished, so much so that the patient may lose as much as four stone during the first three months. This, however, should be followed by a slight increase in weight, due apparently to the deposition of adipose and other healthy tissue. Advantage of this has been taken in the treatment of some forms of obesity, where, however, its course should of necessity be carefully watched and its true results accurately verified.

As regards the urine, the thyroid extract has a diuretic action. Dr Ord has lately made clinical notes on certain changes observed in it, in myxœdema, after the administration of the thyroid extract in glycerine, and has drawn the following conclusions:

(i) The urine is increased in volume.

(ii) The nitrogen excreted in the urine is largely increased, and exceeds the total quantity of nitrogen taken in the food.

(iii) The increase in the excretion of the nitrogen is principally in the form of urea.

(iv) The elimination of phosphoric acid and chlorine is practically unaffected.

Ill-effects, however, such as local inflammation after injection, aches and pains, &c., and relapses are also recorded, and two patients died suddenly ('Brit. Med. Journ.,' August 27th, p. 450). Both these were old people between sixty and sixty-five, and both had weak hearts, death resulting from syncope, which supervened on exercise to which they had not been accustomed.

Therefore aged people or patients with unsound hearts, or those in whom there is any suspicion of endarteritis or periarteritis, should not be chosen, but if not refused, then the precautions in such cases should be more stringent.

The dose should be much smaller than in the more robust cases, the patient should be confined to bed from the beginning of the treatment, and means should be taken to ensure that the directions as to treatment should entail complete rest in the recumbent position. It would appear that myxœdematous patients are peculiarly sensitive to the action of the secretion, for in them very frequent injections render the pulse very rapid and weak, and the skin humid; they also cause tremor of the hands and muscular wasting, as in Graves' disease. Yet, on the other hand,

patients with Graves's disease have been treated by this method, and no increase of their symptoms has been produced. In such cases, if the disease is due (as some affirm) to a hypersecretion by the thyroid gland, then perhaps the amount of secretion present may be so enormous that a slight extra addition makes no difference.

In myxœdema the disagreeable results which may occur from idiosyncrasy, or from the administration of an excessive dose, are now so well known that the name of "thyroidism" has been given to this group of symptoms. It comprises discomforts, disadvantages, and dangers. The discomforts may be of no great practical importance, consisting of malaise, feelings of tightness and oppression in the chest, itching, burning, and other sensations. For example, a patient of Sir Grainger Stewart's had an impression that she would fall to pieces were it not that she was kept together by her skin.

The disadvantages are of more importance,—flushings, nausea, diarrhœa, headache, aching pains in the back, shoulders, loins, or limbs, pain in the eyeballs, a too rapid rise of temperature, palpitation, and great loss of strength. The dangers are very important, as serious risks may be incurred; they are pyrexia, a tendency to syncope, to attacks of breathlessness, to sudden cardiac failure, accompanied by lividity,

epileptiform convulsions, loss of consciousness, and even death.

These dangers, resulting from an over-stimulation of the circulation by means of the thyroid employed, follow in consequence of a temporary failure of the heart's action with increase of backward pressure in the pulmonary circulation. They are most likely to occur in cases with heart disease, after over-excitement or undue emotion, or the too vigorous administration of the gland, and to be aggravated if the thyroid treatment is combined with the use of pilocarpine, a remedy which tends to produce excessive bronchial secretion and pulmonary œdema.

In other cases these results may be caused by the accidental wounding of a vein, and the entrance of the injection into the blood-stream.

Besides the recommendations referred to above for treatment in the serious emergency of cardiac failure, the indications are similar to those for like cases, *e. g.* the use of cardiac stimulants, viz. alcohol, ammonia, ether, strophanthus, digitalis, and caffeine; of counter-irritants and derivatives; the application of mustard and dry cupping, and, in cases with unconsciousness and well-defined cyanosis, it behoves us to remember the mechanical relief which may result from bloodletting. As regards the inconveniences, headache and flushing may be promptly relieved by means of nitro-glycerine, and the aching

pains which may prevent sleep have been much relieved by means of bromidia.

Rigorous antiseptic precautions ought to prevent the occurrence of abscesses and induration at the site of injection.

It was thought at the beginning that the early stages of myxœdema ought to be chosen for this form of treatment, but experience has shown that advanced cases are equally benefited by it.

In children treated by this method, the doses being equal in proportion to those given to adults, there seems to be an absence of the symptoms of discomfort which usually follow in the adult. In children improvement does not develop so rapidly, but the results are equally as good. In all cases there is always a tendency to relapse, but after they have once been practically cured, perhaps an injection every three months will suffice to prevent it.

Although the advantages of the hypodermic method may be many, viz.—

The readiness of absorption;

The sure and more intense effect of the remedy employed, seeing that it does not undergo any alteration, as might happen in the digestive system;

The easy and precise regulation of the dose;

The extent of surface for application;

The fact that the method is always applicable, whatever may be the patient's condition;

—nevertheless the practical inconveniences attending the preparation and adminstration of a series of hypodermic injections, and the occurrence, although rare, of dangerous thyroidism, soon led to the ingestion of the thyroid extract by the mouth (Fox and Benson). An extract in glycerine, which will keep fresh for some time, may be easily prepared; but it is well to bear in mind the importance of having a uniform standard for the preparation, *e. g.* one drachm of the glycerine extract to represent twenty-four grains of the gland.

The menstruum usually employed is one composed of equal parts of glycerine and chloroform water, and ɱxx—the daily dose exhibited—corresponds to one sixth of a gland. In adjusting the dosage some fractional part of a gland may be taken as a standard, and the method is to be commended for its simplicity; and although it is open to the objection, as Mr White points out ('Clinical Society's Transactions,' vol. xxvii), that the weight of individual glands is liable to considerable variation, yet by preparing the extract from a number of glands at one time this objection is removed.

The undiluted glycerine extract is a patent remedy, but an elegant preparation for administration in "mixture" may be made in the following way. The lobes of healthy thyroid glands are taken from sheep, and are triturated with a small quantity of sterilised

sand in a mortar; and the mass is afterwards mixed with glycerine, distilled water, and boracic acid, in the proportion of ʒss of glycerine, ʒss of distilled water and four grains of boracic acid to each lobe. The extract is filtered under a pressure of 400 mm. of mercury, and a sufficiency of chloroform water (B. P.) is added to make a fluid ounce of the liquid. The usual dose is a table-spoonful twice a week taken with two tea-spoonfuls of brandy. All the vessels and utensils must be washed with boracic lotion. The employment of chloroform water effectually covers the flavour and odour of the raw meat.

The thyroid extract may be prepared with glycerine and phosphoric acid, and given in the form of a pill.

Mr Edmund White has obtained a powdered extract, for administration by the mouth, by extracting the active principle with glycerine. Details of the process of manufacture of this will be found in the 'Pharmaceutical Journal,' Sept. 2, 1893, p. 194. It is done by salting out the proteids from a thyroid liquid, known to possess the desired activity, by means of a precipitate of calcium phosphate in the following way:—the glands are first exhausted with a mixture of equal parts of glycerine and water, next acidulated with phosphoric acid after filtering, and then calcium hydrate is added until an alkaline reaction is obtained: the precipitate is finally filtered

out as rapidly as possible, washed, and dried, without heat, over sulphuric acid. These powders are given by the mouth in two- to five-grain doses, each powder of three grains corresponding to one sixth of a gland. Vermehren also, by precipitation with alcohol, has prepared a grey powder from the thyroid extract in glycerine. This is called "thyroidin," and is given in doses of two to five grains. Compressed tabloids have been made from chosen glands which are dried under a low temperature (97° F.), and then pulverised and lightly compressed into discs. These, which contain five grains of the gland in each, may be given to adults in doses of one half to three or four tabloids every day, and, as they do not alter as regards smell or strength, are of very great service,—preferably, perhaps, in private practice, and in cases in which there seems to be a tendency to relapse, or when it may seem advisable to change the form of thyroid treatment. Satisfactory results have been obtained by beginning with small doses and gradually increasing them; for example, two during the first week, three in each following week for three weeks, four during the next fortnight, and so on. One or two doses of White's three-grain powders have been found sufficient to maintain the patient in health.

The enormous value of the thyroid treatment began to be generally recognised when, in October, 1893,

Drs Hector Mackenzie and Fox simultaneously suggested the simple experiment of giving the gland alone by the mouth. Notwithstanding the scepticism, which must have been felt at first, as to whether a gland secretion would be remedial after its exposure to the action of the gastric juice, the extraordinary improvement which followed this method began to command the attention of the whole profession. As a dose, the half, more or less according to its effects, of the raw gland of the sheep was given during the winter; but now a smaller dose, a quarter of a lobe each day, is generally administered. By this means marked success in England, the United States, France, Denmark, &c., has already been obtained, patients of long standing becoming, as it were, new creatures under its use.

Of the many excellent clinical reports illustrating this, few are more striking than one written by Dr Kinnicutt of New York, and published in the 'Medical Record,' October 7th, 1893. In his paper, which is certainly the most complete summary on this subject, he gives the clinical history of a typical case of myxœdema, part of which, relating to the treatment, I am tempted to reproduce at length. After her admission to St. Luke's Hospital, this patient, forty-nine years of age, who had practically been bedridden for a year, left it an active woman.

"On December 10th half a drachm of the minced

raw thyroid gland of a sheep in an equal amount of glycerine was given by the mouth. The temperature, pulse, and urea excretion were alike unaffected by its administration. A like amount was given on the four succeeding days, with similar results. The only subjective sensation complained of by the patient during this period was a slight feeling of dizziness.

"On December 15th one drachm of the raw minced gland was administered in a similar amount of glycerine. The pulse, respirations, and temperature immediately previous were 72, 16, and 97° F. respectively. Five hours later the pulse and temperature were 76 and 98·5° F., the respirations remaining unaffected. The patient expressed herself as feeling no discomfort of any kind. A similar amount of the gland, equivalent to one lobe, was given daily, with a single omission, until January 7th—twenty-three days. The temperature range during this period was between 98° and 100·2° F., the higher point being reached in the afternoon; the pulse rose to 96 on the second day, and constantly ranged from this date between 90 and 106. It is seen that with the administration of the increased dose, the pulse and temperature were immediately affected. The urea excretion also rose directly from 3½ grains to the ounce to 8 grains.

"On December 29th, nineteen days after the first dose of the gland had been given, and two weeks after its use in larger amounts, the improvement in

the patient's condition was very striking. The expression of the face had changed very remarkably; the swelling of the tissues had greatly diminished, the bagginess of the lower eyelids had disappeared, the lower lip was no longer everted and swollen, the saliva had ceased to dribble, the speech had markedly improved, and the thickness of the hands and feet had begun to diminish, the tumefactions above the ear and in the supra-clavicular regions were not palpable, the skin of the palms of the hands and of the feet was distinctly less dry; the scanty hair on the scalp, however, had become still scantier, the reaction of the urine was still alkaline, of rather low specific gravity, and contained rather a large amount of phosphates. The patient expressed a feeling of great comfort, and, moreover, a sensation of warmth which she had not felt for years, and which had developed at the very beginning of treatment. The raw gland had, however, become very distasteful, and she could be persuaded only with difficulty to take it.

"On January 7th, after twenty-three days of its use, its ingestion was followed by vomiting and a rather acute disturbance of digestion, and the treatment was discontinued for ten days. The improvement in the patient's condition was, however, uninterrupted during this period. It was noted that the temperature curve rapidly lost its irregularity and became normal, and the pulse gradually fell to 76—80."

On January 16th, five weeks after the first ingestion of the raw gland, the following note was made :

"The patient is hardly recognisable as the one of a month ago. The myxœdematous signs, as far as the face is concerned, have entirely disappeared. The expression is natural, there is no longer any appreciable swelling or increased thickness of the face, neck, or trunk, of the lips or tongue. The speech has lost its peculiar characteristics.

"The hearing has so much improved that the patient now hears the ordinary conversational voice across the ward, and also the singing in the chapel of the hospital, 150 feet distant. The dryness of the skin has markedly diminished, and beginning desquamation on the hands, feet, and scalp is noticeable. The hands have recovered their normal size, and the feet are markedly thinner. An abundant new growth of fine hair on the scalp and eyebrows is appreciable. With the disappearance of the fulness of the neck a satisfactory examination is possible. The thyroid gland is not appreciable.

"On January 19th the treatment was again initiated, the improvement being continuous, and during the first week in February desquamation of the skin of the entire body occurred ; very large strips, several inches in length and breadth, could be easily removed from the different areas. The process was very rapidly completed, leaving a delicate, elastic, normally moist

skin, and of a natural colour. The entire scalp became thickly covered with a new growth of hair, and the same was true of the eyebrows. A new growth about the pubes was also noticeable. During the early period of the treatment the hair of the scalp which still remained rapidly fell out.

"The patient became cheerful, bright, and the improvement in the mental processes was very marked. Gradually the patient became able to sit up without support, and then to stand, and finally to walk."

The advantages of the thyroid diet over the somewhat risky hypodermic method are many; it is cheaper, of very easy application, it does not require antiseptic precautions, the risk and the dangers which may attend the injections are less, and it determines exactly the same, if not better, results. The voice, and the condition of the blood as regards the red cells and hæmoglobin, improve greatly with use.

The gland should be quite fresh in every case, and as it is said that not more than half the glands derived from sheep, calves, and swine are free from abnormal changes, the necessity of selecting healthy glands is very great. All cattle having the appearance of being overworked should be avoided. Thyroids which are dry, hard, or show any, even if it be the slightest, appearance of suppuration, cystic degeneration, &c., ought to be rejected.

The raw gland is very nauseous, but many ingenious

ways of making this form of diet agreeable have been suggested. The gland can be minced, and afterwards taken either in the form of a sandwich or in wafer-paper, or tempered with salt, pepper, vinegar, or anchovy paste. It can be cut up finely with sharp scissors, and taken at a draught with a glass of brandy and water. It can be fried or eaten underdone with the ordinary food. If an overdose be taken, or if the raw gland does not agree with the patient, there will be symptoms of dyspepsia, viz. nausea, eructations, giddiness, insomnia, and diarrhœa; or there may be excruciating pains in the limbs and pyrexia.

Instead of the raw substance, the expressed juice of the gland, which is tasteless, may be given in milk or water. Fifteen minims of the juice, representing one quarter of the average amount obtainable from one lobe of a sheep's gland, has been given once a week with great results ('Medical Record,' October 7th, 1893).

It has been also suggested to use the thyroid extract as an inunction (Blake, 'Myxœdema, Cretinism, and the Goitres,' p. 25).

For the good regulation of the treatment it is well to make a weekly table whereon the loss of the weight of the patient may be registered. In cases which are relapsing there will be not only an increase in weight, but also in bulk.

The urine ought to be carefully examined in order

to establish a comparison between the amount of mucin excreted daily during treatment, and the amount excreted normally by a healthy person and by a patient with myxœdema who has not yet been subjected to treatment.

Plaster-of-Paris casts taken of the hands before and after treatment, as well as phonographic records, will serve as lasting mementos of the results achieved. It will be necessary to continue this treatment for some time, probably until the end of life; for, although the immediate improvement is very great, there is always a tendency to relapse; perhaps a dose every three months will suffice.

After prolonged treatment in this way it remains to be proved whether or not the remnants of thyroid tissue will be stimulated into activity, whether accessory glands will develop, or whether, as regards a permanent cure, the grafting of the gland will be entirely successful after having been supplemented by injections or feeding.

The question of prognosis is now not what it was, seeing that it can no longer be said that there is no remedy which can influence the progress of myxœdema. The conclusion is that both it and sporadic cretinism are due to the loss of function of the thyroid gland, and this lost function can be restored or even established in cases in which it had never before existed.

In conclusion, the various methods for the modern treatment of myxœdema and cretinism may be recapitulated in the following list:

(i) Thyroid grafting.

(ii) Subcutaneous injection of an extract of the thyroid gland.

(iii) Ingestion of an extract (aqueous or glycerine) of the thyroid gland.

(iv) Ingestion of a dry extract obtained from the thyroid gland in the form of powder, pill, tabloid, or capsule.

(v) Ingestion of the thyroid gland, raw or slightly cooked.

(vi) Ingestion of thyroidin.

(vii) Inunction of thyroidin.

The results in myxœdema, obtained by any of these methods, may well stimulate the efforts to relieve some forms of diabetes, of Addison's disease, and acromegaly by employing, either for grafting or "dieting," portions of the pancreas, supra-renal capsules, and pituitary body respectively. We have already seen how the injection of testicular fluid, of brain, kidney, spleen, muscular and glandular fluids, has been used by Brown-Séquard, Constantine Paul, and others.

These discoveries of science are largely due to experiment upon lower animals; indeed, their good effects would have been impossible except as the

result of such experiments. Thus, had not the value of grafting been proved by such methods upon animals, the operation would certainly never have been attempted on man, and the fund of knowledge acquired by theory would have fallen short of its aim.

Such methods, when carried out with due regard to the dictates of humanity, and with an evenly balanced mind, will be found invaluable to the student of medicine who desires to become a "right loyal and true physician, knowing in his art, well approved in it, and skilled in the cases which may occur; these being the four qualifications of one of the laws of Alphonso the Wise, stated by Aristotle as essential to medical ethics,—"Quáles deben ser los Fisicos del Rey, et qué es lo que deben facer."

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