CASES OF MYXODEMA AND ACROMEGALIA TREATED WITH SHEEP'S THYROIDS; RECENT OBSERVATIONS RESPECTING THE PATHOLOGY OF THE CACHEXIAS FOLLOWING DISEASE OF THE THYROID; CLINICAL RELATIONSHIPS OF GRAVES'S DISEASE AND ACROMEGALIA.

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CASES OF MYXŒDEMA AND ACROMEGALIA TREATED WITH BENEFIT BY SHEEP'S THYROIDS.

Recent Observations Respecting the Pathology of the Cachexias following Disease of the Thyroid; Relationship of Myxœdema, Graves's Disease and Acromegalia.

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Case I. is that of an unmarried lady, now forty-eight years old, and always of delicate health.

I was first called to see her in December, 1885, and at the time of my visit the diagnosis was beyond question, even from her appearance alone.

She had taken cold while menstruating during a visit to the Philadelphia Exhibition of 1876, and it is probable that the myxœdematous symptoms began at about this time; some of them, perhaps, even earlier. She had always been pale, and slow in movement. The family history on the mother's side was markedly neurotic.

The face was clayey-gray, with a yellowish tint, the skin thick, stiff, dry, and coarse. The lips were protuberant and thick, and moved each in one piece, as it were, as she talked. The eyelids were swelled and alabaster-like in appearance, especially the upper, which overhung the eyes so that at times she had to throw the head back a little in order to see. The neck was thick, the hands were large, scaly, and dry, and a similar dry and coarse condition of the skin was everywhere present.

The nutrition of the teeth and nails was defective, and the hair had fallen out except for a few bunches here and there.

Formerly slender and with delicate coloring, she now looked overgrown and old. The limbs were large but not strong, and the skin was so inelastic and so tightly stretched over the legs below the knee, that the masseuse found it impossible to use the ordinary methods of manipulation. No true œdema was noted at this time, but at a later period the ankles pitted deeply on pressure. The swelling of the eyelids was partly watery, and increased during the night toward the side on which she lay.

The pulse was but 60; the heart-sounds free from murmur, but exceedingly feeble. There was a tendency of the head to droop forward, so that it was with an effort that she held it erect. The voice was husky and the tongue thick. The gait was slow and insecure, so that she often stumbled and sometimes fell. She felt weak, and became breathless on slight exertion.

The mental condition was no less striking than the physical. An inconquerable inertia and apathy imprisoned her thought, feeling, and action, so that she could neither plan nor execute effectively, and every trifling duty seemed a mountain to climb; and yet her ineffectiveness did not fill her with real despondency.

Her friends would leave her with one boot on and the other in her hand, and return an hour later to find her in the same condition and attitude. Or what she held would slip from her grasp and she would not stoop to pick it up. Or, at times, she would lean in a stupor against the mantel-shelf, and remain motionless for one or two hours. The nearest duties often passed unfulfilled, and the thought of them failed to rouse her. Yet in spite of her slowness, and lethargy, and lack of initiative, she was neither melancholic nor demented, and would converse intelligently and pleasantly, though without animation, on many subjects. It is interesting to note (see below) that a certain degree of this apathy and slowness was characterstic of her temperament even many years before her illness began.

She slept all night, though often troubled with distressing dreams, but was constantly drowsy in the day. She suffered much from constipation, and later from hemorrhoids, and had an offensive expectoration, which no doubt contributed to give the breath the cadaveric odor which then characterized it.

The menstruation was at that time regular, but profuse; later it became very irregular, and was absent for months together, and her periods would leave her much weakened.

The urine was habitually very pale, and of low sp. gr,, free from albumin and sugar. All the solid constituents were diminished, the amount of urea being 11.78 grm. to the litre (Prof. E. S. Wood).

The thyroid could not be felt. The skin was cool to the touch; and the temperature usually ranged around 95° F. Several times it almost touched 94°; and 97° was rarely, if ever, passed, even in slight sickness.

Blood-counts made during March and April, 1886, showed 3,120,000; 3,200,000; 3,234,000; 4,240,000. The proportion of whites was normal.

The next four years brought little change, except that in winter she would be worse, in summer better.

In the summer of 1891, however, a new symptom showed itself, namely, a synovitis with great external swelling, first of one knee, then of the other, brought on by a trifling shock or wrench, due to stepping heavily, the first time out of a carriage, the next time out of a horse-car. In one of the cases reported very early by Dr. Ord, the rupture of both patella tendons occurred in a similar manner, and the excessive swelling has been several times ob-

served. The synovitis ran a very indolent course, and the appearance of the knee, with its thickened tissues, was so peculiar as to suggest the presence of some other process than simple effusion.

Up to the 1st of June, 1892, no treatment had brought material benefit, though persistent massage had given the patient much comfort. In June, 1892, I began a series of tri-weekly injections of a glycerin and carbolic extract of the sheep's thyroid, prepared as recommended by Dr. Murray.

Slight signs of improvement began to show themselves by the end of one or two weeks. In the course of six weeks the improvement in color, strength, and manner attracted the attention of everyone who knew her, even the children of her neighborhood, and was further confirmed by the appearance of a growth of fine hair all over the head, and a marked rise in pulse and temperature.

The temperature varied, but by the end of August, perhaps earlier, it ranged pretty constantly between 96° and 97° F. Menstruation, which had been absent so long, recurred in July, August, and September, but such recurrences had occasionally happened, and it was still profuse and painful.

The swelling of the eyelids varied in amount, but during August it was almost absent, and that of the ankles had greatly lessened.

With the advent of the colder weather of September and October, I saw with regret that her improvement, hitherto steady, seemed to have suffered a check. She began to look pale and to feel languid, the swelling of the eyelids reappeared, and she complained of pain in the chest on slight exertion. Attributing this in part to an interruption of the treatment during the first ten days of October, I tried giving the injections more frequently than ever, part of the time almost daily, though at first without marked effect.

In November she began the treatment by the mouth, as recommended by Mackenzie and by Howitz, of Copenhagen, and took five or six sheep's thyroids a week (or more strictly, five or six lobes, as the sheep's thyroid consists of two separate lobes).

During the next month, and even after the final stage of improvement had been fairly entered upon, she complained much of a sense of thumping in her head, and while her mental condition was becoming steadily more natural, her appetite and strength seemed for a time rather to fail.

Ever since the outset of the treatment, she had noticed at times a sense of flushing and dizziness after the injections, such as has been noted in the reports of some of the English cases, but neither this effect nor the increased secretion of urine which others have noted was at all striking.

On December 9th, an estimation of the hæmoglobin by Fleischl's apparatus gave 55 per cent. Toward the end of December there was another period of depression in which she complained of increased thumping in the head and ears, and of nausea and languor, especially in the morning. These symptoms seemed at least partially attributable to an excess of thyroids, of which she had taken four glands a week, though these periods of depression did not invariably attend the use of the larger amounts.

This sense of illness was, however, attended by a rise of pulse and temperature rather than a fall, the pulse reaching 78 on December 18th, and the temperature 98°. And furthermore, it was plain that the whole character of her nutrition was becoming more normal, though it was not in all respects satisfactory. On December 21st, when I had not seen her for nearly three weeks, it was evident at the first glance that the condition of myxœdema was giving place to one of simple anæmia. She complained a great deal at this time of itching, which others have noticed likewise, perhaps from the action of the thyroids, but more probably from the changes taking place in the skin.

It was difficult to say whether she had actually grown paler or less pale, so unlike was her present complexion to that of the clay-like mask that she had worn so long. Unfortunately, she could not easily be weighed, but it was clear that she was rapidly growing thinner and slenderer, while her hands were becoming softer and more shapely. The clothes that she had worn were now hanging in folds, and in fact she became at this time really too thin, and with still further improvement she has gained flesh somewhat.

The opening of the new year was marked by her discarding her wig in favor of her new growth of dense and soft hair (now about four inches long) and by her beginning to take the thyroids in the form of powder, skilfully prepared by Parke, Davis, & Co., at my suggestion.

I had been in correspondence with them for this purpose for a number of weeks, and did not learn until later that similar methods were being adopted in Sweden and England. Fifteen grains of this powder represents one lobe of a sheep's thyroid. The taste is found nauseous by some patients, and does not disappear for many hours. These objections are mainly obviated by the use of capsules, or "enteric" pills, which do not dissolve in the stomach.

Not only had her face and figure by this time changed so that acquaintances occasionally failed to recognize her, but her voice had grown markedly firmer and clearer, and her manner alert and responsive.

An accurate examination of the blood made by Dr. J. J. Thomas gave the following result:

Reds . .	5,700,000	Polynuclear whites	66.4 per cent.
Whites . .	7,000	Mononuclear " .	21.6 "
Hæmoglobin	61 per cent.	Lymphocytes . .	10.04 "
Proportion of whites	1 : 800	Eosinophiles . .	2.0 "

No increase in size of reds. A few myelocytes.

The menstruation recurred normally and almost painlessly in January, February, March and April, appearing exactly at the expected date. For two weeks in February and March she took no thyroids, and toward the close of that time there were signs of a recurrence of symptoms, a firm non-œdematous swelling appearing in the legs above the ankles. The mental condition remained good, and on resumption of the thyroid powders the slight swelling soon disappeared.

Since the treatment was begun, the neck, waist, and arms have diminished about three inches in girth, and the old shoes and gloves have, so to speak, discarded themselves. She is still an anæmic and delicate person, as she always was, but as regards any distinct myxœdema she is practically well.[1]

The temperature is usually normal, but is occasionally half a degree too low.

CASE II. is that of a lady fifty-five years old, and is particularly interesting, both because the improvement was very rapid, and from the fact that previous to the onset of the myxœdematous symptoms the thyroid was much enlarged, and that moderate but constant tachycardia was present. The patient has been under the care of another physician, and I have seen her only incidentally, except during the first period of the disease, when I tried for some time to reduce the size of the goitre by electrolysis. The case is also of interest from the fact that the patient's cousin and aunt had myxœdema in a pronounced form, and eventually died with it, the latter as an elderly person, the former in middle life. The aunt had been for many years crippled with rheumatoid arthritis. Though the patient had led an active life, she had been anæmic and had suffered much from palpitations in childhood and adolescence.

The case seems to be one of those where an exciting cause of the disease may well have been anxiety and emotion, acting on an intense and sensitive temperament. The thyroid first began to enlarge about ten years ago. The tumor was unusually hard, much harder than the normal gland, and there were no vascular murmurs such as are often seen in Graves's disease. There was no exophthalmus,[2] but the pulse was always moderately rapid—from ninety to one hundred and twenty. In view of the important question as to the possible relationship between Graves's disease and myxœdema, it is interesting to bear in mind that we have here a case where, in the presence of a manifestly hereditary tendency to myxœdema, the first actual change was this thyroid disease, with at least one of the Graves's disease symptoms. (Perhaps, however, the tachycardia was purely reflex. See below.)

It is also a noteworthy fact that the patient's health failed considerably during the first period, and that besides dyspnœa, which may have been due to pressure, she suffered much from anæmia and debility. As her health had previously been fairly good[3] it is reasonable to suspect the thyroid disease as having

[1] An examination of the blood made since this paper was written has shown that the anæmia has not improved of late, but rather grown more severe, though in other respects the patient is doing well.

[At the present time, which is about six weeks since this foot-note was written, the patient reports herself as doing well in all respects. An interesting point has shown itself with relation to the question of dose. The patient, namely, had been taking a capsule containing two and a half grains of thyroid powder every day. Although in most respects she did pretty well with this, it was evidently not quite enough, because a slight but well-marked œdema of the eyelids gradually made its appearance.]

[2] This is doubtful. One of her physicians thought it was present.

[3] As a young girl she had been delicate and had suffered much from palpitation, but later her health had been much better.

been responsible for the falling off at this period, the more so that with the recent thyroid treatment not only the myxœdema but also the anæmia has for the most part disappeared. The myxœdematous changes first showed themselves two years ago, at the time of the menopause, and have been unmistakably characteristic; the presence of the alabaster-like swelling and pallor of the eyelids, lips, and face, the dryness of the skin, the increased size of the hands, the gross enlargement of the body, slightly subnormal temperature, thickness of the tongue, and slow speech leaving no doubt as to the diagnosis. The urine contained a trace of albumin, and occasionally a few casts. Mental changes have not been present.

The treatment with the thyroid powder was begun about February 15th, since which time the patient has taken one powder of fifteen grains, which is the equivalent of one lobe of a sheep's thyroid, every second day.

The improvement was more rapid than in the first case, perhaps because the disease was less advanced and because the patient's previous health had been better. There is still some swelling of the legs, with ordinary œdema, but the patient's face has regained its delicacy and size and color of fifteen or twenty years ago. The thyroid is still large, though not so large as before. It will be very interesting to follow the condition of the urine in order to see whether the renal changes disappear. At present casts are still to be found, though they were absent in the three or four examinations made during the year previous to the beginning of the treatment.[1]

I have also notes of three other patients who are taking the thyroids with benefit. One of them has acromegalia of rapid onset and typical form. No enlargement of the jaw is present, but the big hands and feet, rapid pulse, with tendency to palpitation and moderate muscular atrophy, place the diagnosis beyond question.

She came first to the out-patient department of the Massachusetts General Hospital, and was seen by Dr. G. M. Garland, who kindly gave me the opportunity of examining her. Later, she entered the

[1] The course of this patient since the original report was written presents some interesting features. After she had been doing well for some months, the thyroids were omitted in order to test the result. For the first month after this there was little change in her condition; then the myxœdematous condition began to return, and by the end of a second month, when she presented herself for re-examination the first time, the change in the face was almost as great as ever. The œdema of the limbs, however, had not returned, and this is noteworthy, because an examination of the urine showed an entire absence of the albumin and casts that had been found previously at each analysis. Not only this, but the thyroid gland had enlarged very much in size, and the pulse had become quicker, suggesting the condition of partial Graves's disease, which was characteristic of the first period. The treatment was resumed, and in the month that has elapsed the patient has greatly improved. A sharp pain in the limbs came on, which was probably a symptom of the transition period, but this has now disappeared again under a continuance of the thyroid treatment.

wards, in the service of Dr. F. C. Shattuck, and there she improved somewhat under tonic treatment and sodium salicylate.

Some weeks after her discharge, however, I looked her up and found her still feeble and unable to work. Under fifteen grains of the thyroid powder every second day she has gained steadily, so that now, at the end of three weeks, she works with her hands for two hours daily.[1]

Of the other two cases, one stands apparantly nearer to acromegalia, the other to myxœdema, though in both the diagnosis is doubtful. The latter is of especial interest from presenting atrophy of the optic nerves, which is more common in acromegalia than in myxœdema, though seen in the latter disease (Hun and Prudden, Wadsworth, Jones). The former is under the care of Dr. G. C. Stearns, of Leicester, but is taking thyroids at my suggestion. A letter received yesterday reports that the improvement goes steadily forward, both as regards general strength and the appearance of the face and lips. There is a large swelling of the neck, probably a thyroid, which is diminishing in size under treatment; and, in fact, both patients consider themselves as decidedly better.

There are many questions of detail with regard to the new treatment by thyroid preparations which are of great practical importance. The following seem to me especially so:

Is the method by the stomach equally effective with that by injection, and is there anything to choose between the powder prepared by evaporation, the gland itself, and the extract precipitated with alcohol as recommended by Vermehren?

Must the dose by the stomach be larger than that by injection, and, if so, for what reasons?

[1] The recent history of this case has been very important. Some of the symptoms have continued to improve markedly, others not so much. The enlargement of the hands and feet has practically disappeared. They are, to be sure, very large, but the patient says they were always so, and I consider this point to be of decided interest in connection with the fact noted elsewhere in this paper, that patients subject to these trophic disorders sometimes show traces of the disease in their early years of life. Dr. C. L. Dana, of New York, in a paper read at the last meeting of the American Neurological Association, has pointed out that there is probably some relationship between gigantism and acromegalia. Certainly my patient is an unusually large woman in all respects, and not only as regards her extremities, though these are particularly large. She can now wear boots that she could not get on at all when her symptoms were at their height. The other two patients seem to have distinctly improved in general health and slightly as regards their large features and extremities.

What is the cause and significance of the rapid loss of weight so often noted, and may it occur in ordinary obesity, or with healthy persons, under the use of thyroids?

What is the cause and significance of the other symptoms observed during the thyroid treatment, especially those of cardiac origin?

Are signs of renal irritation brought on or increased, and under what conditions?

Some of these questions can already be answered fairly well. The method by the stomach has not failed in any genuine case, and although one of the best of English observers at one time asserted that four or five times as large a quantity must be given to get the same effect as by subcutaneous injection, yet moderate quantities are sometimes so effective that we have no reason to conclude that any considerable part of the dose passes unabsorbed in most conditions of the stomach and intestine. Some good chemical or physiological test is, however, much needed to enable us to study these points and to compare the different preparations.

The loss of weight is an early sign of improvement, but it sometimes goes beyond the requirements of health; and this fact, coupled with the observations of Dr. A. Barron, of Liverpool, on the effects obtained in obesity,[1] suggests that the thyroid secretion may, under certain conditions, modify the tissue-changes even of healthy persons. A myxœdematous patient of Laache's lost more than nine kilogrammes, or about nineteen pounds, in three weeks, and my first patient must, at one time, have lost weight almost as rapidly.

Immediately after the injections, and even the stomach doses, of thyroid, there is sometimes a rise of temperature and pulse, increased secretion of urine, faintness or headache, and other symptoms; as the treatment goes on these symptoms may continue for a time, and may be associated with prostration, cardiac weakness, anginoid, neuralgic, or other pains (Laache), and even albuminuria (Laache).

[1] Dr. Barron has very kindly written to me that he has used the treatment in five cases of ordinary corpulence. One lost twenty-eight pounds in six weeks, three a moderate amount, and all lost more or less. I am trying it in two typical cases, but have no results to report as yet.

[Since this foot-note was written one of my obese patients has lost forty pounds in weight under the thyroid treatment. Another patient, who has been trying the same treatment under the care of my colleague, Dr. Coggeshall, has lost forty-seven pounds.]

(Note also the increase in signs of renal irritation in my second case.) It is striking and important that these unpleasant signs sometimes last for weeks after the suspension of the treatment.

Dr. F. C. Shattuck will no doubt call attention to an important case which he kindly asked me to see with him, where attacks of palpitation with anginoid pain continued for several weeks after the cessation of a rather active, though short, course of treatment which had in other respects been remarkably effective for good. The fact that these effects last so long after the treatment by thyroids has been stopped, and that, on the other hand, they have failed to appear in some cases where large doses have been given, or at any rate do not necessarily appear at once (Vermehren) (my first patient has taken repeatedly thirty grains of the powder without noticeable effect), render it unlikely that they are wholly due to a direct action of the thyroid extract regarded as a drug. At any rate, other explanations suggest themselves as more probable.

One is that through an increased excitability of the cardiac centres, or from some other cause, the heart is called upon for increased action at a time when its muscular walls are in an abnormal state, or when its coronary arteries, which are liable to be thickened, are not supplying it with sufficient blood; another, that the products which are absorbed so rapidly from the diseased tissues act as irritants. It will be remembered that two of Murray's cases died while their improvement was in full progress, from sudden heart failure brought on by trifling exertion. One of these patients was known to have had cardiac disease, the other was assumed to have had a fatty heart.

At any rate, the action of the thyroid extract is not in all respects the same in health as in cases of myxœdema. Fenwick finds that diuresis does not occur in health, nor usually with myxœdematous patients unless they are under some slight excitement.

As regards the question of renal irritation, I would call attention to my second case, where, in spite of rapid improvement in other respects, the number of casts in the urine increased, and to Laache's case in which temporary albuminuria came on.

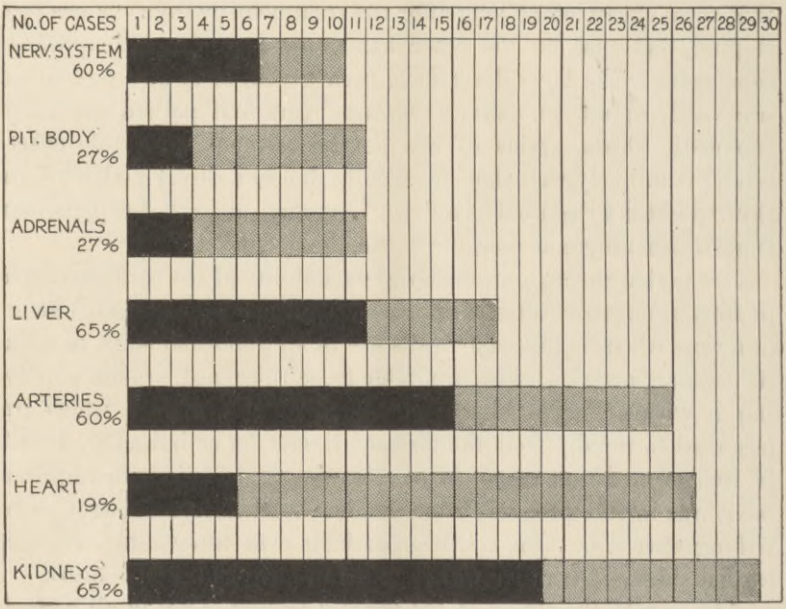
In another case, recently reported (Holman), the urine during treatment contained very large quantities of mucus.

Before leaving this part of the subject it must be noted that not only have the cases of myxœdema, successfully treated by animal

thyroids, been gathering like a rising tide, but that myxœdematous cretins have likewise been shown to be susceptible of a considerable degree of improvement (Bramwell, Affleck, Carmichael, Gibson, Vermehren, and others).

The point has not attracted as much attention as it deserves, that the "directly" hæmatopoietic functions of the thyroid, if they are

Diagram 1.



The length of the columns indicates the number of cases in which the corresponding organs were stated to have been specially examined. The dark portion indicates the number of cases in which the organ was found diseased. The percentages are given in round numbers.

of real importance, ought not to be met by ingestion of the thyroid secretion. As a matter of fact, the anæmia of my first case does not seem inclined to pass away with the myxœdematous symptoms.

I shall confine myself, in what follows, to the pathological side of the subject.

To indicate, for reference sake, the percentage of frequency with which the different organs are diseased, I have arranged the results of the post-mortem examinations, including those published since

1888, in the form of a diagram, which, of course, must be taken as having only a relative and provisional value, since the autopsies are few, and the observations often incomplete and probably inaccurate.

I am not tempted to refer in detail to the varied anatomical changes to which the different organs are liable, because so little that is of fundamental importance has appeared since the able paper of Hun and Prudden, and the report of the Committee of the Clinical Society of London in 1888, and especially since the masterly review of the functions of the thyroid by Horsley in 1890. Two experimental researches are, however, worthy of special mention. One is that of Hofmeister, who removed in young rabbits the main part of the thyroid but not the glandules of Gley. This is supposed to leave the rabbits practically uninjured, and, indeed, their health does not apparently suffer, though the hair is apt to become a little coarse and the body relatively short and thick.

In fact, however, a series of other changes occur. The growth of the bones is checked; the epithelium of the convoluted tubules of the kidney is altered; the ovaries undergo a premature ripening, with an immense development of follicles. The hypophysis cerebri enlarges, but the spleen and thymus do not, and no histological changes were found in the central nervous system or in any of the abdominal organs.

The second research is by Capobianco, of the University of Naples, and has reference to the condition of the *nervous system* in the acute stage of the cachexia after thyroidectomy in dogs. They are fully confirmatory of the older observations of Rogowitsch, and show clearly how profoundly the circulation and nutrition of the brain, the medulla, the cord, and the nerve roots may be altered. The fact that other observers have found only circulatory changes, with œdema (see Horsley's paper) or swelling of axis cylinders (Kopp), shows that there are great differences in the degree to which these results are produced, but for this very reason we should scrutinize carefully before giving the verdict, "normal"; and the more so when we recall that changes in the electrical irritability of the cortex cerebri (Schiff, Horsley) and the peripheral nerves (Awtokratow, Schwartz) are found.

The discovery by Hodge, of Clarke University, that simple fatigue leaves its mark on healthy nerve-cells—even physiological fatigue, as

that of bees after their day's flight—should be borne in mind in this connection. Not only do these observations show the possibility of recognizing slight changes in nucleus and protoplasm, but they point out—what is too little regarded—that in estimating the effects of poisons or of other causes of impaired nutrition upon the central nervous system, we ought to know what conditions as regards exertion and fatigue had been present shortly before death. A man or animal who has taxed his poor or poisoned nervous centres will certainly have induced histological changes that otherwise might be wholly absent, and the exertion necessary for this result may be an amount which would ordinarily appear trifling.

It would be extremely interesting to see Hodge's experiments repeated on animals with the cachexia thyreopriva. The probability that positive evidences of an increased liability to fatigue would be found is foreshadowed by the experiments of Manfredi Albanese, which point to an increased susceptibility to fatigue on the part of the spinal cord in the serious condition which follows removal of the supra-renal capsules.

No doubt the case is different for the *chronic stages* of myxœdema and cretinism.

We do not know about liability to fatigue, but no histological changes were found, at any rate, by Hofmeister in his rabbits, or by such careful observers as Hun and Prudden in their cases of myxœdema. There are no histological changes, indeed, that are distinctly characteristic of the nervous centres of cretinism (Bourneville), though the arrangement of the convolutions is often peculiar.

Langhans and Kopp have made a careful study of the peripheral nerves after thyroidectomy and in cretinism, and have found a series of interesting and peculiar alterations in the endothelial cells of the perineurium and endoneurium, as well as in the lymph spaces and the bloodvessels, arranged in minute foci here and there, and especially common in the smaller nerves. The paper is one for histologists to discuss. Langhans at first thought these appearances to be peculiar to goitrous diseases, but this is very doubtful (Schultze, and Langhans himself).

The *blood* presents no constant changes except those of acute anæmia, and in the acute stages increased venosity (Horsley). The red cells have been found larger (Kraepelin), but also smaller than

normal; the proportion of whites increased and normal; eosinophiles increased in one case (Ehrlich); myelocytes present in one (Case I.).

As to the final cause and nature of the changes which constitute myxœdema and cretinism, that is a riddle the solution of which we can approach but cannot reach. That the blood becomes toxic is inherently probable, and is confirmed by the fact that although usually harmless[1] if transfused into healthy animals, it precipitates the cachexia in the case of animals deprived of their thyroids (Fano, Zander, Rogowitsch, Fuhr); while, on the other hand, the cachexia may be mitigated by the infusion of healthy blood. Gley asserts that the toxicity of the urine is also increased.

The skin, the kidneys, the ovaries (Hofmeister, Langhans), the liver, the heart and pericardium, and other organs and tissues, also show signs of irritation and sometimes of degeneration. This is doubtless sometimes mucinoid in character, but mucin has not always been found, even in the skin, and Jürgens shows how complex the change which we call mucinoid really is. We do not yet know whether mucin, when it does occur, is merely a sign of degeneration or whether it is itself a poison. That it is the chief or only poison in myxœdema is highly improbable.

There are, moreover, some phenomena which seem to be less easily explained as the result of irritation and degeneration than as evidences of a sort of variation in structure, analogous, perhaps, to that which follows castration.

The curious fatty tumors of the neck, so characteristic of myxœdema and myxœdematous cretinism, are not easily accounted for as results of irritation; the changes in the ovaries of Hofmeister's rabbits were interpreted by him as a sign of follicular hypertrophy or premature ripening; the myxœdematous cretin is not only a diseased and degenerate individual, but may be regarded as a different variety, and this appears even in his mental characteristics.

If one looks for other instances of alteration of structure with which to compare this, the most striking and, possibly, the nearest is that of eunuchism from castration, by which the bull is changed to the ox, and the cock to the capon. The analogy would be more significant if it could be shown by experiment that the effects of castra-

[1] Gley finds the blood of dogs after thyroidectomy to cause convulsions in rabbits.

tion could be prevented by frequent injections of testiculin; indeed, the analogy would not hold if the results of this experiment turned out negative. So far as I know, it has never been tried, but it seems to me a reasonable experiment, and a logical outcome of the suggestive observations of Brown-Séquard and D'Arsonval.

The next point to which I wish to call your attention is with regard to the incomplete or partial forms of the thyroid cachexias.

The attention of physiologists and pathologists has hitherto been mainly directed to the study of the diseases due to complete, or nearly complete, destruction of the thyroid; and the opinion is current that the functions of the gland may be as well performed by a part as by the whole, because it has been found that when a piece of any considerable size is left, the cachexia does not, as a rule, occur. Usually the remaining piece grows larger. Sometimes the accessory glandules, which are embryonic in character, also increase in size, and probably in efficiency, though they never grow to the size of the original gland. A compensatory enlargement of the hypophysis cerebri may also, it is thought, occur.

An additional argument for the view that a part of a thyroid will serve for the whole is apparently furnished by the recent experiments of Beresowski. He removed enough of the gland to cause cachexia, and found that in the course of a few days distinct processes of repair had set in, as indicated by karyokinetic division of the glandular epithelium. This hyperplasia ceased, however, long before the piece of the thyroid had reached the full size of the gland, and the reason for this was supposed to be that the vital needs of the gland had been met.

In spite of the large amount of truth in these generalizations, it is in order to inquire whether we really have sufficient grounds for believing that the thyroid is so unnecessarily large, and, if this is not the case, whether we may not learn to discover and relieve diseased conditions associated with a partial destruction of the gland.

It is important to note, as indicating the complex nature of the problem, that myxœdema may fail to occur even when the true glandular epithelium of the thyroid has been replaced by a cubical variety, apparently secreting no colloid; and, indeed, a small part of a gland so altered may suffice. This is illustrated by the history of a case of Graves's disease reported further on in this paper, and by

the experiments of Halsted and Welch upon dogs (see foot-note on page 18, and discussion).

As regards the argument drawn from the cessation of the compensatory hypertrophy at a certain point, it seems to me extremely improbable that the amount of regeneration is exactly proportional to functional requirements. The law of repair is more complicated than this, and that is indicated in the present case by the fact that Ribbert found a true regeneration to follow the removal of comparatively minute pieces of the thyroid (see also Neumeister).

It would be an interesting research to see how much, or rather how little, of the thyroid must be removed before changes in growth and nutrition can be detected, especially in the light of Hofmeister's experiments, which show that rabbits may present them in spite of retaining, by the aid of their carotid glandules, apparently good health.

The studies of dosage during the treatment of cretinic children by sheep's thyroids, will no doubt throw much light upon this matter of the amount of thyroid secretion needed for full compensation, and meantime some clinical evidence is already forthcoming to show that the amount of thyroid sufficient for life, and fair health, is not necessarily sufficient for all the functions of the gland.

Some of the most important forms of cachexia from thyroid disease, not severe enough to cause myxœdema, are the following:

1. The early history of myxœdematous patients sometimes gives evidence of the presence of analogous forms of degeneration.

Two cases have been reported within a few years (Loewy, Merklen), where myxœdema came on when the patients were between twenty and thirty years old; yet both were of dwarf-like stature, and presented certain slight mental peculiarities which, without stamping them as cretins, suggested a congenital deficiency of thyroid action.

Struck by these cases, I turned to the abstracts published by the Committee of the Clinical Society to look up the early history of the patients who became myxœdematous before their twentieth year; that is, cases of myxœdema belonging to the period antecedent to senile involution, and I found these histories, incomplete though they are, to be of much interest. Four such cases are recorded, and in at least three of them, in spite of the scanty record of antecedents, there had been

signs of degeneration, such as very low bodily weight; slight mental weakness; small, broad, and depressed nose; and extremely large tongue, indicating, perhaps, as in the cases first cited, a partial and unrecognized cretinoid state existing since childhood.

It is noteworthy that my first patient was not only anæmic and lacking in robustness, during her early life, but also showed some degree of the lethargic temperament which afterward became so very marked. The second patient was anæmic, and suffered from palpitation of the heart, even in girlhood.

2. Cretinism is a disease of many degrees, and some of the cretins show a fair intelligence, a few a first-rate degree (comp. Bircher, and a celebrated case cited by Langhans). Yet their skulls are of the type now considered as probably, or possibly, characteristic of thyroid disease. In myxœdematous cretinism, which is the lowest type, characterized by unossified fontanelles and synchondroses (occasionally premature ossification), dwarf-like stature, tendency to umbilical hernia, etc., the thyroid is greatly atrophied, sometimes absent. In other forms the atrophy is only partial (Hanau), and portions of the gland may look healthy. Furthermore, the removal of a cretinic thyroid may cause myxœdema (Bircher).

3. Goitrous persons, in districts where the disease is endemic, are generally of inferior type, though, of course, it is not certain that the thyroid disease is the cause of this.

In my second case, which is probably typical of others, it is worth considering whether the anæmia and debility of the pre-myxœdematous, but goitrous, period may not have been an early stage of thyroid cachexia. At any rate, myxœdema sometimes comes on quickly, but oftener slowly, and in the future it will be of great importance to learn to recognize the preliminary symptoms.

Another fact, of which we should never lose sight, is that myxœdema, or tetany, and perhaps other signs of the thyroid cachexia, may follow temporary disease of the thyroid, from which the patient eventually recovers, and may then pass away. Not only does this happen after partial thyroidectomy, but in the course of syphilis (Kocher), and as a result of ordinary goitre (*v.* Horsley's paper, *Brit. Med. Journ.*, 1890.)

As regards the question of the *compensatory hypertrophy* of the *hypophysis*, it is certainly true (Rogowitsch, Stieda, Hofmeister)

that thyroidectomy done on dogs and rabbits is usually followed by enlargement of the hypophysis, which comes so near the thyriod in structure and origin, and it would seem also that the thyroid may enlarge after removal of the hypophysis (Vassale and Sacchi). On the other hand, it is not accepted as certain that this enlargement means increase of functional activity.

To express a complicated matter in a few words, it is generally conceded that the hypophysis contains two kinds of cellular bodies, the "chromophiles," and the Hauptzellen (Stieda and Rogowitsch) or "nucleated protoplasm" (Schönemann).

When the gland enlarges there may be found an increase in the number of chromophile cells, or an enlargement of the Hauptzellen; and there is almost always an increase in the colloid contents of the gland. The increase of the chromophile cells has been thought (Lothringer, *Arch. für mikroscop. Anat.;* cited by Vassale and Sacchi) to be of functional significance; but Schönemann, on the basis of a careful study of the hypophysis of a cretin, came to the opposite conclusion, namely, that the chromophile cells are degenerated forms, and are finally to be converted into colloid.

Vassale and Sacchi have recently made an ingenious experiment which seems to favor the view of Schönemann. Removing the hypophysis from an ox, they divided it into two parts; and while one of these was preserved in alcohol for comparison, to indicate the normal histology, the other was introduced into the abdomen of a rabbit and left for three days, presumably to undergo slow degeneration. The chromophile cells in the latter half were found to have increased greatly in number.

The same observers deny that the mere increase in colloid matter ought to be taken as a sign of increased functional efficiency, either in the case of the hypophysis or the thyroid, unless it is accompanied with indications of active cell-growth of the glandular epithelium, with karyokinetic appearances, and this, they declare, does not occur in either organ simply from extirpation of the other. They do, however, regard the two organs as physiologically similar, and this is important for the pathology of acromegalia, which seems to me a disease kindred to myxœdema, though the bond may be but that of a Scottish cousinship.

Hofmeister's experiments, which are especially valuable because his

rabbits remained alive and well, and the hypophysis was given from three to six months in which to show its supposed compensatory growth, are confirmatory, as he thinks, of the observations of Rogowitsch and Stieda. He finds, as they did, not only an enlargement of the whole organ, but an increase in the size of the hauptzellen.[1]

The question is therefore still open for further research, but hereafter increased size cannot be taken as a sure sign of increased efficiency.

One suggestion thrown out by Hofmeister is worthy of comment, namely, that the large size of the sella Turcica, several times noted in cases of cretinism, indicates that the hypophysis had been hypertrophied. Klebs makes the same remark with reference to a case of acromegalia. As bony changes are, however, of regular occurrence in both of these diseases, the increased size of the sella Turcica admits of a different interpretation, and Schönemann distinctly notes that while the sella Turcica of his cretin was large, the hypophysis was rather small. Possibly it had been enlarged at an earlier period. Certainly the hypophysis is not always enlarged either in cretinism or myxœdema *at the period at which the post-mortems have been made.*

It is next in place to consider what other symptom-complexes, besides myxœdema, are associated with disease of the thyroid, and in what that association probably consists.

The diseases to be considered are exophthalmic goitre, acromegalia and certain forms of obesity.

1. The reasons for ranking Graves's disease among the thyroid cachexias were clearly set forth and ably championed by Moebius in 1891, and since then various writers have taken sides in the discussion (*v.* the abstracts by Moebius himself in Schmidt's *Jahrb.* for the past two years). Especially valuable are the monographs of

[1] There are several reasons for concluding that the colloid is not the important part of the thyroid secretion, but an envelope, or a by-product. Even its presence is not essential.

The valuable researches of Halsted and Welch [see Discussion], made some years ago, but not yet published, show that in the regeneration of the thyroid which follows mutilation, the histological character of the gland may undergo great change. The epithelium tends to become high and cubical, instead of flat, and the colloid to disappear. Canizzero (Deutsche med. Wochen., 1892, p, 184) has made similar observations.

A closely similar change has been noted by Councilman in a case of Graves's disease (referred to below).

Wölfler, of Graz, and the able paper of Wette, who has had a large experience with thyroid diseases in all their aspects, as assistant in the surgical clinic at Jena.

It must certainly strike anyone who studies the matter, that there is a certain likeness between the acute nervous symptoms of the first stage of the cachexia following either complete or partial thyroidectomy, and the nervous symptoms of Graves's disease; and, on the other hand, a certain contrast between the latter and some of the symptoms of chronic myxœdema. This argument from the comparison of symptoms does not, however, fully stand close criticism.

There is no real contrast, for example, between the sweating of Graves's disease and the dry skin of myxœdema, if the former is due, as is probable, to central excitation of the sweat nerves, and the latter to disease of the cutis.

It may be true that there is an analogy between the nervous erythism of the first stage of the cachexia thyreopriva and Graves's disease; but if this be so the cause is not evident. For in the one case we have to do with symptoms associated with absence of the thyroid, while in the other we have to do with symptoms associated with the presence of an enlarged thyroid, and actually curable, sometimes, by thyroidectomy. It is possible that irritation of the vagus and sympathetic is a factor common to both cases.

But there are other arguments of greater weight in support of the thyroidal theory of Graves's disease.

In the first place, myxœdema sometimes closely follows Graves's disease, or even, perhaps, accompanies it (Sollier; Von Jaksch, cited by Gauthier; *Clin. Soc. Reports;* my own second case), or the two diseases may occur in different members of the same family (Hadden, Virchow). Above all, thyroidectomy, or other operations on the thyroid, have proved of late years unexpectedly successful in the treatment of Graves's disease. About forty cases have been treated in this way, mainly by German surgeons, in all but three or four of which improvement or cure resulted. To this number I can add one case, which is, I think, the first to be reported in this country.

The operation was done in February, 1893, by Dr. J. C. Warren, at the Massachusetts General Hospital. The patient seems to be steadily, though slowly, improving. The whole gland seemed to

have been converted into a firm mass of adenomatous structure, with high cubical epithelium and without colloid, so far as examined. (Councilman.)[1]

The probability of a connection of some sort between Graves's disease and myxœdema is made stronger by including the case of acromegalia, which bears a certain likeness to both of the others, presenting the rapid pulse, the tremor, and the sweating of the skin characteristic of Graves's disease; together with trophic changes in the bones and integuments of the head and limbs analogous, perhaps, to those of myxœdema.

On the other hand, the experimental evidence with regard to the cause of Graves's disease, unsatisfactory as it is, favors rather strongly the view that it is due to the injury of certain nervous arrangements; and no theory should pass muster that does not attempt to account for the extraordinary manner in which practically the whole Graves's disease complex springs almost instantaneously into existence in persons with healthy thyroids under the influence of intense emotion. Sometimes, if the emotion quickly subsides, the symptoms may soon pass away (Gowers). My colleague, Dr. F. Coggeshall, has seen an exactly parallel case. The patient was a young girl, and the symptoms followed immediately on great excitement attending a whipping, but subsided in the course of a few weeks.

My own opinion as regards this complicated matter is that some such statement and explanation as that given by Wette is correct, but may be extended and modified. He thinks that goitre is one of the most important causes of Graves's disease, but not by any means the only cause; that the goitre may excite the cardiac and ocular symptoms, either by direct irritation of fibres of the cervical sympathetic or by indirect irritation of the sympathetic centres; and that many of the general nervous symptoms are perhaps due to the action of toxic substances formed by disordered metabolism within the diseased gland.

The explanation which would be most satisfactory is one which would include this, and at the same time cover the cases where Graves's disease comes on without antecedent thyroid disease, and I think that such an explanation can be hinted at if we do not take our physiology too narrowly.

[1] v. Foot-note on page 18 respecting the researches of Halsted and Welch.

The most probable hypothesis, though it can only be stated with infinite crudeness, seems to me to be as follows:

The Graves's disease complex, in common, probably, with most other neuroses, is the distorted correlative, or caricature, of one or several *physiological arrangements*[1] in which the nervous system plays the central part. The thyroid has an abundant and mobile circulation, and is supplied with nerves from the vagus and sympathetic. It is thus in position to inhibit (as occasionally seems to occur; see Wette) or to accelerate the heart, and on the other hand it is liable to swell almost like an erectile organ when the heart is acting strongly and its own vasomotor apparatus is weakened. When enlarged, the thyroid is liable to irritate the sympathetic and the other nerves in its neighborhood, and thus, in its turn, act as a centre of disturbance. These results almost certainly occur in many cases of thyroid disease (comp. Wölfler, Wette, and an able paper by Schranz, which I regret my lack of space to cite at length). It is even conceivable that one of the functions of the thyroid in health is to act as a regulatory apparatus for the heart, and it is further conceivable that there is a quasi-physiological connection of the following sort between the tremor and exophthalmus of Graves's disease, the disordered action of the heart, and the disease of the thyroid:

When a person is suddenly called upon for close attention, he fixes his eyes and holds his breath, his muscles stiffen, and his heart beats faster. If the attention changes to rage or fear, the eyes open wider, the heart palpitates, the voice changes, the hand trembles, the face and neck may become turgid from vasomotor paralysis, and even the circulation and secretion of the bowels may become affected.

As calm is restored these symptoms may pass gradually away, but the heart is slow to recover its tone. Judging from the fact that Graves's disease may immediately supervene on such events as this, we may assume as possible that the heart sometimes never recovers its tone, and that the delicate vascular apparatus of the erectile thyroid (which Schranz makes largely responsible for the origin of goitre) is also liable to suffer permanently.

Eventually, nutritive changes may occur (deposition of fat in orbits, etc.); and a morbid complex of symptoms, interdependent

[1] Compare Porritt, London Lancet, 1888, i. 164.

and correlated with each other, is formed, and becomes crystallized into what we call a disease.

When any member of this complex is induced, the others are likely, by association, to follow, and a tendency to the complex as a whole may possibly be inherited like a tendency to any other disease, or to a monstrosity. The exciting cause may be any one of many.

Tachycardia without exophthalmus or tremor occurs so frequently with ordinary goitre that it hardly deserves to be called abortive Graves's disease, but it may at least be an analogous affection.

The operation of thyroidectomy in Graves's disease—which, by the way, may be successful when it consists only in the removal of a sarcoma (Tillaux) or a cyst (Tessier, cited by Gauthier,)—may be supposed to act by breaking in upon the vicious circle of influences through which the disease is maintained. The extirpation of a part of the growth usually causes the rest to shrink (Wolff), just as iodine or external cauterization or electrolysis or division of the isthmus of the thyroid may cause the same result, and it is probably this and not the reduction of the thryoid secretion by removal of part of its secreting tissue that makes the operation of value. Mechanical and perhaps chemical irritations of the thyroid nerves are removed ; a new set, as it were, is given to the action of the nervous centres, such as more favorable mental surroundings may give, and in favorable cases the old equilibrium is restored. It must not be forgotten that it is just as possible to produce this result from one side as from the other. Absolute repose for the nervous system, if it can be secured, as it sometimes can, is occasionally as effectual in causing the disappearance of the goitre as the thyroidectomy is in quieting the nervous excitement and the heart.

It is not probable that Graves's disease is related to the functions of the thyroid as a trophic organ, or, at any rate, that it is due to either an increase or a diminution of the normal secretions of the gland. That it is not due to an increase of the normal secretion is demonstrated both by anatomical considerations (coexistence with a small or practically small gland) and by the fact that the myxœdema, which is not compatible with an increased secretion of the thyroid, sometimes follows closely on the heels of Graves's disease, or even accompanies it. Neither can we refer it to a diminution of normal secretion, or we should meet it more often in connection with the invo-

lution of the thyroid. Moreover, it has often happened that all the symptoms of Graves's disease have come on with extreme suddenness, in consequence of strong emotion, in persons with normal thyroids, and have again disappeared almost as quickly. Again, it apparently is not cured by preparations of thyroid extract.

It is possible that disordered metabolism, due to a vitiated thyroid secretion, helps to keep up the nervous symptoms of Graves's disease, but this theory is in need of more evidence than it has yet adduced.

2. Acromegalia probably stands as near to myxœdema and diseases of the thyroid or kindred organs as Graves's disease, if, indeed, the bond be not closer.

It is more distinctly a sort of dystrophy than Graves's disease is, and affects much the same parts that are involved in myxœdema, namely, the bones and integuments of the face and extremities, and eventually, perhaps, of the whole body; for, as Klebs points out, the reason that the ends of the long bones show the growth the most is that the resistance there is least. Occasionally both myxœdema and acromegalia have an exclusively or almost exclusively hemiplegic distribution.

The growth of the hair and nails is apt to be impaired in acromegalia, though not to the same extent as in myxœdema, but, on the other hand, the skin often perspires freely, as in Graves's disease. Tremor is also common, and attacks of well-marked palpitation are of frequent occurrence.

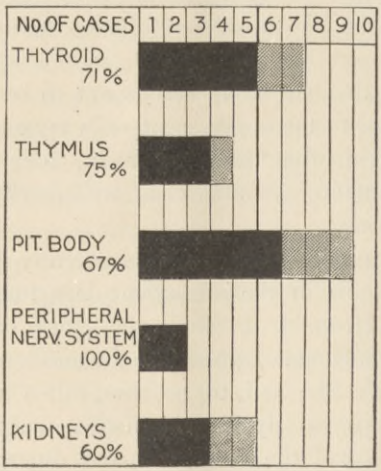
In the case of a middle-aged woman, recently under observation in the wards, and now in the out-patient department of the Massachusetts General Hospital, I found the pulse one morning 180, though from her phlegmatic appearance I should not for an instant have expected this. She had, to be sure, taken a dose of thyroid powder two hours previously, but on another occasion when she had not done this I found the pulse 120, and during her stay in the hospital, under the care of Dr. F. C. Shattuck, it ranged from 90 to 100, though she was kept perfectly still.

Klebs, who has studied the pathological anatomy of acromegalia quite extensively, explains the rapid pulse on mechanical grounds, believing that the disease originates in an affection of the thymus and that vascular changes occur by which the labor of the heart is

increased. It would not be fair for one who is no pathologist to offer a criticism of this theory in detail, but with the tachycardia of Graves's disease before our eyes it would seem more reasonable to seek a physiological than a mechanical explanation, as in the case of Graves's disease. I do not, however, mean to deny the importance of the thymus, or to maintain that acromegalia is distinctly of thyroid origin like myxœdema. I cannot dwell, for want of space, on the recent views of Marie and Marinesco, or on those presented in the monograph of Duchesneau, published in 1892.

Duchesneau calls attention especially to the occasional occurrence of muscular atrophy, but the theory by which he accounts for it, namely, pressure of hyperplastic connective tissue on the nerve roots, is not, I think, the true one. This atrophy is present in a typical form in the case recently at the Massachusetts General Hospital, though without other signs of nerve-root pressure, but so, also, is it

Diagram 2.



Acromegalia—ten autopsies.

present in a case of Graves's disease which I have had the opportunity of studying closely for many years, and in several other reported cases of that kind. The explanation given by Duchesneau would certainly not apply here, and, on the other hand, the occurrence of

the atrophy in both these diseases forms another bond of union between them, though its nature is still so obscure.

I have said nothing as yet of disease of the hypophysis in acromegalia, and to save time I present the evidence on that point and others in the form of a table and diagram.

3. It is not certain that the dystrophic affections due to thyroid diseases are fully covered by myxœdema and the others that have been mentioned; and in this connection three communications, two by Dr. F. X. Dercum and one by Dr. F. P. Henry, in 1888, 1890, and 1892, are especially important. They describe three interesting cases, characterized by great and widespread hyperplasia of the subcutaneous fat, especially accentuated at certain parts of the body, and attended by pain and muscle-degeneration indicating the presence of neuritis. Perspiration was diminished or absent, and in this and other respects the cases suggested myxœdema. That which makes them especially interesting, however, is that the thyroids of two of the patients, who died while under observation, were indurated and infiltrated with calcareous deposit.

The name first suggested for this disease by Dr. Dercum was "A Subcutaneous Connective-tissue Dystrophy of the Arms and Back, Associated with Symptoms resembling Myxœdema." Dr. Henry first described the second of the three cases, and proposed the name "Myxœdematous Dystrophy." Dr. Dercum, in his final communication, says:

"All of these cases lack the peculiar physiognomy, the spade-like hands, the infiltrated skin, the peculiar slowing of speech, and the host of other symptoms found in true myxœdema.

"It would seem, then, that we have here to deal with a connective-tissue dystrophy, a fatty metamorphosis of various stages of completeness, occurring in separate regions, or, at best, unevenly distributed, and associated with symptoms suggestive of an irregular and fugitive irritation of nerve-trunks, possibly a neuritis. That this, however, does not embrace the whole truth is evidenced by such symptoms as the diminished sweating, the headache, and the contraction of the visual fields noted in Case I.

"Inasmuch as the swelling and the pain are the two most prominent features of the disease, I propose for it the name 'Adiposis Dolorosa.'"

Dr. Dercum further makes the good suggestion that the condition of the thyroid gland should be examined in all cases of obesity. The thyroid is rarely examined as a matter of routine, and least of

all microscopically, unless attention is especially called to it, so that our knowledge of the frequency with which this or that change is present, or as to the amount of variation in structure which is compatible with health, is still but slender.

A year ago Dr. F. C. Shattuck was good enough to ask me to see with him a very interesting case which deserves a place in some such category as this. Perhaps, indeed, it is a case of myxœdema, though, I believe, the improvement under thyroid treatment has not been very marked, except as regards the condition of the skin. The patient was a lady of about twenty, and the signs and symptoms consisted mainly in an increase in the subcutaneous fat, with changes in the skin not quite characteristic of ordinary obesity and somewhat suggestive of myxœdema, a change in the nutrition of the palms and soles, and a marked and peculiar discoloration and brittleness of the nails, associated with an irritability and excitability which finally developed into insanity. I trust that Dr. Shattuck will report the case at greater length.

List of Authors referred to in the Text.

Affleck, Lancet, 1893, i. 419.
Avtokratow, St. Petersburg. med. Wochenschr., 1888, p. 105.
Baumler, Internat. Congress, Berlin, 1890, ii. p. 137.
Beresowsky, Beitr. z. path. Anat. u. allgem. Path., Zeigler, 1892, vol. xii. 1.
Biondi, Berlin. klin. Wochenschr., 1889, p. 464.
Bircher, Samml. klin. Vorträge, 1890, No. 357.
Bourneville (et Bricon), Arch. de Neurol., 1890, xix. p. 217.
Bramwell, Lancet, 1893, ii. p. 25.
Capobianco, La Riforma Medica, September, 1892; Arch. Ital. d. Biol., 1893, tome xviii.
Carmichael, Lancet, 1893, i. p. 580.
Chopinet, Comp.-rend. Soc. de Biol. de Paris, 1892, vol. iv. pp. 602-7.
Christiani, Arch. de Phys. norm. et path., 1893, i.
Dercum, Amer. Journ. Med. Sciences, November, 1892.
Drobnik, Arch. f. Anat. u. Physiol., 1887.
Duchesneau, Monograph. Paris, 1892.
Fano, Archivio Med., vol. xiii. p. 365.
Fenwick, Lancet, 1892, ii. p. 941.
Fuhr, Arch. f. exper. Path., 1886, p. 407.
Gauthier, Lyon Méd., 1888; see also Schmidt's Jahrb., 1893.
Gibson, British Med. Journ., 1893, i. pp. 14 and 58.
Gley, Bull. Méd., May 20, 1891; Arch. de Phys., 1892-93.
Hadden, Clin. Soc. of London, 1885.
Hanau, British Med. Journ., October 4, 1890, p. 786.
Henry (F. P.), Journ. Nervous and Mental Dis., March, 1891.
Hofmeister, Fortschr. d. Med., 1892, p. 81 et seq.
Holman, British Med. Journ., 1893, i. p. 114.
Horsley, British Med. Journ., 1885; 1890, ii. 201; 1892, i. 431; Internat. Beiträge, i. 396. Virchow's Denkschrift, 1890.
Howitz, Lancet, 1892, ii. p. 1213.
Hun and Prudden, Amer. Journ. Med. Sciences, 1888, xcvi. pp. 1 and 140.

Jaksch, Von, Prager Med. Wochenschr., 1892, xvii. p. 49; Schmidt's Jahrb., 1893, p. 22.
Jones (W. Makeig), British Med. Journ., 1888, i. p. 252.
Jürgens, St. Petersburg. med. Wochenschr., 1889, vi. pp. 447 and 449.
Klebs, Allgem. Path., 1889, ii.
Köhler, Berlin. klin Wochenschr., 1892, Nos. 24, 29, and 30.
Kopp, (J.), Virchow's Arch., 1892, 128, p. 290.
Laache, Deutsche med. Wochenschr., 1893, p. 257.
Langhans, Virchow's Arch., 1892, 128, pp. 318 and 387.
Lemke, Deutsche med. Wochenschr., 1892, No. 11.
Loewy, Berlin. klin. Wochenschr., 1891, p. 1130.
Manfredi-Albanese, Arch. Ital. d Biol., 1892, xvii.; Schmidt's Jahrb., 1893, p. 222.
Marie et Marinesco, Arch. de Méd. expérimentale. Paris, 1891, 3.
Merklen, Mercredi Méd., 1890, i. p. 571; Bull. et Mém Soc. méd. des Hôp. de Paris, 1890, vii., 3d series, pp. 859, 870.
Moebius, Deutsche Zeitschr. für Nervenheilkunde, 1891, p. 400.
Murray, British Med. Journ., 1892, ii. p. 449.
Neumeister, Diss., Bonn., 1888.
Osler, Johns Hopkins Hosp. Bull., 1892.
Ribbert, Virchow's Arch., 1889, vol. cxvii.
Rogowitsch, Arch. d. Phys., 1888, ii. 433; Beitr. z. path. Anat. u. allgem. Path., Zeigler, 1888, iv.
Schönemann, Virchow's Arch., 1392, vol. 129, p. cxxix.
Schranz, Arch. f. klin. Chir., 1886, xxxiv.
Schwartz, Schmidt's Jahrbücher, 1889.
Sollier, Rev. de Méd., 1891, xii. p. 10.
Stieda, Diss., Konigsberg.
Tillaux, Bull. de l'Acad. de Méd., 1880, second series, tome ix. p. 401.
Vassale and Sacchi, Rivista Sperimentale di Freniatrie e Med. Legale, 1892, vol. xviii. fasc. 3, 4; Arch. Ital. de Biol., 1893, tome xviii. p. 385.
Vermehren, Deutsche med. Wochenschr., 1893, iii. p. 255.
Virchow, Trans. of Berl. med. Verein, February 2, 1887.
Wadsworth (O. F.), Boston Med. and Surg. Journ., 1885.
Wette, Arch. für klin. Chir., 1892, vol. xliv.
Wolff, Deutsche med. Wochenschr., 1893.
Wölfler, Chirurgische Behandlung des Kropfes.
Zanda, Archivio Med., vol. xiii. p. 365.

Recent Clinical and Pathological Reports not referred to in the Text.

Abercrombie, Clinical Rep., Brit. Med. Journal, 1889, ii. p. 1097.
Anderson, Clinical Rep., Med. Times and Gazette, 1884, ii.
Babec, British Med. Journal, 1893, i. p. 10
Barron, Liverpool Med.-Chir. Journal, January, 1893.
Barton, Dublin Jour. Med. Sciences, 1893, p. 431.
Beach (Fletcher), Myxœdematous Cretinism. Internat. Congress, Berlin, 1890, ii. 136.
Baumgarten, Path. Anat. der Myxœdema. Berlin. klin. Wochenschr., 1888, p. 195.
Beadles, British Med. Journal, 1892, ii. 1386.
Beaty, Dublin Jour. Med. Sciences, 1893, p. 375.
Benson, British Med. Journal, 1893, i. p. 795.
Brandes, Clinical Rep.
Buchanan, Glasgow Med. Journal, 1892, p. 329.
Buzdygan, Allgem. Med. Ent. Zeit., February 4, 1893.
Campbell, Montreal Med. Journal, 1889, i. 478.
Caspary, Berl. klin. Wochenschr., 1888, p. 196.
Clarke, British Med.-Chir. Journal, 1889, vii. p. 258.
Cocking, British Med. Journal, 1889, 1, p. 478.
Corkhill, British Med. Journal, 1893, i. p. 8.
Cunningham, British Med. Journal, 1892, ii. p. 1286.
Davies, Trans. Clin. Soc., London, 1888–89, xxii. p. 327; 1891–92, xxv. p. 306.
Deaver (J. B.), Journ. Amer. Med. Assoc., August, 1891.

Dercum, American Journ. Med. Sciences, 1893, cv. p 268.
Duckworth, Trans. Clin. Soc., 1892, xxv. p. 224.
Dyson, Sheffield Med. Journal, 1892-93, i. p. 30,
Ehler, Semaine Médicale, 1892-93.
Finlay, Internat. Clin., 2d series, ii.
Fox, British Med. Journal, 1892, ii. p. 941.
Garré, Beitr. z. klin. Chir., 1890, vi. p. 478.
Grawitz, Berl. klin. Wochenschr., 1886, p. 96.
Hale (*G. E.*), British Med. Journal, 1892, ii. p. 1428.
Harris, Lancet, 1892, i. p. 798.
Henry, British Med. Journal, 1893, i. p. 737.
Hernot, Asso. Français pour l'Avancem. d. Sci., Rochelle, 1892.
Hurd, Lancet, 1888, i. p. 41.
Kaufmann, Fortschr. d. Med., 1893, i. p. 11.
Kraepelin, Deutsche Arch. für klin. Med., 1891, xlix. p. 587; Neurol. Centralbl., 1890, lx. p. 65.
Kovalewski, Arch. de Neurol., Paris, 1889, xviii. p. 422-432; Arch. Psichiat., Charkov, 1888, xii. p. 1.
Lannois, Arch. de Méd. expér. et d'Anat. Path., 1889, i. pp. 470, 590.
Lindemann, Centralbl. f. allgem. Path. u. path. Anat., 1891, ii. p. 13; Schmidt's Jahrb., 1892.
Mackenzie, British Med. Journal, 1892, ii. p. 940; Lancet, September, 1890, p. 999; Journ. Ment. Sci., 1889-90, xxxv. p. 206; Deutsche Zeit. für Nervenheilkunde, 1891, p. 400.
Mackew, Monograph (Contrib. à l'Etude de Myx.), Paris, 1888, p. 60.
Manasse, Berlin. klin. Wochenschr., 1888, xxv. p. 585; Münch. med. Wochenschr., 1888, p. 773.
Mosler, Deutsche med. Wochenschr., 1888, xiv. p. 411; Berlin. Klinik, 1887-89, xiv.; Wien. med. Bl., 1888, xi. pp. 897 and 934; Arch. f. path. Anat., 1888, cxiv. p. 442.
Nauwerck, Mitth. aus der Chir. Klin. zu Tübingen, i. p. 440.
Nixon, Trans. Royal Acad. Med. Ireland, 1887, v. p. 9; 1889, vii. p. 55; Lancet, 1889, i. p. 793; Med. Press and Circular, 1889, xlvii. p. 457; Dublin Journ. Med. Sci., 1889, lxxxvii. p. 369.
Oliver, Internat. Clinics, 2d series, vol. ii.
Ord, Wien. med. Wochenschr., xl. p. 1745.
Packard, Trans. Coll. Phys. Phil., 1892, 3s, xiv. p. 6.
Paton, Glasgow Med. Journal, 1887, xxvii. p. 425.
Pratolongo, Gazz. d. Hosp. Milano, 1888, ix. p. 43.
Report of a Committee of the Clinical Society of London on Myxœdema. Trans. of Clinical Society, 1888; supplement to vol. xxi.
Robin, Gaz. hebd. de Méd., Paris, 1892, xxix. p. 451; Bull. Soc. Franç. de Dermat. et Syph., 1892, iii. p. 303.
Romme, Tribune Méd., Paris, 1889, xxi. pp. 261 and 292.
Sanquirico, Arch. Ital. de Biol., 1884, p. 390; Fuhr, Arch. f. exper. Path., 1886, p. 407.
Schwass, Berlin. klin. Wochenschr., 1889, xxvi. p. 463.
Shapland, British Med. Journal, 1893, pp. 738 and 739.
Shaw, British Med. Journal, 1892, ii. p. 451.
Thomson, Edinburgh Med. Journal, 1887, xxxiii. p. 933.
Tresilian, British Med. Journal, 1888, i. p. 642.
Uffalnsy, Pesth. med. u. chir. Presse, 1887, xxiii. pp. 868 and 881.
Walker, Lancet, 1888, xxi. p. 1.
Watt, Medical Record, New York, 1888, xxxiii. p. 97.
White, British Med. Journal, 1889, i. p. 699.
Whitwell, British Med. Journal, 1892, i. p. 430.

DISCUSSION.

Dr. F. C. Shattuck: I wish to mention rather than report three cases of myxœdema, two in private, one in consulting practice, during the past year. I shall report them fully at some future time.

Upward of a year ago a single lady, of twenty-nine years, was brought to me with symptoms dating back a number of years, but much aggravated within a few months, Her appearance had so changed that people did not recognize her. She had grown very stout, with supra-clavicular pads and peculiar trophic disturbances of the finger-tips, hands, and nails. Combined with this was a yellowish discoloration of the skin, most marked on the palmar and plantar surfaces, but also distinguishable on the trunk. Dr. Osler saw her with me on one occasion, and aptly compared the hands in color and surface to a goose's foot. Her mental condition was one of rather undue elation. Sus pecting myxœdema, I sent her to Dr. J. J. Putnam, taking care that he should not know my suspicion. He was at first not disposed to agree with me, but has since that time, I believe, concurred. As soon as I could make arrangements to do so, early in May, 1892, I injected weekly a glycerin extract of a sheep's thyroid in three doses. The strictest precautions were observed, and no abscess formation resulted at any time. The injections were kept up for about three months. The skin improved very much, but from undue elation she passed into a condition of suicidal melancholia, which continued more or less up to the present time. About two months ago she began to take Parke, Davis & Co.'s desiccated thyroid extract by the mouth, fifteen grains twice a day, and continued it for five weeks. It was then stopped on account of pains in the legs, and afterward resumed. She is essentially no better, though I feel that she has been fairly subjected to the treatment. In spite of this failure to gain, I believe the case to be one of myxœdema. Dr. C. F. Folsom had the care of her during my vacation last summer. Since then I have seen her only once or twice, as she lives out of town and is unable to be brought in. But I have been kept informed as to her condition.

The next case is that of a gentleman of sixty nine years, whom I saw first two and a half months ago. His main symptoms were great sensitiveness to cold, constant watering of the eyes and running at the nose, weakness, and a tendency to diarrhœa. The skin of the hands in particular was very harsh; the lips were swollen, the lower pendulous. He said he was perfectly well until five months before. I thought I recognized an early case of myxœdema, and put him on the desiccated thyroid, 15 grains twice a day in capsules. Before many days he began to complain of pain in his legs and then in his chest near the cardiac region. The dose was diminished to 7½ grains twice daily. The myxœdematous symptoms rapidly abated, but I was soon compelled to stop the extract on account of very severe noctural paroxysms of pain like that of angina, demanding morphine hypodermatically, several

nights, as much as two grains, in half-grain doses. This was accompanied by great tenderness just outside the left nipple, slight tenderness about this spot, and inability to lie on the left side. As the pain came on, the pulse would rise to 120, the normal rate being about 70. After three weeks' intermission I resumed the extract, at first 1 grain every second day, now 1 grain daily. His whole appearance has undergone a marked change, and he says he feels well—better than for two years. Both he and his wife now date his symptoms back further than they did at first.

The third case, that I saw in consultation, is of many years' standing, but was seen only very recently. Very marked improvement has already taken place, and her friends note the great change in her appearance, which was highly suggestive of Bright's disease. She has had much palpitation since she took the extract, 7 grains three times a week.

The special points to which I wish to call attention are the failure of the treatment thus far in a case which seems undoubtedly one of myxœdema, and the toxic symptoms noted more or less in all three—namely, pains in the legs, palpitation, and severe angina.

We are dealing with a very powerful agent, and should be very careful until we are more familiar with its dosage than we are at present. Among the many points upon which experience will enlighten us is the relation of the dosage to the duration or intensity of the disease. Finally, the descriptions as laid down in the books apply to old and very marked cases. As we learn to recognize the early stages of the affection we shall find that cases are pretty common.

Dr. Welch: I wish to say just a few words in regard to the subject of extirpation of the thyroid gland. I reported some years ago, at a meeting of this Association, some results that Dr. Halsted had obtained from extirpation of the thyroid gland in the dog. We found a singular alteration in the structure of the gland which has been referred to to-day as an hypertrophy of the gland. Perhaps no better name could be given to the changes, but the change is so complete an alteration of the structure of the gland that it is doubtful if anyone would, under the microscope, recognize, in an advanced degree of the change, sections of the organ as thyroid gland at all. So far as I know, no one except Dr. Halsted has accurately described these lesions in the gland. In these so-called hypertrophied glands the appearance of follicles has disappeared and the lumen of the follicle is filled up with papillary growths from the walls of the follicle. There is complete disappearance of the colloid substance from the lumen of the gland, and the low cubical epithelium has become high cylindrical epithelium and more granular than normal. This change, although called hypertrophy, is a very peculiar and remarkable alteration of the gland, which does not correspond to what one would understand by hypertrophy *a priori*. Another point is that this change, designated as hypertrophy, occurs as the result of interference of various kinds with the gland. Dr. Halsted had gone over the whole subject thoroughly, and has found that a very severe operative interference in the neighborhood of the gland, or a

simple handling of the nerves or a ligating of the nerves in the neighborhood, or disturbing the tissues around the gland, frequently results in this same alteration in the gland. Then it occurred to us that this condition might be found normally in the dog's thyroid. We examined the glands of various dogs used for experiment in the laboratory, and found now and then, especially in cases which had been operated upon for intestinal suture and also for experimental peritonitis, that the glands presented this same change, although there was no operation done about the neck. Then we examined the thyroid gland in something over one hundred dogs taken in series at the pound of Baltimore, and found that a very small per cent. of the animals had this same enlargement and alteration in the structure of the gland. Of course, all this means that the thyroid gland subserves some very important function, although it sheds no clear light on the nature of this function.

Another point which has been brought out since that report is the possibility of removing a great many times the weight of the normal thyroid gland, by proceeding in this way: Dr. Halsted takes away one thyroid gland and a part of the other, but not enough to kill the animal. The part that remains behind hypertrophies. After waiting for a certain time, say six weeks or two months or longer, the remaining portion is bisected. This operation is repeated again and again, and a great many times the normal weight is taken away and absolutely no symptoms appear. During all this time the remaining portion of the thyroid is altered in the manner before described. I think that anything that bears upon these changes in the thyroid gland may prove hereafter of importance in the understanding of the function of the gland. Horsley has gone over the whole subject very thoroughly, and it is quite clear from his review that it is not possible to draw any definite conclusion as to the functions of the gland.

Dr. Putnam: With regard to the interesting remarks of Dr. Welch, we have recently had a patient with exophthalmic goitre on which Dr. Warren operated at my suggestion, removing about two-thirds of the gland. The part removed was afterward examined by Dr. Councilman, who found apparently the whole structure to be a dense homogeneous mass, and apparently the entire structure made up of what he called an adenomatous condition with high cubical epithelium without any colloid anywhere. It is interesting to note that if only a very small portion of such a diseased gland is left, it seems to be sufficient, as Dr. Welch has said, to prevent the peculiar cachexia from coming on.

Dr. Starr referred to the fact that the sheep's thyroid was sometimes found diseased. Both Dr. Burr, of the Brighton abattoir, the inspector there, who was kind enough to secure the glands for us, and also Parke, Davis & Co., found that large numbers of them were diseased. Dr. Burr found about one-third of them diseased and these were rejected.

Dr. Starr also referred to the resemblance between some of these cases and cases of nephritis in their outward appearance, and that is very striking. In two cases, to my knowledge, the diagnosis of nephritis was made, and one of

these I have already referred to. Then I know of two other cases where the changes were present in such form as to strongly suggest nephritis. They occured in elderly people. It is a subject for investigation whether some of the obese elderly people whom we see with more or less of this œdematous condition are not really subjects of myxœdema, and capable of being improved by thyroid treatment. Dr. Shattuck's case, I think, was a man somewhat advanced in years.

In my first case which I reported, the anæmia has been very constant. It has been very difficult to get her to have much of an appetite or to get rid of the very pale color which she presented. This is also a very interesting subject for investigation, whether the cause of the anæmia may not sometimes persist after the most striking myxœdematous conditions have passed away.

DR. STARR: The only word I have to say is in regard to the necessity of varying doses of the drug somewhat in accordance with the reaction of the patient. That fact has been illustrated in the history of my cases. In one case under the care of a nurse the dose was run up to 22 drops of the glycerin extract three times a day, or 66 drops daily, which is equivalent to two and a quarter glands in a day. This was not followed by any apparent ill-effect. The patient improved constantly. The large dose was given owing to a misunderstanding between the nurse and myself, and I reduced it immediately, when I discovered it, to the original dose of 10 drops three times a day, and that dose has been continued. It seems to me that there may be a possible idiosyncrasy in some of these patients. A fourth case, that I did not report, that is at present under treatment, began with 8 drops, and the patient is now taking 16 drops three times a day, without any decided change in her temperature. This seems to me to indicate that different individuals are differently susceptible to the thyroid extract, and in some cases, especially in Dr. Thompson's case, we did not begin to get any effect at all until the dose was run up to 18 drops of the extract three times a day. Referring to Dr. Shattuck's case, it would seem questionable whether it is proper to conclude that the thyroid extract would not do any good in such a case. It would be better to gradually increase the dose until you give pretty large doses—as large as you dare to give in connection with the case.

Recently in a discussion in Edinburgh on myxœdema, in the *Edinburgh Medical Journal* for May, 1893, out of a large number of cases reported in that journal—I think nearly seventy—there were but two cases of failure to relieve the patient by the use of this thyroid extract.