

for these defects are obvious, but often beyond reach. Overfeeding often causes insomnia, if it does not make the drowsiness of indigestion, causing heavy sleep in the early evening and miserable wakefulness afterward; and overstimulation, especially with tea and coffee, is often fatal to good sleep. These troubles are always correctable. A loaded large intestine often keeps a sensitive person awake for half the night, when a prompt evacuation by an enema, a glycerin suppository or a quick-acting saline, relieves the insomnia for the time completely. Foul air to breathe is a frequent cause of wakefulness; for this the remedy is fresh air in great abundance; and people do not take cold in well ventilated bedrooms.

When people are up and about they rarely become sleepy because their brains are tired. They often thus are sleepy, but this is mainly due to fatigue of the body or to some disarrangement of the digestive organs. Sleep comes normally with a normal and unabused body that has been fatigued a little and then been put to rest, and it is helped by cessation of active thinking, by darkness, by stillness, by mental tranquillity and a happy spirit. These things are first to be secured if possible; then the sleep comes as a natural consequence and, with hardly an exception, in sufficient amount. The sleep is secondary, not primary; these other things are primary and of great importance.

We must not count the hours of our slumber for fear it is not enough; that would break the charm of the influence and spoil the game. We may keep a record if we like, and it may be useful for our amusement and to help to fix the exact amount of sleep (which now no man knows) that, in our social zone, is physiologic for the man, woman and child of the present century with their varying orders of enlightenment and manifold grades of work and play. But this question can never be settled by the one poor slave of insomnia or by a thousand of them, and the question can wait. It profits each such unfortunate to neglect the race interests for his own, and to put his mind, in the calmest sincerity, to the task of saving himself from his thralldom—and the task need not be hard nor its benefits uncertain.

### THE TREATMENT OF THYROIDISM BY A SPECIFIC SERUM.\*

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As the atypical forms of exophthalmic goiter are common and often overlooked on account of the nomenclature, it would be more accurate and at the same time less confusing to designate the condition as hyperthyroidism or simply thyroidism. The cases can be classified somewhat in the order of frequency of their occurrence in the following groups:

1. Simple chronic exophthalmic goiter or thyroidism of moderate severity with all the symptoms which gave origin to the name.

2. Atypical thyroidism which includes many of the early cases and those with more or less irregular symptoms, such as absence of goiter or of exophthalmos or of both; or those which complain chiefly of gastrointestinal disturbance with pain.

3. The chronic toxic cases of thyroidism or severe forms of the disease with slight fever, which may be the terminal stage of the common atypical form, or show little or no exophthalmos or goiter from the outset.

4. The acute toxic thyroidism presenting a clinical picture which Dr. W. G. Thompson has aptly compared to that of malignant endocarditis. These patients show little or no exophthalmos and a small soft thyroid and suffer from fever which may be quite high.

5. The psychopathic or neuropathic cases of thyroidism, which are a comparatively rare but, from a therapeutic standpoint at least, an important group. They give symptoms which sooner or later indicate organic change in the central nervous system and are only relievable in the early stages of the disease.

#### SYMPTOMS OF THE DIFFERENT TYPES OF THYROIDISM.

The most characteristic symptoms are those dependent on the vasomotor and nervous disturbances. The cutaneous blushing and feeling of heat, the "nervousness," tremor and often insomnia and the tachycardia with a soft, weak pulse are quite constant in all cases.

The exophthalmos and goiter may each vary within such wide limits that they should be considered as much confirmatory as positive signs. The subjective feelings of general discomfort, weakness, throbbing of the heart, dyspnea and frequently abnormal thirst must be borne in mind, as they are generally the first to disappear in any given case if the serum therapy is to succeed, while the other symptoms usually improve very slowly.

The *atypical group* includes some of the incipient cases which show no goiter nor exophthalmos, but can be recognized by the vasomotor and nervous disturbances; and the cases with goiter of long standing which not infrequently develop marked thyroidism quite suddenly and have no exophthalmos; and, finally, the cases usually with no exophthalmos but some goiter, which at irregular intervals suffer from pain referred to the abdomen or thorax and evidently due to excessive fermentation of food. At these periods the pulse becomes very rapid, but otherwise the whole clinical picture is one of acute indigestion, and unless the goiter were noted in conjunction with the tachycardia the probable cause of the difficulty is easily overlooked.

The *chronic toxic* type of this disease presents no particular difficulties in diagnosis, except that I have seen it occur and give every evidence of ultimately proving fatal with a decreasing exophthalmos, goiter and pulse rate, the greatest danger seeming to lie in the exhausted and degenerated heart muscles. It is in these chronic cases that the bad secondary lesions of blood stasis and general anasarca dependent on the impaired cardiac action become so prominent, and unless there is a considerable goiter or exophthalmos the true cause of the trouble may not be detected.

The necessity of the recognition of *acute toxic thyroidism* needs considerable emphasis. Though the condition is quite uncommon, I believe that it is by no means so rare as is generally supposed, nor so difficult to recognize after attention is called to it. Judging from the few cases I have seen and known about, this particular condition must have a very high mortality, and yet I believe that of all the different types of exophthalmic goiter this is the most amenable to the serum treatment. The history of such a case usually covers a few weeks of the common vasomotor and nervous symptoms which more or less rapidly become worse and are accompanied by fever until the clinical picture, as Dr. W. G.

\* Read in the Section on Surgery and Anatomy of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906.

Thompson has described it, is almost exactly that of malignant endocarditis. There are the flushed and sunken cheeks, dry tongue, rapid labored breathing, tumultuous heart action, the nausea, vomiting and diarrhea of any toxic state and often thromboses or extravasations of blood in the neighborhood of the peripheral vessels. There may also be enlargement of the liver with pain and evidence of perihepatitis. The terminal stages are accompanied by delirium and finally coma, and as the urine may contain albumin or sugar the possible errors in diagnosis are evident. There is usually no exophthalmos, at least there was none in the few cases I have seen, and about the only characteristic feature among all the symptoms is the thyroid enlargement. Without some increase in size of this organ open to detection by sight or touch, I do not believe the correct diagnosis can be made except by the most careful exclusion of all other possible conditions and by the trial of the antithyroid serum. Fortunately the thyroid, though small, is generally at least palpable and this is a valuable guide.

The *psychopathic or neuropathic* forms of thyroidism constitute a small but important group of cases, and when there is taken into consideration the evident poisoning of the nervous system, which is so prominent a feature of this disorder, the only wonder is that pronounced disease of the brain or spinal cord or peripheral nerves does not more often supervene on the usual insomnia and general state of mental and nervous excitation. In looking over the histories and recalling the individuals it is quite possible to trace the progress of the psychic changes from the mild forms of alternating exaltation and depression through a melancholic stage to pronounced delusions with homicidal tendencies. Of two bad cases of this description which I have seen, one after recovery and the other in the intervals of the malady, could recall to memory all their disordered imaginings and acts and were more or less aware of their disordered character during the period in which they suffered from mental derangement, but they were controlled by overpowering impulses. In the beginning these patients ought to be curable; but after organic changes in the nervous system have occurred any great improvement is probably impossible.

#### A SPECIFIC SERUM.

The preliminary report on the treatment of exophthalmic goiter by a specific serum published in February, 1906,<sup>1</sup> contained statements which must now be somewhat modified. The serum is made by separating the nucleoproteids and thyroglobulin from the human thyroid gland and injecting these bodies into the peritoneal cavities of rabbits, dogs or sheep. The inoculations are continued at intervals of from five to six days for about six weeks and the animals are then bled from the carotid. The serum thus obtained presumably contains an antibody or cytotoxin which is specific in its action on the thyroidal epithelium and an antibody or antitoxin for the thyroglobulin which is believed to be the active and, in diseased states, the toxic product of the gland. I formerly attempted to draw some clinical distinction between the antitoxic and cytotoxic elements in the serum, but more extensive experience has shown this to be probably erroneous. Hence, as the antitoxin has at the best a more or less theoretic existence, while the cytotoxin can be demonstrated in the test tube and

all the clinical phenomena can be explained by the action of the cytotoxin which is certainly present, I shall mention only the cytotoxin.

Nevertheless, a serum made by excluding all the globulin and using only the nucleoproteids from a pathologic thyroid (exophthalmic) seems at least dangerous (Case 38), while neither the normal nor the pathologic serum made in the usual way by combining the nucleoproteids and thyroglobulin in the injections, has produced, at the worst, anything more than severe symptoms.

Early in our experience the need of some means of standardization of the different sera became apparent, and Dr. Beebe devised an agglutinin reaction by which an estimate could be made in any given sample of serum of its cytotoxin activity. The complicated details of this test will be found in his article; it is enough to state here that minute fragments of human thyroid gland suspended in salt solution can be agglutinated by a specific antithyroid serum in a manner quite similar to the agglutination of typhoid bacilli in the Widal reaction. The more pronounced and rapid is this antithyroid agglutination the more effect will the serum exhibit clinically, although, unfortunately, this is not a very reliable therapeutic guide. Nevertheless, it is of considerable assistance in judging of the presence or entire absence of any active constituent in the serum yielded by any particular animal. In other words, some animals were found to yield a serum which gave no agglutinin test and in such instances the effect on the patient was entirely negative. At the same time it was demonstrated that only a large gray buck of the Belgian hare species of rabbit could be at all relied on; white rabbits have been found to be of practically no use. The dog, which in respect to the quantity of serum obtainable would be a very desirable animal, produced a serum showing in the test tube slight activity; but the sheep was considerably better, although a great quantity of thyroids were required for the inoculations; and the material used for immunizing purposes is not inexhaustible even if its character which, I believe, is a very important factor in the results, is not considered. For the sake of brevity in description, I shall call the serum obtained by inoculating rabbits with the combined nucleoproteids and thyroglobulin of the pathologic thyroids of this disease, the pathologic serum. For our supply of these glands we have to thank Dr. Charles Mayo, of Rochester, Minn., who has kept us pretty well provided with the organs he has removed at operation.

By normal rabbit, dog or sheep serum is meant an antitoxic or antithyroidal serum obtained by inoculating these animals with the combined nucleoproteids and thyroglobulin separated from the normal human gland.

It is worth noting at the same time that the nucleoproteids in the pathologic gland are in far greater abundance than in the normal gland, and, as the character of these proteids may differ from the normal, so there may be some difference in the serum which can not be detected chemically, but which when tested clinically does produce a different result. At first the normal serum seemed entirely unsatisfactory and the pathologic serum appeared to be the only hope, but now, fortunately, the discrepancies between the effects of the two sera have not been found to be so great as was formerly believed. The normal serum generally shows a less active agglutinin reaction than the pathologic and those specimens of sera which may be considered of maximum ac-

1. THE JOURNAL A. M. A., Feb. 17, 1906.

tivity have only been obtained from one or two out of a great number of rabbits and then were made by inoculations from the pathologic gland. In the administration of the different sera a certain proportion of the patients hitherto have not reacted at all to the normal serum, or if they did the result has appeared harmful rather than beneficial, and a few patients have not improved unless given the very best grade of pathologic serum which can be obtained only from exceptional animals. There is much yet to be learned, however, both about the dosage of any given serum and the frequency of its administration, and I have hopes that the normal serum can be made effective in a much greater proportion of cases than it has been in the past. For if a change for the better can once be established in a patient's condition the normal serum and even the less active specimens of normal serum have generally proved capable of checking the more or less frequent exacerbations of thyroidism. On the other hand, the normal dog serum, although by the agglutinin test the least active of all the sera, has seemed in a few instances to have given the best results.

#### STATISTICS.

Our statistics include a total of 90 cases, of which 23 have been cured of all symptoms of thyroidism, 52 have been more or less improved and 11 have failed to improve (as yet) and four have died. Of the latter, one was an acute toxic case who immediately after the administration of the serum passed from an apparently moribund to a convalescent condition, but later, as the recovery was very slow, I operated on her with a fatal result. The second was in a chronic toxic state and, after improving under the administration of the serum, went home and some six weeks later suddenly dropped dead. At the autopsy there was found a pronounced status lymphaticus. The third case, one of the very acute toxic type, died, after improving in pulse, respiration and temperature, with every evidence of a hemorrhage into the respiratory center and, I think, in spite of the serum and not because of its administration; too little apparently was given to prevent the toxic extravasation of blood. The fourth patient was losing ground and died soon after the administration of the serum, which in this instance differed from the other sera in that it was made only from the nucleoproteids, and hence was a pure cytotoxin (Case 38).

In the 54 personally treated or supervised cases, 15 patients have been cured and 29 improved; six cases were failures and four deaths occurred. In many of the improved cases the patients, I think, are really cured, but as several months must elapse before the result can be determined they can not yet be passed on, and the same can be said of those which have apparently failed. I have several times been surprised to find patients whom I have dismissed as unbenefited after a short trial return a few weeks or months later showing considerable change for the better. I believe, therefore, that if even the slightest improvement in almost any one subjective or objective symptom can be detected within the first two weeks of treatment there is a fair prospect of ultimate cure. If a patient does not at first respond, different grades of sera should be tried, as well as sera from different species of animals, and, if possible, that which I have called the pathologic serum; by varying the dosage and intervals and noting the results much more success can be expected than under any other method of treatment.

#### PROGNOSIS.

In judging the probable results of the injections the most important factors to be considered are, first, the kind of thyroid possessed by the patient and, next, the duration of the disease and its clinical type. Histologically it is possible to recognize four fairly distinct types of gland; one of these shows increased vascularity, another simple hypertrophy with increase of colloid, and another great increase of epithelium, while in the fourth type there is a marked anatomic change with a loss of the greater part of the thyroid structure. The last represents the terminal stages of a chronic thyroidism and is probably hopeless from a therapeutic standpoint. Some clinical distinction can also be drawn between these different kinds of thyroids. Patients who have soft thyroids respond more easily to the serum than the patients with hard glands and, as a general rule, the smaller the organ the better is the prognosis. The large, hard glands with an irregular and nodular surface, especially if the superficial veins of the neck are numerous and dilated, are, I believe, incapable of much, if any, betterment and belong in the fourth histologic class.

As to the type of the disease, the acute toxic cases with fever seem to do the best with the least serum and at the same time they show the least reaction; and there also seems to be little difference whether the normal or pathologic serum is used, provided, only, it is known to possess considerable activity by the agglutinin test. Apparently this is because the thyroid has not had time to become greatly altered and is approximately of normal structure. I think, however, that the pathologic serum is a little better than the normal for these cases, but the difference is so slight that it is well within the limit of error in observation. But all the chronic forms of the disease respond better to the pathologic than they do to the normal serum and, although the distinction is far from being exact, the variation in the kind of serum required points to the probable condition of the thyroid. As a general rule the more nearly normal it is the better will the normal serum act.

The chronic toxic types of the disease with severe symptoms both of thyroidism and of the secondary lesions dependent on disturbed circulation present the worst prognosis and are the least amenable to this or, in fact, to any form of treatment. The thyroids of these patients are generally large and hard and of irregular outline and the veins of the neck numerous and dilated. As histologically there is very little of the original gland structure left in these cases, it is difficult to conceive of any benefit from a specific antithyroid serum. Nevertheless, one such patient (Case 34) for a time at least improved.

Of the atypical chronic class, those whose chief complaints have been disordered digestion accompanied by fermentation, abdominal or thoracic pain and bad tachycardia, have also generally proved therapeutic failures. The psychopathic and neuropathic cases must, of course, have a poor prognosis unless the original toxemia can be checked before organic nerve lesions have been produced.

#### THE REACTION TO INJECTIONS.

The reaction to the injection of the serum is of two distinct kinds. One is fortunately rare and occurs within about five minutes of the injection. There is a sudden dilatation of all the superficial capillaries; this "blush" may be succeeded by cyanosis and is accompanied by a feeling of distressing dyspnea and faintness with rapid

and feeble pulse; nausea and vomiting and diarrhea follow. These somewhat alarming symptoms pass off in an hour or sooner, if diffusible stimulants are administered, but the patient remains weak and uncomfortable for about a day.

The other reaction is fairly constant and, as a general rule, seems a necessary preliminary to the subsequent improvement. At the point of the injection there is immediately some burning sensation which is followed within a few hours by considerable swelling and erythema which may extend from the shoulder to the wrist when the injection is made in the arm, and continues for several days. This erysipeloid edema has sometimes been much more pronounced with the pathologic than with the normal serum, but the pathologic serum, though causing greater local redness and swelling, gives rise to less pain than the normal. Then at about the same time or some twelve hours after the injection there is generally some fever with increase in the tachycardia or irregular heart action and often diarrhea which may last a day or so. If another injection is given in the other arm before the subsidence of the swelling in the first arm the latter will be made worse and the constitutional symptoms intensified. Indeed, I believe by pushing the serum or gently increasing the dose there might be produced a fatal result. At all events, by repeating the dose too often the patient can be so exhausted that harm rather than good is the immediate consequence. In only a few instances have I seen this constitutional reaction postponed till the end of five or six days; and then it seemed to be connected with menstruation, which began in these particular patients about that time. For the serum, if administered just before or at the beginning of menstruation, may cause the ordinary reaction to be increased, and hence the date of the monthly period must always be ascertained and an injection postponed until the flow of blood has at least nearly ceased.

#### ASSIMILATION OF THE SERUM.

In the administration of the serum the patient should be put to bed for the first week; no restriction in diet is necessary beyond plain wholesome food without stimulants, except in the toxic cases and in patients with diarrhea who will need more or less careful feeding. Then 1 c.c. of a serum which has been proved fairly active by the agglutinin test is given hypodermically into the subcutaneous tissue in the back of the upper arm between the skin and muscular fascia. I have always selected this region, as it is accessible and free from veins and is loose enough to permit of considerable swelling without undue pain or danger of sloughing. The local reaction around the point of injection is best treated by a wet dressing of a 1 to 60 or 80 solution of carbolic acid in water and the constitutional reaction which appears a few hours later, by the administration, every three or four hours, of about three grains of iodid of potassium with about five minims of the tincture of strophanthus. The iodid of potassium has apparently a specific effect on the thyroidism and aids greatly in checking any rapid or irregular heart action. After all signs of the reaction have subsided there should be some improvement in the subjective symptoms. If an active pathologic serum has been employed the improvement occurs a little earlier and is a little more marked than with the normal serum. The restlessness, the feeling of discomfort, the insomnia, and the "thumping" of the heart subsides first and then the pulse becomes slightly slower and stronger. The best results are ob-

tained by giving from four to eight injections of 1 c.c. each every third or fourth day or sometimes at shorter intervals, but waiting each time until the previous reaction has subsided. Some degree of immunity at least to the constitutional reaction seems finally to become established. The acute toxic cases with fever, as stated previously, have not shown any reaction, but after the first day have improved steadily and quite rapidly so there seems no reasonable expectation of any disagreeable reaction in these cases. As they are the most dangerous type of the disease and very apt to prove fatal, especially if they show any degree of cerebral symptoms, the possibilities of the reaction should be disregarded and an active serum pushed by the administration at intervals of 24 hours of 1 c.c. at a dose which may be increased by one-half a c.c. each 24 hours until some noticeable improvement is obtained or until a half-dozen doses have been given.

All the other forms of the disease do not do so well, and some judgment is necessary to determine both the amount of the dose and the frequency of its repetition. About 1 c.c. of an active serum has proved a useful average quantity, but some variation may be required. A small dose of five or ten minims, especially if the serum is not very active, seems to stimulate the thyroid and to make the general condition appreciably worse; and a large dose of 2 or 3 c.c. has produced such alarming symptoms of rapid and irregular heart action that I believe a fatal result could thus be obtained. But within these limits a certain amount of experimentation is necessary; if the usual 1 c.c. dose does not prove beneficial after a couple of trials, 1.5 c.c. or 2 c.c. can next be employed. It will often be found that this change will cause less reaction and more benefit than decreasing the amount. Occasionally, however, .5 or .25 c.c. of very active serum yield the best results; or a serum from another species of animal can be tried. Then after giving some half-dozen injections at intervals of three or four days the subsequent repetitions have to be considered. Too frequent and too long continued treatment seems to do harm rather than good and to produce a condition of muscular weakness and prostration which is as bad or worse than that due to the primary thyroidism. Therefore, the serum should only be administered about once a week for three or four months and after that at longer intervals. Exacerbations of the thyroidism may appear from time to time, but always less and less frequently until finally the patient remains well. As a guide in the administration of the serum a vicious circle hypothesis for the etiology of the condition of thyroidism is of some service. All that is necessary is to break this circle by the inhibitive power of the serum on the thyroid epithelium and then to give no more injections than are demanded to keep it broken until a return to the normal equilibrium is obtained. This seems to require months, but the present indications are that it will occur in the majority of the cases, and I am beginning to have some hopes for even the chronic toxic cases. But a favorable outcome can not be hastened by increasing the quantity or frequency of the dose and, except in the acute toxic cases with fever, which alone are strikingly amenable to this treatment, there is nothing spectacular in the recovery. It is very slow and often intermittent.

The changes in the size and character of the thyroid perhaps better than anything else give an idea of what may be expected as to the rapidity of the general improvement. In the average case the circumference of

the neck has shrunken about one-quarter of an inch a month, at first and then remained stationary for some weeks and later again decreased until it reached the normal size in a perfect cure. A thyroid which is smooth and large and rather soft, in other words one which has undergone simple hypertrophy at first softens and diminishes in size quite perceptibly and rapidly, apparently from loss of colloid and congestion. Then there is a long period when very little shrinkage or change can be detected, except a slightly lowered position. During this time it becomes firmer and harder at menstruation or in slight exacerbations of the disorder which generally indicate a repetition of the injection. Later, or at the end of four or five months, it may once more soften and be gradually reduced to a normal size. On the other hand, a thyroid which is hard at the outset shows the first sign of improvement by becoming softer. I do not believe that the large glands, whether soft or hard, ever entirely disappear, for at least one of these patients who has remained entirely free from all symptoms, even the exophthalmos, for several months still has a quite perceptible fibrous goiter. Occasionally also after the administration of the serum patients complain of some soreness or pain in the region of the thyroid or throat but I have never under these conditions noted anything like active inflammation in the gland. Those who have recovered completely have required about six months of treatment and observation before all signs of the disease, or more accurately of overactivity of the thyroid, have disappeared. But if improvement in almost any one symptom, either subjective or objective, can be detected during the first week or two of treatment, even if the pulse or other signs do not respond, the case should not be given up immediately as hopeless. Slight variations can be made in the dosage of the serum or another kind of serum should be tried, bearing in mind that some patients, especially these with chronic toxic or severe symptoms of long duration and generally possessing hard or very vascular thyroids, will not respond at all to the normal serum, but will to the pathologic, or sometimes only to a particular pathologic serum of exceptional activity.

A few patients, especially those in middle life or older, who generally have small thyroids with slight or no exophthalmos and rather severe nervous symptoms, show a somewhat peculiar reaction. They improve in sleep and in the restless discomfort, and then if the injections are continued they become weaker and are made worse than ever. But if as soon as the initial improvement is noted, the injections are suspended and the patient put under the best hygienic outdoor conditions, they will gradually improve very much and at the end of two or three months, treatment can be resumed. It requires considerable judgment, coupled with some experience not to give such cases up as hopeless at the end of the first week, but many of the patients I believe will ultimately recover if patience is practiced along with the regulation rest treatment combined with the serum administered at long intervals. It is possible that some element of myxedema may here be involved and that thyroid feeding rather than antithyroid injections may be indicated.

The convalescence in these as in all the other rather severe forms of thyroidism is very like that from typhoid fever or any other exhausting disease, and is exceedingly slow and often interrupted by exacerbations of the process which should be met with another injection of the serum. But after a patient has once made good progress towards recovery and then shows signs of relapse it is

noticeable that almost any normal or pathologic serum, if administered without delay, will stop the symptoms. At the best, a moderate proportion of the chronic cases of this disease, especially those patients past middle age and with hard glands can not be benefited by either the normal or pathologic serum and for these, after a fair trial for at least a month, I think that surgery offers the best hope.

To correct an erroneous impression of this serum which seems to be prevalent, I must repeat that only in the rare acute cases can any quick results be expected and then there is a long period of convalescence before recovery is completed. The majority of the patients respond very slowly and several weeks may elapse before they are evidently improved. I believe, however, that with greater experience in the preparation of this peculiar remedy and with care and patience in its administration many of the chronic cases can finally be greatly benefited if not ultimately entirely cured.

The details of all the histories can be found in *The Transactions of the Association of American Physicians of 1906*. Only typical examples of two cases are given here and in addition two of the four fatal cases. In the other two fatal cases the patients had first been improved by the serum and the deaths took place long after the cessation of the injections; one from operation and subsequent very acute thyroidism, and the other apparently on account of a condition of status lymphaticus. Of the two fatal cases here given, the first (Case 37), I think, died from an unusually acute and severe form of the disease and not at all because of the administration of the serum.

The fatal ending in Case 38 might with some reason be ascribed to the effects of the serum, although it must be borne in mind that the disease was rather acute and severe and the patient had previously been losing ground. She received a serum made entirely from the nucleoproteids of a thyroid gland taken from a patient who had died of exophthalmic goiter. It differed from the other sera in not having any globulin combined with the nucleoproteids in the inoculations and so should serve as a warning for using great care in the administration of such a serum. I had several times previously given this same serum in much larger dosage (though at not quite such short intervals) and seemingly with benefit to others, but since this experience I have never dared to give a pure cytotoxin at less intervals than five days or a week, as the effect may be cumulative, and cause no symptoms for two or three days.

CASE 13.—J. McG., age 27, single, female, has been nervous for years, but first noted typical signs two years ago. She had been confined to bed for a month, with loss rather than gain in strength. There was a moderate-sized soft goiter; neck measured 14 inches in circumference; pulse was from 110 to 130 with throbbing heart and pulsating thorax.

*Treatment.*—January 12 to 22, she received in divided doses 5 c.c. of normal rabbit serum and 1 c.c. of pathologic serum with slow improvement in subjective symptoms and slightly lowered pulse rate. She left the hospital for home a little stronger, with less heart throbbing and with the neck  $\frac{3}{4}$  of an inch less in circumference. Pulse was 110. After this at intervals at first of four days and later of a week she received injections of different normal and pathologic sera, apparently improving more under the latter than the former and with more reaction. The pulse during March remained about 100 but of good quality. The thyroid was firmer and a little smaller, and she was able to resume work. The last injection was given April 14, and May 6 the pulse was 84, the thyroid small and again soft. The neck  $12\frac{1}{4}$  inches in circumference and the general condition normal. Since the first of March



she has been working steadily as an office nurse and stenographer and has been conscious of no physical disability. At present (August, 1906) there is no exophthalmos, no tremor, no abnormal subjective symptoms, the pulse is about 80 and though there is still a slight fullness of the neck, it is so slight that she can be reported as cured.

CASE. 32.—A. P., aged 29, single, Swedish domestic, entered the Presbyterian hospital under the care of Dr. W. G. Thompson, Dec. 11, 1905.

*Examination.*—She had a temperature of 102, pulse of 120, and respiration of 25 to the minute. There was a slight but perfectly plain, soft symmetrical goiter, precordial heave, marked pulsation in the cervical vessels and evident dyspnea, but no exophthalmos. She was very weak and tremulous, and had some nausea and diarrhea. She gave a history chiefly of this and "nervousness" and sleeplessness for only the past two weeks, and had therefore an acute type of the disease. The condition grew rapidly worse, and December 16 the temperature was 104, the pulse 136 and the respirations 36; the tongue was dry and hard, there were ecchymotic spots in various parts of the body and evident thrombosis in some of the veins of both legs. The picture was one of a severe and probably fatal toxemia.

*Treatment.*—December 16 and 17 she received 1 c.c. and on the 20th 2 c.c. of a very active pathologic serum and no other medication then or afterward. There was no appreciable reaction and after the second dose there was a very marked improvement in all the symptoms. December 22 the temperature, pulse and respiration were practically normal.

*Result.*—There ensued a steady though rather slow progress toward recovery. She was up and around the ward in the middle of January with no signs of the disease, except weakness, some anorexia and a soft thyroid which could be felt, but was not perceptible to sight. She left the hospital in February apparently well and when last seen on April 30 was on her way to make a visit in Sweden and presented no sign of disease.

CASE 37.—M. R., aged 18, single, female, first noted a soft goiter in October, 1905. For this she was given thyroid tablets. A month later she fainted in the gymnasium and symptoms of exophthalmic goiter were evident. After cessation of the thyroid feeding the thyroidism subsided but reappeared in December after a tonsillitis. During the next three months she became normal except for a small soft goiter. In April there were again slight signs of thyroidism but these disappeared until on May 4 a severe gastroenteritis occurred after some indiscretion in diet. On May 5 and 6, the signs of Graves' disease quite suddenly recurred and became severe with headache, great restlessness and tachycardia. On May 7 the pulse was counted at from 200 to 210. The respiration was labored and between 30 and 40 to the minute. On May 8, 9 and 10 she received 1 c.c. of a moderately active pathologic serum without any reaction except a slight and transient local redness. The heart action and respiration began to improve on May 9 and on May 11, the pulse was about 90 and good, and the breathing 23 to the minute. The intense headache on May 8 and the restlessness grew worse and on May 10 stupor developed and deepened into coma on May 13, and a right-sided, incomplete hemiplegia was then noted and this was soon followed by Cheyne-Stokes respiration. Breathing then stopped completely about 10.45 a. m., and as the pulse continued at from 110 to 120 but of good quality, artificial respiration was begun and continued until 5 p. m. The condition then became worse and the patient died. No autopsy was permitted.

*Remarks.*—I believe that the cause of death was a hemorrhage into the respiratory center and that the fatal ending took place not because of, but in spite of the serum. The administration of serum should have been begun earlier and pushed more vigorously. It is worth noting that just after respiration ceased at 11 a. m. on May 13, I gave 2 c.c. of an active normal serum in the preparation of which much thyroglobulin was used and hence, theoretically, the serum contained considerable antithyroglobulin. About two hours after its administration there was a noticeable improvement and natural respiration was possible for about 20 minutes. Respiration then again failed and could not be restored.

CASE 38.—A. G., aged 15, single, female, had suffered from typical symptoms of the disease, but with no exophthalmos for about four months.

*History.*—She entered the Presbyterian hospital in January, 1906, and received all the usual treatment with a steady, slow deterioration. She was given different specimens of serum without any change and reacted only to a very active pathologic serum from one particular rabbit. This reaction consisted in an exacerbation of all symptoms with fever, lasting for about twenty-four hours after the injection and followed by a brief improvement and almost immediately by a recurrence of all characteristic symptoms.

*Examination.*—May 20, 1906, the pulse varied from 130 to 150. There was a hard symmetrical goiter of moderate size. The neck measured 13 inches in circumference; the heart was dilated and overacting; the temperature ranged between 99 and 101 and the patient was so weak as to be unable to sit up in bed without fainting.

*Treatment.*—A very active pathologic serum made only from the nucleoproteids of the thyroid of a patient who had died of this disease, was employed. This was used as no other serum had shown the least effect (except one, and that only with transient benefit). At 10 a. m. and at 11 p. m. May 20, and at 10 p. m. May 21 she received 10 minims of this cytotoxin. There resulted only a slight local erythema until the morning of May 26 and then the temperature dropped from 100 to 96, the pulse began to rise rapidly from 130 to 180, and the patient became extremely restless, vomited frequently, and in the afternoon passed into a condition of stupor. On the previous day the goiter, which had been hard, began to soften and shrink, and during the afternoon of May 23 could only be made out as a small soft mass not much larger than the normal gland. The circumference of the neck in these two days decreased from 13 to 11¼ inches. Three c.c. of an active normal gland serum were then administered in the faint hope of averting the apparently fatal result, as the normal serum can be supposed to contain at least some antithyroglobulin. Some hours later the pulse fell from 180 to 120 but the stupor continued and the patient died at 11 p. m., May 23. With great difficulty, the house physician, Dr. Mason, obtained only the thyroid gland, which showed the following changes as described by Dr. James Ewing.

*Examination of Thyroid.*—The material received for examination consisted of a portion of one lobe of the thyroid removed 2 hours after death and measuring 2.5 × 3 cm. This tissue was strikingly light yellowish in color as though very fatty and anemic; the consistence was greatly reduced; no colloid could be detected except in a very few small cystic areas from 1 to 2 m.m. in diameter. Although in general very anemic, the tissue showed a few pin-point hemorrhages. The tissue was hardened in 80 per cent. alcohol, in Zenker's fluid, and in Orth's fluid. Sections showed the usual changes of an active toxic form of exophthalmic goiter. There were visible marked cellular hyperplasia, many new alveoli, a few miliary hemorrhages, extreme granular degeneration of tubule cells, and extensive exfoliation of these cells. Much of this exfoliation appears to be due to traumatism applied during removal of the gland. Staining by osmic acid after fixation in Muller-formol shows comparatively little fatty degeneration. The colloid is limited to a few large alveoli containing semifluid colloid mixed with many exfoliated cells. The only changes that seem possibly referable to action of the serum are the anemia and the acute degeneration of the cells. Otherwise, the changes do not differ from those seen in the average case of acute fatal exophthalmic goiter.

**Philippine Plants.**—The *Philippine Journal of Science* issues a supplement dated April 15, 1906, containing a systematic description, by E. D. Merrel, of the flora of the Lamao Forest Reserve, comprising 1,151 species in 611 genera from the musci, vascular cryptogams and flowering plants, but not the fungi algæ and lichens. Four hundred and eighty-five species are trees and 201 shrubs and woody plants. The monograph contains 142 pages, but it is admitted that a large number of species occurring in the district have not been catalogued.