

A contribution to the clinical study of exophthalmic goitre / by William Pepper.

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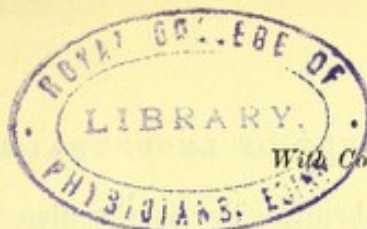
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A CONTRIBUTION TO THE CLINICAL STUDY OF EXOPHTHALMIC GOITRE.

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MANY names have been applied to the peculiar condition of disease characterized by rapid action of the heart, protrusion of the eyeballs, and enlargement of the thyroid gland. Most of them are open to the objection of not indicating definitely either the principal symptoms, or the essential character of the affection. It is on this account that I much prefer the name "Exophthalmic Goitre" to either that of Graves' disease, or of Basedow's disease, by one or the other of which it is most commonly described.

Exophthalmic goitre is not a distinct and specific disease in the sense that typhoid fever and acute croupous pneumonia are, but still it has a perfectly well-established claim to its place in our nosology. It is true that in well-marked cases there are certain features which are dependent on the anæmia which is so frequently present, and others which are due to the general neurasthenia that is usually attendant. But apart from these, there is the clearly defined group of symptoms first mentioned, which are so peculiar and so constantly associated in this disease as to clearly establish its separate identity, and to show that it is connected with some special morbid condition. A good idea of the cause of exophthalmic goitre in its aggravated form may be gathered from the following history.

CASE I.—R. T., a tall, spare woman of nervous temperament, when about 27 years of age, suffered a severe disappointment in a love affair. Soon afterwards she began to present symptoms of impaired nutrition, loss of color, emaciation, debility, etc. She became much more highly nervous and excitable. At the same time the action of the heart became rapid and excited, and the thyroid gland enlarged. There was marked irregularity of menstruation. There was a marked anæmic bellows murmur over the base of the heart. The carotid arteries pulsated violently, and were the seat of a strong

thrill and aneurismal bruit. There was also pulsation of the thyroid gland, with thrill and murmur. Under the use of iron, digitalis and tonics, she improved so much that she discontinued treatment. Before long she suffered from a return of all the above symptoms in an aggravated form, and, in addition, there was prominence of the eyeballs; but again she found relief, and during the next five years she had several similar relapses, though each time the symptoms were more advanced. The degree of enlargement of the thyroid varied considerably, being extremely marked at times. Both lobes were equally affected.

The prominence of the eyeballs also varied much from time to time; during several of the attacks, being so extreme that the eyelids would not close over them. On several occasions there was slight conjunctivitis, always easily relieved. The attacks were always marked by a great increase in her debility and nervous excitability. The heart's action never regained its normal state, but continued rapid and easily excited by slight causes. At times the pulse was exceedingly rapid, 130 to 150 in the minute. After several such attacks her general health became permanently impaired. The bellows murmur became harsher in character. The area of cardiac dulness increased, and the sounds of the heart became sharp and weak, indicating the development of dilatation with slight mitral insufficiency. Œdema of the feet and other evidences of impaired circulation now appeared. In the spring of 1864 she again came under my observation, and in far worse condition than at any previous time. She had been suffering greatly for some time, and had for several years used stimulants freely. The heart's action was very rapid and feeble, and there was violent pulsation in the cervical vessels. The thyroid gland had diminished somewhat in size, but was hard and inelastic. The eyeballs still protruded greatly; there was no inflammation of the cornea or conjunctiva. There were œdema and ascites, and a few days later jaundice appeared and was soon followed by death.

At the post-mortem examination, the heart was much enlarged, and its cavities, especially the right ventricle, extremely dilated; both the mitral and the tricuspid leaflets presented thickening along their edges and were slightly insufficient. The thyroid gland was still enlarged; its tissue was dense and very hard from interstitial fibroid change. It was infiltrated with serum, but there was no cystic degeneration. The cervical ganglia of the sympathetic nerve were not examined.

It may be observed, in the first place, that in the above case the subject was a woman, and experience shows that exophthalmic

goitre occurs more frequently in the female sex. Of 38 fully developed and undoubted cases of which I have preserved more or less full notes, 31 occurred in females, and 7 in males; and the same preponderance of females obtained in over 30 more or less typical cases which I have not used in the preparation of this sketch.¹ The disease is more frequent in early adult life, but it has been met with at all ages. The earliest period at which I have met with a fully developed case was at ten years, and on the other hand I have seen several instances of it at the age of fifty-five, sixty, and even later.

Before proceeding to consider more fully the causes, it is desirable to have a definite idea as to the pathological condition present in this affection. It will be seen at once that the leading symptoms are dependent upon a disturbance of the action of the heart, and of the carotid arteries with their branches. The disturbance of the heart itself is nearly always one of the most marked symptoms, but it must be clearly understood that the other symptoms cannot be directly traced to this disturbance of cardiac action. Exophthalmic goitre may exist in its most intense degree without any organic changes in the heart. It is indeed true, that when the disease has been long continued, evidences of serious impairment of the heart's function often appear; but these are usually to be explained by degeneration of the walls of the heart, with dilatation of its cavities consequent upon prolonged anæmia and malnutrition. Again, while it is further true that exophthalmic goitre sometimes appears in patients who are subject to organic disease of the heart, there is always in such cases an additional element of morbid vascular action, while innumerable cases of organic heart disease of all types occur without the presence of the characteristic symptoms of exophthalmic goitre. Since, then, organic heart disease is either an accidental coincidence or a late complication, it is evident that the intense functional disturbance of the heart, which is so constant and so early a symptom, must be due to some morbid condition of the ganglia and plexuses of nerves controlling its action.

The only satisfactory explanation of the remarkable symptoms connected with the cervical vessels and thyroid gland and the eye-balls, is to be found likewise in a morbid state of the vaso-motor nerves controlling the carotid trunks and their branches. The thyroid arteries are greatly dilated, and the enlargement of the gland which takes place is found to depend anatomically upon extreme

¹ These cases have occurred in private practice, or at the medical dispensary service of the University of Pennsylvania. The latter cases were recorded by Dr. R. G. Curtin.

dilatation of the vessels in its substance, together with infiltration with serum and some hyperplasia of the gland tissue. In like manner the protrusion of the eyeballs, about which so many theories have been advanced, is now recognized as being due to swelling of the post-ocular intraorbital fat, from hyperæmia with œdema and sometimes with hyperplasia.

Accordingly the view which is now almost universally held, with regard to the explanation of the symptoms of exophthalmic goitre, is that there is a morbid condition of the cervical sympathetic ganglia and the cardiac plexus of nerves.

Attempts have been made to show that this morbid condition is really connected with grave anatomical lesions of the nervous ganglia involved, and a few cases have been recorded by reliable observers, where such lesions have been actually detected. It may, however, safely be affirmed, that while such grave lesions undoubtedly occur, and may serve as a cause of this peculiar affection, it is by no means necessary that they should exist for it to be intensely developed. Examinations of undoubted cases by other competent observers have failed to reveal any lesions of these parts. I have myself had the opportunity of making a post-mortem examination of three cases. In one the cervical ganglia were examined carefully and found to be healthy. In one they appeared healthy on superficial examination, but were not examined microscopically. In one they presented slight increase of pigmentation of the nerve cells, and some apparent increase of interstitial fibrillar tissue.

The frequency with which cases of the most aggravated type recover entirely is destructive to the view that actual organic lesions of the nervous ganglia are necessarily or even frequently present.

Finally all analogies with other parts of the nervous system would favor the view that a state of reduced and exhausted activity of these ganglia might fully account for the striking symptoms produced. I believe myself that in the great majority of cases the condition is of this latter kind; and while in some instances exophthalmic goitre is due to organic disease of the nervous system, it is more frequently only a modality of neurasthenia, that is to say, a state of exhaustion of nervous power with irritability, specially localized upon the cardio-carotidean tract. We are familiar with other instances where such a morbid condition of nervous system affects special localities, but in none is the localization more definite or the symptoms more characteristic than in the affection we are considering.

In returning to examine more at length the causes of exophthalmic goitre, we will be struck with the fact that they seem to be exclusively such as are apt to produce depression and exhaustion of the

nervous system, if not actually organic disease. In most instances there will further be found a previous state of nervous susceptibility and weakness, constituting the familiar nervous temperament which must be regarded as a predisposing cause. Not rarely the exciting cause will be found to be some sudden and severe shock to the emotional nervous system. Thus I have known in several instances the initial symptoms to date from a sudden and severe fright; from disappointed affections; from severe and wearing anxiety in connection with marriage; from protracted strain in supporting severe reverses of fortune, etc. etc.

In other instances the causes are of a more directly exhausting character, as for example, rapid, repeated, and frequent pregnancies, exhausting lactation, profuse and repeated hemorrhages, etc.; of all of which I have seen several instances. In addition to these well recognized causes, I have met with several cases in which, conjoined with interference with nutrition and exhausting discharges, there was a marked element of prolonged reflex irritation, which incline me to believe that the peculiar morbid state of the nervous centres affected in this disease may be induced both directly through the influence of various depressing causes, and also indirectly through the exhausting effects of severe and long-continued reflex irritation. The two following cases may be cited in illustration of this point, as well as on account of the interesting symptoms and course which they pursue.

CASE II. *Chronic Intestinal Catarrh; Extreme Nervous Disturbances; Anæmia; Exophthalmic Goitre with rapid Action of Heart; Rapid Loss and Gain of Flesh; Recovery.*—Miss A., æt. 20, although generally healthy, had always been nervous. She had always been used to eating unwholesome food, candy, cake, sugar, with quantities of tea and coffee, and insufficient food of plain nourishing character. In the summer of 1876 she attended camp meeting, was subjected to great nervous excitement, and was much exposed at same time. Severe diarrhœa resulted and was not checked. No attention was paid to diet or to avoidance of exposure. The stools were frequent; twelve to twenty on some days, thin, whitish, and fetid. This condition became chronic. Soon afterwards, in September, 1876, she noticed palpitation of the heart, with dyspnœa, and enlargement of the thyroid gland. She grew weak, and lost flesh rapidly. She became extremely nervous, and very lachrymose, so that she wept on the slightest cause. Her temper was not particularly changed, except that she became more petulant. Frequently, an ordinary remark quietly addressed to her would cause a burst of tears. By Christmas, 1876, exophthalmos began, and rapidly increased until her eyes

were very prominent. She continued in about this same condition, despite medical treatment, until October 20, 1877, when I first saw her. The diarrhœa had persisted with the same character of stools. Menstruation had ceased five months previously. She had lost much flesh, her weight being scarcely ninety pounds, whereas fourteen months previously it had been one hundred and forty pounds. Her appearance was shocking on account of the extreme exophthalmos and the very large goitre. She was unable to close the eyelids. The action of the heart was constantly rapid, and frequently it rose as high as 175 to 185. There was a soft anæmic cardiac murmur over the base. The thyroid gland pulsated very strongly, and was the seat of a strong diffused thrill, and of a loud, shrill murmur. When the stethoscope was applied over the temporal fossæ, to the anterior part of the parietal bone on either side, a distinct high-pitched murmur was audible.

She was immediately placed on the use of skimmed milk (of which she soon drank two quarts daily) with stale bread, and two soft-boiled eggs daily. Nitrate of silver with opium in pill form were given, and fifteen drops of tincture of digitalis thrice daily. The diarrhœa was soon controlled, after which dialyzed iron was substituted for the silver and opium, and bromide of potassium gr. viij was given in combination with the digitalis. All of her symptoms improved rapidly, and she gained flesh quickly. She soon wearied of the restricted diet, and about the middle of December she stopped all treatment, and returned to the use of a mixed diet. Diarrhœa soon returned and she rapidly lost the flesh she had gained; and all of her symptoms, the cardiac excitement, goitre, and proptosis again increased. On February 7, 1878, I saw her again and directed a return to a similar diet, and to the use of silver and opium for a time, to be followed later by digitalis and dialyzed iron. The diarrhœa was again checked readily, and rapid improvement commenced immediately and continued without any interruption. The dialyzed iron was increased gradually from ten to forty drops, and its effects were definite and gratifying. If suspended for even two or three days she asserted that she missed its tonic influence. Her gain in weight was as follows: from Feb. 7 to March 19 (forty days), from one hundred to one hundred and twenty-five lbs.; from March 19 to June 20 (ninety-three days) from one hundred and twenty-five to one hundred and forty-two (seventeen lbs.). She seemed to make blood and flesh so rapidly that, at that time, the dose of dialyzed iron was lessened to ten drops. She increased to one hundred and fifty pounds in the course of six weeks, having gained sixty pounds in all within a period of nine months. There

was a correspondingly rapid improvement in the nervous symptoms. She ceased to be lachrymose, and lost to a great extent the morbidly excitable, impressionable character she had before presented. Her color became healthy. The prominence of the eyes disappeared almost entirely by June 20, 1878, and when I last saw her, Dec. 14, 1878, it had not returned. The enlargement of the thyroid gland had also gone. By June, no hæmic murmur could any longer be heard over heart, neck, or temple; and all pulsation, thrill, and murmur had gone from the region of the thyroid gland. Menstruation returned in May, 1878, after an absence of fifteen months, and subsequently continued regularly. The pulse still continued somewhat too rapid, and was readily accelerated by effort or excitement. Up to December, 1878, she still continued a diet chiefly of milk and farinacea, with but little meat, and no tea or coffee.

CASE III. *Chronic Intestinal Catarrh; Anæmia; Exophthalmic Goitre; Rapid Action of Heart; Repeated Epistaxis; Rapid and Extreme Emaciation; Recovery.*—Mrs. — was sent to me in August, 1878, by Dr. Birnie, of Maryland. She was about 22 or 23 years old, and had recently been married. From 1870 to 1873 she resided in an unhealthy locality, and there began to have occasional spells of feverishness which soon became accompanied by diarrhœa. These attacks would usually last three or four days at a time. There does not seem to have been any fully developed malaria. After returning to her home, which was in a healthy mountainous district, she continued to have occasional spells of diarrhœa with feverishness. She did not, however, lose much flesh or strength. In spring of 1876, enlargement of the thyroid gland and prominence of the eyeballs was first noticed. At that time she weighed one hundred and four pounds. In June, 1877, a severe attack of diarrhœa began and continued until the following October. During this time she rapidly lost weight until she reached sixty-eight pounds. The enlargement of the thyroid gland and the exophthalmos also increased rapidly and attained proportions as great as at any subsequent period. After the cessation of the diarrhœa in October, 1877, she began to gain weight, and during the ensuing winter reached one hundred and eight pounds. There was, however, no improvement in the condition of the eyeballs or of the thyroid gland. She continued weak also, and with marked excitement of heart's action.

Diarrhœa returned in June, 1878, but for some time previously she had been losing in strength and probably in flesh. By the time I first saw her in August she weighed less than seventy pounds. The character of the discharges in all the attacks of diarrhœa was similar; thin and watery, with particles of undigested food, but

without either blood or pseudo-membrane. There has been very frequent complaint of pain at the lower part of the abdomen. In addition to the above symptoms, there have been for several years quite frequent and copious hemorrhages from the nose. Menstruation has always been scanty and irregular, and lately has been absent entirely for a number of months; it occurred twice in 1877, and three times in 1878. During the summer of 1878, œdema of the ankles frequently appeared towards evening.

On examination in August, 1878, her condition appeared very alarming. She was extremely emaciated and feeble. The immense protrusion of the eyeballs, and the enormous enlargement of the thyroid gland gave her a shocking appearance. She was unable to cover the corneæ, but no inflammation had occurred. Emaciation was extreme; her weight did not reach seventy pounds, and the skin and mucous membranes were bloodless and slightly sallow. The tongue was tremulous, red, and smooth. Appetite was capricious and somewhat abnormal. The bowels were moved frequently, from four to eight times in twenty-four hours, the character as above given. Respirations were frequent and increased markedly by the slightest exertion. The pulse was very small, weak, and frequent; in the sitting posture, it averaged 140. Exertion brought on severe palpitation. The heart sounds were sharp and feeble, with strong hæmic murmurs at the base, and along the pulmonary artery. The carotids throbbed excessively, and the thyroid was the seat of strong diffused pulsation and thrill, with loud humming murmur on auscultation. No venous hum could be heard on ausculting the temples. There had been frequent epistaxis of late. The feet and ankles were cedematous. The urine was pale, of low sp. gr. 1009-1010, but contained no albumen.

She had already used iron, tonics, bismuth, and ergot. I now directed her to use an exclusive diet of milk and arrowroot, to have absolute rest, and to take a pill of nitrate of silver, gr. $\frac{1}{5}$, with powdered opium gr. $\frac{1}{4}$ thrice daily. She went directly to the sea-shore, but the climate did not suit her; and although she had gained somewhat when I next saw her in September, the diarrhœa and attacks of epistaxis continued. She was then directed to remain in bed for several weeks, the diet was restricted to light broths, milk and water, and arrowroot, and pills of sugar of lead and opium were given. The diarrhœa was soon checked; she was thoroughly anointed daily with oil, and her diet was cautiously enlarged. In consequence of febrile symptoms with a tendency to night sweats, she took for a time six grains of quinia sulphate daily in divided doses. On September 25th, there was such marked im-

provement that she returned home to Baltimore, and resumed the use of nitrate of silver and opium, as the stools, although solid, were too frequent. Dialyzed iron was also given, at first in doses of eight drops three times a day. The nitrate of silver was continued for more than two months, with occasional short interruptions. The iron was increased to thirty drops three times a day, and was continued until May 1, 1879. The diet was rigidly restricted for several months, and then cautiously enlarged.

Improvement was steady and rapid. Menstruation became regular in March, 1879. By February her weight had gone up to one hundred and two. The prominence of the eyeballs had almost disappeared, and there was marked decrease in the enlargement of the thyroid. The heart's action was still too rapid and readily accelerated. Epistaxis became very rare. Since then, until the present time, May, 1879, the improvement has continued. There is still a tendency to rather frequent movement of the bowels from trifling causes, and for this she has again resumed nitrate of silver and a more restricted diet. There has been still further reduction in the size of the thyroid. She is now bright and active, and would not be recognized by any one who had first seen her in August, 1878.

It will be seen from the above cases, and from what has been said, that anæmia is a very frequent attendant on this disease. The fact has long been recognized that, in all conditions of neurasthenia, anæmia, both general and of the nervous centres, is a most important factor. This certainly holds true in regard to exophthalmic goitre. In many cases a well-marked state of anæmia is produced before the characteristic symptoms appear, and it may be safely regarded as a powerful predisposing cause. When the anæmia has become marked, and a state of general susceptibility and weakness has been developed, it needs only some special circumstance or some special pre-existing vulnerability to localize the morbid action upon the ganglia and nerves involved in exophthalmic goitre, in order that the symptoms of this affection may be induced. In some cases, pronounced anæmia does not precede, but follows the characteristic symptoms, but it is then also due to the continued operation of the depressing causes. It may be concluded that anæmia is one of the most constant conditions in exophthalmic goitre, though among my notes of thirty-eight cases, I find twelve in which no positive anæmia existed. There does not seem to be any organic lesion of the blood-making tissues, such as the spleen, lymphatic glands, or marrow of bones. In those cases where I have examined the blood, there has been no increase in the number of white corpuscles, but merely a marked decrease in the red globules; though I believe the

accurate enumeration of the blood corpuscles in this disease is still a desideratum.

The three chief symptoms, as already mentioned, will repay more minute study. It is true that, in some cases, one or the other of them, as either the disturbance of the heart's action, the enlargement of the thyroid gland, or the protrusion of the eyeballs may be wanting; but it is certainly rare in well-developed cases, for any one of them to be entirely absent, although they present frequent variations in degree of intensity. The disturbance of the heart's action is the most constant, and is usually the first to appear. The pulse becomes unaccountably rapid. Sometimes the patient is scarcely conscious of this, while with others there is a sense of præcordial distress, with at times severe spells of palpitation and tumultuous action. I have occasionally known the pulse to have continued rapid, presenting unusual resistance to the controlling influence of digitalis and other remedies, for a long period before the other symptoms ensued. The pulse rate usually rises to 120 and over, and in severe cases I have known it 150, 160, and even 180, and this for considerable periods of time together. The heart's sounds are usually sharp and clear, and later are apt to become feeble, even if valvular disease is absent; and a murmur or murmurs will usually be heard at some period of the case. These are generally soft and blowing in character, systolic in time, and located over the base of the heart, extending along the great vessels. In some cases they may be due to irregular muscular action, but undoubtedly are for the most part anæmic in character. It is perhaps due to the impaired nutrition usually attending, that such intense and prolonged excitement of the heart's action does not more frequently become associated with hypertrophy. But the symptoms may persist for a considerable time without such a result; and usually it is only when advanced malnutrition and anæmia have gravely impaired the tenacity of the heart's muscle that passive dilatation occurs. In connection with the anæmic murmurs referred to over the heart, I would call attention to the unusual points at which such murmurs may be heard in these cases. Russell speaks of strong bruits over the cervical vertebræ. I have heard them there myself, and in Case II. have described the loud murmurs which were audible over the temporal fossæ, as well as over the vertex. The murmur which is frequently heard over the thyroid gland is diffused and prolonged, but may be quite high pitched and shrill. I may here allude to the violent throbbing often observed in the arteries and veins. This is especially marked in the tortuous and enlarged thyroid vessels and in the carotids and jugulars, but it is not rarely met with, also, in the abdominal aorta, where it may be intense

and cause serious distress. A distinct thrill may often be felt over the throbbing vessels, and much more rarely over the heart itself. Its presence is very easily accounted for, by the violent excitement of vascular action and by the altered condition of the blood. As would be expected it is most constant and intense over the thyroid gland. These same conditions quite often lead to strong and annoying subjective sensations of sound in the head, resembling the beating of hammers, the dashing of water, the ringing of bells, or loud whizzing or purring.

The enlargement of the thyroid, the second of the characteristic symptoms of this disease, is also very constant. It appears early and usually attains considerable magnitude in marked cases. I have more frequently observed both the lobes to be equally enlarged, though in some cases the enlargement is not symmetrical. It will be noted that the enlargement of the thyroid gland varies remarkably from time to time. In females it is not unusual for it to increase at or before the menstrual period. At such times I have known sudden and abrupt increase in the enlargement to occur in a single hour, even causing great distress to the patient. As a rule, a sense of fullness and weight is all that is complained of, but at times there may be an occasional feeling of oppression with some difficulty in deglutition. In but one case have I known pain in the thyroid to be complained of. The enlarged gland pulsates distinctly, and when grasped by the hand, we find that this is attended with distinct distension of its substance. In addition to the pulsation, there are also a marked thrill and a distinct murmur. The thyroid enlargement varies with the intensity of the general symptoms. At different periods of the same case, it may vary from a slight degree to a swelling so enormous as to cause great deformity. As the symptoms subside and the case approaches a favorable conclusion, it diminishes and even disappears entirely. The gland is at first painless, elastic, and soft, though at times it may be extremely tense. In long-continued cases of unfavorable character, it may diminish in size, but become hard, dense, and resisting from a fibroid change. It is not unusual for a certain amount of serous infiltration of its tissue to occur; but any cystic degeneration, such as is met with in some other conditions of this gland, is of rare occurrence in this disease. There is no relation between this thyroid enlargement and true goitre. Where the latter disease is endemic and frequent, exophthalmic goitre is no more liable to occur than elsewhere. It is important to note this distinction, as I have met with not a few cases of true goitre, associated with some disturbance of the heart, which has caused some difficulty in diagnosis.

The protrusion of the eyeballs is one of the most important symptoms, especially in a diagnostic point of view. The increased action of the heart and the thyroid enlargement usually become marked before the exophthalmos reaches a high degree, but von Graefe pointed out the fact that if a patient, even in the early stages, be requested to look downward, the upper eyelid will be seen not to follow perfectly the ball, so that a segment of the cornea and a part of the sclera will remain visible. This test may be safely applied in suspected or doubtful cases in the early stages. I have already mentioned the anatomical changes (hyperæmia, œdema, and sometimes hyperplasia of the intra-orbital fat) which produce the protrusion of the eyeballs. In severe cases this protrusion becomes so marked that the patient is unable to close the lids. Inflammation of the conjunctiva is by no means common, considering the long continuance of such exposure of the globe of the eye. I have seen several mild attacks of this trouble, and there are cases on record in which serious inflammation with ulceration of the cornea has occurred. The vision is not impaired. It will be very frequently (14 in 27 cases) observed that the pupils are dilated, though they still respond to light. When the protrusion of the eyeballs reaches an intense degree, so that the sclerotic, with its enlarged vessels, is widely exposed; and when the enormous enlargement of the thyroid, with the fulness and violent pulsation of the cervical vessels causes extreme disfigurement of the neck; while the anæmic and emaciated appearance of the patient brings into bolder relief these conditions, the physiognomy of this disease is one of the most striking and hideous that can be conceived.

There are a few other symptoms which require mention. Menstrual disorders are among the most frequent of these. It would also appear that they occasionally act as the cause of exophthalmic goitre, since it seems probable that the prolonged reflex irritation from a diseased uterus, acting upon a system predisposed, may serve as the exciting cause. More frequently by far, however, the uterine disturbances appear as symptoms and are dependent upon the anæmia and neurasthenia. In more than one-half of my cases, irregularity or absence of menstruation occurred, and this was especially marked in the cases I have here cited. In one instance the menses were absent for three months before the attack, but more frequently, as in Cases II. and III., amenorrhœa does not appear until marked anæmia has been developed. As long as menstruation continues, the enlargement of the thyroid and the exophthalmos may sometimes be noted to increase as each period approaches, and to again subside after the menstrual flow begins. So, too, when amenorrhœa has existed for

some time, I have noted a marked reduction in the size of the thyroid to attend the reappearance of the menses.

The *nervous symptoms* play an important part in the course of this disease. Those which are most marked are the extreme mobility and susceptibility of the nervous system. The patients become extremely irritable and frequently capricious or perverse: sometimes, as in Case II., they are excessively and ludicrously lachrymose, or they present fits of hysterical excitement, alternating with brooding depression of spirits. These conditions are always aggravated by fatigue or excitement. Vertigo and pains in the head are both occasionally complained of; the former was a marked symptom in no less than 19 out of 38 cases. Allusion has already been made to the subjective sounds, which are similar to those experienced by other anæmic patients, and are frequently observed in this disease. In some cases, excessive sensations of heat of the surface of the body are complained of, so that the patient can with difficulty bear even light clothing by day or by night. Another symptom, which may be referred to the influence of the vaso-motor nervous system, is the occurrence of profuse and sometimes irregularly distributed sweating of the surface, with or without flushing. The disturbance of the heart's action has been carefully described, but in a considerable proportion of my cases dyspnœa was also present in a marked degree. It is usually of a paroxysmal character and attends the spells of palpitation of the heart. More or less shortness of breath may, however, be constantly caused by exertion. It is probable that the dyspnœa is in part due to pressure of the enlarged thyroid upon the larynx and trachea.

Disorders of digestion are very frequent and of the utmost importance in this disease. Dysphagia occasionally occurs; of 38 cases, 8 complained of it in a marked degree, and 2 others in a less degree. I would, however, call especial attention to the fact that in some instances the starting point of the disease appears to be some severe irritation of the gastro-intestinal mucous membrane. I have seen exophthalmic goitre rapidly follow a severe spell of gastro-hepatic catarrh with much vomiting; and I have cited Cases II. and III. especially on account of the evident connection between the chronic intestinal catarrh and the subsequent development of exophthalmic goitre. The interference with nutrition, so caused, undoubtedly predisposes to this affection, and the reflex irritation from the inflamed mucous membrane probably aids in exciting it.

It seems to me that uterine disease of certain sorts probably occupies a similar relation in some cases.

Besides occasionally serving as a predisposing cause, gastro-intes-

tinal irritation is a very frequent complication, and aggravates the affection considerably. In much more than one-half of my cases, dyspeptic disturbances of greater or less severity existed. The appetite is capricious, at times poor, at others craving and unhealthy. The stools frequently indicate a deficiency of bile, and there are often other evidences that—as might be expected from the state of the central circulation—the liver is congested; this is especially apt to be severe when dilatation of the heart has been developed. In cases accompanied with extreme anæmia, there is of course danger of fatty degeneration. In the first case I have here cited, the extreme degree of this change presented by the liver was probably chiefly due to the anæmia, and only in part, if at all, to the use of stimulants. It is not rare for jaundice to make its appearance towards the close of fatal cases.

Among the most interesting and remarkable symptoms connected with the processes of nutrition and assimilation, is the rapid variation in weight presented by some patients with this affection, when accompanied with chronic gastro-intestinal catarrh. Russell (*Med. Times and Gaz.*, Sept. 2, 1876, p. 251) alludes briefly to this peculiarity; but it is better illustrated by my Cases II. and III., to which the reader is referred.

The hemorrhages and dropsies, which are of frequent occurrence, are usually due to a watery state of the blood. Epistaxis is the most frequent form of hemorrhage; in Case III. it was of such rapid recurrence and large extent as to constitute a source of danger. Edema of the feet is the usual form in which dropsy appears, here as in other anæmic states. It is only when the power of the heart has failed from fatty degeneration or dilatation, and when the alterations of the blood have become very marked, that general anasarca or internal serous effusions are observed. The urine very rarely contains albumen.

It is not necessary to dwell upon the diagnosis of this disease. It is only in the early stage, when von Graefe's mode of detecting slight protrusion of the eyeballs will be of signal service; or in cases of true goitre in anæmic subjects with rapid action of the heart, that any difficulty can be experienced.

The prognosis is, as a rule, favorable, unless dilatation of the heart with or without degeneration of its muscle, has supervened. In the latter case, the existence of marked dyspnœa, of pulmonary congestion, of general venous stasis, or of extensive dropsical effusions would be apt to usher in the fatal stage. Repeated hemorrhages, extreme anæmia, rapid loss of flesh, intractable diarrhœa, or jaundice, are also grave symptoms as indicating extreme depravation of blood

and interference with important functions, but still they are by no means necessarily of fatal omen, and the cases here given may serve as illustrations of the extent to which they may be present and yet a favorable result be secured.

In 38 cases the result was unknown in 2; 4 died, of whom one was never under treatment, and had organic heart disease; 12 were cured, and 20 were relieved, and improved very markedly by treatment.

The prognosis must, however, be very guarded as to the probable duration of the symptoms. Under any curative treatment, the affection is apt to be prolonged for many months; and it is only when we can succeed in detecting and removing all predisposing or exciting causes that may aid in maintaining it, and in placing the patient under the most favorable hygienic conditions, that a more rapid cure can be effected. Even after the subsidence of the exophthalmos and of the thyroid swelling, and when the general symptoms are greatly improved, the rapid action of the heart, with tendency to attacks of palpitation on small provocation, is apt to continue for an indefinite time.

Treatment.—The results of treatment in exophthalmic goitre are usually spoken of as uncertain and unsatisfactory, and some authors, as Niemeyer, express doubts as to whether its course is modified by remedies. I am satisfied that this is the consequence of the adoption of special modes of treatment, based upon some partial theory of the disease, and employed with but little reference to the peculiarities of the individual case.

There are, indeed, certain remedies which would appear to be almost always indicated, because the conditions they are designed to remove are constantly present. Among these is digitalis, which is the most appropriate and useful remedy for the disturbance of cardiac action observed in this affection. This drug may, therefore, be used with advantage in most cases; but there are a few points of caution that may merit mention. Occasionally digitalis disagrees positively with the stomach, whether given in pill, tincture, or infusion; and, by the increased gastric irritation produced, really aids in maintaining sympathetic palpitation of the heart. This remark applies to the treatment of exophthalmic goitre as well as of all forms of palpitation. Digitalin will occasionally do better than digitalis in such cases; but bromide of potassium with belladonna, or with small doses of aconite, will perhaps act more favorably.

Ergot has been recommended in the treatment of exophthalmic goitre on account of its power of causing contraction of involuntary muscular fibre, and thus of favoring reduction of the calibre of the

dilated vessels. In a number of cases in which it was given, I have certainly seen a favorable change occur in the symptoms; though, as the ergot was not the only remedial agent employed, I cannot say how much of such result was due to its action. It is open to the objection of being apt to lessen appetite and disorder the stomach if long continued.

Iron is in almost every case without exception to be administered in this affection. It is called for not only by the anæmia, so frequently present, but by the extreme mobility and weakness of the nervous system. In some cases the results of its administration in large doses are very brilliant. There can be no reasonable doubt as to its remarkable action in Cases II. and III. The form in which it is given, and the dose, must be carefully determined in each case. In general, it may be said that very large doses of whatever preparation is selected must be given. So much discussion has occurred as to the value of dialyzed iron, and my own experience with it in suitable cases has been so gratifying, that I take pleasure in pointing to the marked effects which, in Cases II. and III., are certainly in large part to be attributed to its action.

But underlying this medicinal treatment, and of even greater importance, is a most careful study of the causes, of the condition of the general nervous system, of the principal functions and secretions, and especially of the diet and digestion. A rigid attention to hygiene must be insisted on. If there is any source of exhaustion or irritation—and sometimes such causes are only to be detected by close questioning and examination—it must be removed.

If digestive derangements exist, all other treatment must be suspended until they are rectified. A carefully restricted diet—if necessary, limited to milk, buttermilk, soups, broths, and light farinacea—must be insisted on in such cases, especially if chronic intestinal catarrh with diarrhœa exists. If evidences exist of congestion of the liver, an occasional gentle mercurial, followed by a mild saline laxative, may be called for.

If, conjoined with weakness of digestion, there exists general nervous debility, and marked over-action of the heart, I should strongly advise almost complete rest in bed, associated with gentle massage, and mild and pleasant diversion of the mind. The neurasthenia, the anæmia, the increasing failure in heart power, call for prompt and thoroughgoing treatment; and, without the advantage of such a restorative basis of treatment as the above, remedies will produce but little good. In cases of less severity, attended with marked nervous symptoms, but with less debility, gentle travelling or change of scene will prove valuable.

Careful attention should be paid to the complete cure of any local irritation co-existing. Such irritation is chiefly liable to be found in connection with the gastro-intestinal or the uterine mucous membrane. In the latter case, suitable local or general treatment should be instituted. In the former, when a chronic catarrhal state of mucous membrane exists, I would recommend in combination with careful diet, the use of nitrate of silver. I believe that this remedy, while exerting the very best local action, is at the same time a nervous tonic and antispasmodic of great value.

Vegetable tonics, especially quinia and strychnia, will be found of much benefit in many cases, from time to time.

Galvanization of the cervical sympathetic has been recommended, apparently on theoretical grounds, and I am not aware of any reliable clinical evidence in its favor; though I should, *a priori*, expect it to be of service.

The enlargement of the thyroid gland requires no special attention or treatment. It fluctuates with the changes in the severity of the other symptoms; and subsides, finally, as they are permanently relieved. Those modes of treatment, especially the use of interstitial injections of iodine or of other substances, which are of so much value in true bronchocele, are not to be recommended in this disease.

When the protrusion of the eyeballs is extreme, a light bandage may have to be worn to prevent irritation of the conjunctiva. Von Graefe even recommended that, in extreme and threatening cases, the opening of the eyelids might be diminished by a surgical operation.

