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Shelby E. Shannon

University of Nebraska Medical Center

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SENIOR THESIS

HISTORY AND SYMPTOMS OF EXOPHTHALMIC GOITER

SHELBY E. SHANNON.

Definition:

A constitutional disease apparently due to an excessive; probably an abnormal, secretion of an enlarged thyroid gland showing pathologically diffuse, parenchymatous hypertrophy and hyperplasia. It is characterized by an increased basal metabolic rate with the resulting secondary manifestations, with a peculiar nervous syndrome, and usually, exophthalmos, with a tendency to gastro intestinal crisis of vomiting and diarrhea. The cause of altered pathology and activity of the thyroid gland is not known. (Boothby)

(16) The first case of ~~exophthalmic~~ goiter was described in 1802 by Flajani of Rome. He relates the case of a young Spaniard who developed a tumor in his neck. This tumor, which he recognized as thyroid, extended laterally both to the left and right and had a median sulcus. It was accompanied by continuous dyspnea and an extraordinary palpitation of the heart. The veins over the goiter were swollen as if varicose, and the patient was run down and emaciated. Here are at least two of the cardinal manifestations of the well known syndrome, goiter combined with violent heart action. Flajani mentions having seen similar cases in all of which he obtained improvement by the continued use of cold compresses. These changes that he had observed were probably spontaneous remissions.

(1-16) A far more complete and clearer description, however,

is that of Dr C. H. Parry, the distinguished physician who practiced in Bath between 1780 and 1816. Parry's observations are recorded both in his "Elements of Pathology and therapeutics", published in 1825. Parry's first case, (seen by him in 1786), which is one of the series of which he gives the fullest account, showed the following symptoms and signs: Palpitation, especially on exercise, increased force and frequency of the heart beat, full, hard and irregular pulse, rate 156, nocturnal attacks of dyspnea and constriction in the chest with the spitting of a small quantity of blood, violent stitches of pain beneath the sternum, a large bilateral swelling of the thyroid, distention of the carotids, and exophthalmos. The description is sufficiently clear to establish a diagnosis of exophthalmic goiter and the only important manifestations, as we know the disease today, not specifically mentioned are tremor, sensation of warmth and increased appetite.

He cited four other cases with goiter, palpitation and violently beating carotids, and three others with goiter and palpitation. In none but the first is exophthalmos mentioned, and it is quite possible that several of them may have the adenomatous type of goiter rather than the exophthalmic.⁽¹⁾ He thought the function of the thyroid was to serve as a diverticulum in order to avert from the brain a part of the blood, which, urged with

to great force by various causes, might disorder or destroy the function of that important organ. His powers of observation were great but his deductions as to function were less accurate.

(2-16) The next account is that by R. J. Graves of Dublin, published first in the "London medical and surgical journal", in 1835, and second, three years later, in his "Clinical Lectures". He observed three cases of violent and long continued palpitation in females, in each of which the same peculiarity presented itself-that is, enlargement of the thyroid gland; the size of the gland, at all times considerable greater than natural, was subject to remarkable variations in every one of these patients. The gland became larger when palpitation was severe and as the palpitation subsided the gland became smaller.

(2) Graves goes on to say that this palpitation lasted more than a year in the three cases.

With this increase in size of the gland with the palpitation led Graves to the idea that the thyroid may be erectile tissue and this enlargement was due to engorgement of the gland.

In his first three cases he does not mention any eye signs, but in his fourth he gives the symptoms of tachycardia and asthenia, and observed that the eyeballs were enlarged so that when the patient slept, or tried to shut her eyes, the lids were incapable of closing. When

the eyes were open the sclera around the cornea was more prominent.

He also noted that there was a remarkable disproportion between the beats of the radial and carotid arteries. The pulsations of the latter were more violent, causing a throbbing of the neck and accompanied by a loud rustling sound.

(16) Precisely the same observation was made independently by Von Basedow, a district physician in Germany, who published in 1840 an excellent account of the syndrome. The writer reports four cases, all clearly ~~exophthalmic~~ goiter, and gives much more detailed descriptions than either of his predecessors. In his first case he mentions increased sweating, asthenia, emaciation, amenorrhoea, palpitation, tachycardia with small radial pulse, oppression in the chest and dyspnea, protrusion of the eyeballs, exhilarated and careless mental attitude, together with enlargement of the thyroid.

His second patient showed asthenia, obstinate diarrhoea, loss of flesh, night sweats, ~~exophthalmos~~, dyspnea, oppression in breast, tremor, ringing heart beat, hasty speech, warm skin, excessive appetite, enlargement of the thyroid. The cardiac impulse became diffuse, and a saw like noise was heard in the carotids. This patient improved getting back to a good state of nutrition and a fair degree of health, but the fast heart

and exophthalmos persisted.

He cites another case where exophthalmos was present and corneal infection developed and patient lost the sight in both eyes.

(16) Exophthalmic goiter has been variously called after these four writers: Flajani, Parry, Graves, and Basedow. Flajani's account is so incomplete that to Parry really belongs the priority, and to Basedow the credit for the most complete description. Graves gives no hint of knowing of the work of Parry or Flajani, nor Basedow of that of Flajani, Parry or Graves.

In 1864 Von Graefe stressed the fact that the lag of the lid behind the globe in downward rotation is independent of the exophthalmos. Either sign may exist without the other. He believed it sympathetic in origin, due to an affection of sympathetic innervation of the levator palpebrae.

(16) In 1879 an attempt was made by Felchne to produce the disease experimentally. This writer believing that the manifestations of exophthalmic goiter strongly suggested an abnormality of the sympathetic nervous system, partly stimulation, concluded that the cause must lie in either the peripheral ganglia or the brain. Since there are marked vasomotor changes and since the vagus center is near the vaso-motor center, he suspected the brain. To test the theory he either incised or cauter-

ized the upper quarter of the inner portion of the corpora restiforma in rabbits. By these operations he claimed to have produced some of the signs of Basedow's disease. Usually he got tachycardia and **exophthalmos**, occasionally goiter, never all three of these in one animal, but various combinations of the two. The rabbits with **exophthalmos** also showed the sign of infrequent winking as is seen in human with Basedow's disease. The pupils were uninfluenced but **exophthalmoscopic** examinations showed dilated arteries in the fundi. He further found that if one enucleated the eye of a normal rabbit there was but little bleeding of the cut artery, but if one enucleated the **exophthalmic** eye, there was profuse bleeding. He believed that **exophthalmos** in his rabbits was due to engorgement behind the globe, and that the goiter likewise was due solely to engorgement. The tachycardia he considered due to reduction of vagus tone, by analogy, he felt that human Basedow's disease was due to the same.

These observations were interesting, but it is definitely known now that the enlargement of the gland is due to hyperplasia, but the engorgement may be a factor. (16) The next important advance was the recognition by P. Marie in 1883, confirmed by Charcot in 1885, that tremor is a consistent sign in **exophthalmic goiter**. This tremor Marie describes as involving in the most marked

cases the various muscles of the body but frequently it is found only in the extremities. Sometimes it is so marked as to interfere with the movements of the hands, sometimes so slight as to be only detectable by having the patient extend the fingers. It is rapid, about eight and one half tremors per second, while those of paralysis agitans and senility are five to six. Marie also gives an excellent description of the disease and gives a number of the now well known symptoms and signs: Polyuria, glycosuria, albuminuria, diarrhea; he also describes the diarrhea and points out that it is without colic, paroxysmal, and having a sudden beginning and ending. In addition increased sweating and a morbid and unsatisfiable appetite are among the frequent symptoms, and angina pectoris, tachycardia, cough without expectoration, and such skin manifestations as pigmentation, vertigo and urticaria, also occur. Any of these taken singly Marie believes might be explained by a derangement of sympathetic or vagus, but when one finds also cerebral symptoms such as epileptiform attacks, paralytic attacks, hemiplegia, paraplegias, hemianaesthesia, and aphasias, as claimed by Ballet, and choreiform movements, hemichorea and nystagmus, as found by himself, it seems more reasonable to say that the disease is a general neurosis rather than a neurosis of any particular nerve.

(14) Charcot is in general agreement with Marie, but

has a somewhat different conception of tremor, which he says differs from all those seen in neuropathology, being more rapid (eight to nine per second). The digits do not tremble themselves; on the contrary the tremor is general. It puts in play all the great muscles of the trunk and members, but it does not appear that it ever occupies the muscles of the head or extremities.

(16) Charcot suggests that Vigouroux discovery (the electric resistance of the skin is decreased in ~~exophthalmic~~ goiter) might serve as a quantitative measure of the intensity of the disease and as a means of differential diagnosis in formes frustes, or atypical and borderline cases, much as we use the basal metabolism today.

In 1886, Moebius observed an important eye sign, insufficiency of convergence, and gives a description of the condition. It consists in an inability to converge on near objects of which the subject is unaware, for it produces no double vision but only a feeling of tension. It is not related definitely to ~~exophthalmos~~ and may occur in diseases other than ~~exophthalmic~~ goiter. He considers there is no question of a true paralysis and that the ~~exophthalmos~~ alone cannot be the cause. He supposed that ~~exophthalmos~~ made the eye movements in general, more difficult. The eye muscles, like other muscles, are atrophic in ~~exophthalmic~~ goiter and this weakness shows itself first in convergence, as might be expected, since

this is recognized as the most strained eye movements.

(16) The next work of importance done on ~~exophthalmic~~ goiter was by Fredrich Muller (1893). He opened the way to an understanding of the role of the thyroid or its hormone in the regulation of metabolism in several of its phases. In connection with a detailed clinical and post-mortem examination of five cases, he described and discussed nearly every phase of the disease, but perhaps of most significance are his demonstrations of thyroid hyperplasia as manifested by the high columnar epithelium and deminished lumina of the acini, and his discovery in one of his cases of an increased rate of protein metabolism. He also infers from the paradox of an increased ingestion of food combined with loss of weight, that there must be a metabolic anomaly, an accelerate katabolism in Basedow's disease.

(16) Muller also believe that ~~for~~ the production of exophthalmic goiter two factors were necessary: a neurogenous and a thyrogenous, or in other words, an hereditary or acquired neuropathic disposition plus a sickness of the thyroid. This view remains tenable today, although we should modify the theory he advances, the metabolic acceleration is dependent upon the nervous changes.

Muller's view very shortly was confirmed by Magnus and Levy who showed that total katabolism, as measured by the gas exchange, is increased over normal not only in ~~exophthalmic~~ goiter, but also in normal persons on the

ingestion of thyroid gland. This marks the beginning of our present concept of thyroid function, and makes possible the interpretation of a greater portion of the clinical symptoms and signs of ~~exophthalmic~~ goiter.

(16-34) The next bright spot in the history was contributed by Cannon in 1914. In six cats the anterior root of the right phrenic nerve was fused with the right cervical sympathetic cord. Four of the cats lived and presented the symptoms of tachycardia, diarrhea, falling of the hair and unusually excitable. The respiratory metabolism was increased in all four cats. One of the cats showed ~~exophthalmos~~ on the side of the operation.

(5-16) The next important step in the understanding of the clinical types of thyroid disorder was the recognition by Plummer in 1913 of two distinct types of toxic goiter, the one being true hyperplasia with thyrotoxicosis, that is to say ~~exophthalmic~~ goiter, the other hyperthyroidism resulting from adenomatous tumor of the gland. ⁽³³⁾ Then in 1923 Plummer demonstrated the specific detoxifying action of iodine in large doses, which has proved to be such an important factor in diagnosis and preparing the patient for surgery.

There is probably no other disease in medicine which offers such a multitude of symptoms as does ~~exophthalmic~~ goiter; some clinicians fail to observe some of these

symptoms because they look for the four cardinal symptoms tachycardia, exophthalmos, enlarged thyroid and tremor. It has been proven in some of the large clinics that one or more of the cardinal symptoms -----

ptoms may be absent and yet the case is exophthalmic goiter and many times a diagnosis is missed.

The symptoms and signs are referable to the thyroid gland, circulatory system, nervous system, respiratory system, vaso-motor system, genito urinary system, gastrointestinal system, muscles, eyes and skin.

Discussions of the symptoms by systems:

(a) Thyroid. (8-19-21-25-35)

(35) The thyroid gland is usually enlarged, altering the contour of the neck. Easton has not seen any cases in which enlargement was absent on examination and in which a history of previous enlargement was also negative. Murray on the other hand, found 4.4%, without enlargement. Dock saw one case without enlargement. Kessel, Hyman, and Lande state that diffuse enlargement of the thyroid is more frequently absent than present when the onset is after the 33rd year. Many patients have goiter who seem unaware of it, and this causes some of the difficulties in studying the order in which the symptoms of the disease evolve. There may be merely a slight fullness but more commonly there is a moderately large goiter. The tumor may show slight or marked pulsation. The goiter is much more frequently general than local, and the normal shape of the lobes may be indicated, especially during deglutition. In approximately three-fourths of the cases, the right lobe seems larger

than the left. When apparently affecting one lobe only, the right lobe is more frequently the larger one. These two findings apply to clinical appearances. The explanation is that the right lobe is more anterior and within view and touch. Variation in size, from day to day, depends chiefly on the amount of blood within the organ. On palpation the thyroid is usually smooth and soft, and the enlargement is diffuse and rounded.⁽¹⁹⁾ In old standing cases, the surface tends to be less smooth, even a little nodular and the consistence is firmer. At this period, the gland has frequently contracted and may have become even smaller than the average. In these, a history of previous thyroid enlargement may be obtained both in the primary and secondary forms of Graves's disease, although in primary cases the enlargement does not exist in advance of the toxic symptoms. When the age of goiter cannot be learned from the history, the difficulty in classifying cases as primary or secondary is very much greater. Palpation may nevertheless show the goiter to be an old standing one, in a case presenting recent toxic symptoms, in these circumstances, the case is obviously a secondary form. The gland may be a little tender, but this is more frequently observed in nodular forms of hyperplasia, the so called adenomata of the thyroid with toxic signs. Pulsation of the gland may be both visible and palpable. The pulsation is expansive and a systolic

thrill is felt in the more vascular forms presenting active symptoms. In these a systolic mormur is usually audible not only over the lobes of the thyroid but also over the isthmus. Less frequently there is a diastolic murmur or a continuous murmur with systolic accentuation. The murmurs are produced within the vessels of the thyroid, or less frequently in external vessels compressed by the gland. ⁽³¹⁾ When a murmur is heard in an enlarged thyroid it is an important finding in differentiating exophthalmic goiter from toxic adenoma.

(21-35) Enlargement of the thyroid may occur with the onset of the disease. Occasionally it occurs quite suddenly. There is no constant relationship between the size of the gland and the severity of the symptoms. When however, the enlargement is soft and vascular, severe symptoms are associated. As a rule, local discomfort from the goiter is slight or absent. Occasionally there is a choking sensation, especially if the left lobe is enlarged. The large volumn of a goiter may cause dyspnea when the trachea is compressed, especially by retrosternal growth of the thryoid, when definite nodules are felt, they are most frequently retention cysts, or areas in which nodular hyperplasia has occurred.

(b) Eye. (6-8-22-35)

The symptoms referable to the eyes are numerous. There may be an excessive tear secretion or an un-

usual dryness of the eyes which may occur before evolution of the syndrome or after. A feeling of pressure behind the eyes is a more frequent symptom.

(35) Protrusion of one or both of the eyes, (exophthalmos) occurs in from 65 to 83% of the cases, this varies in different clinics. Exophthalmos is, in part, due to the increased blood and lymph supply, to the muscles and other structures, and to the edema in the orbital socket, whereby the space available for the eyeball is reduced. The effect of this in a conical shaped cavity would be to project the eyeball. (8) The hypothesis that the musculus protrusory bulbi and the orbital muscle of Muller play a considerable part, possibly the chief part, has many supporters, although there is no satisfactory evidence that these muscles are alone capable of projecting the eye in the human subject. Landstrom has, by special staining methods, demonstrated the presence of the musculus protrusor bulbi in man. It forms a cylindrical band around the eye anterior to its equator. Fibers run out and forward to be attached to the fascia of the socket. The shortness of the fibers and the obliquity of their course render doubtful the causation of high grade exophthalmos by the action of this muscle.

The orbital muscle of Muller is a small non-striated muscle, which bridges the sphenomaxillary fossa behind the orbit. It has a sympathetic nerve supply. In old

standing cases there is sometimes an increase of retro-orbital fat. The deposition of this fat cannot be the primary cause of the exophthalmos, which may develop with remarkable suddenness and vary in degree from day to day. The persistence of protrusion, in chronic cases and in those who no longer show other symptoms of Grave's disease is explained by the presence of excessive retro-orbital fat, which has slowly accumulated probably during periods of remission and recovery.

(8) Another theory of causation of exophthalmos is supra-renal insufficiency.

(35) The exophthalmos may occur either early or late. In a certain proportion of cases there is no exophthalmos, or one eye only may be protruded when the thyroid is enlarged, on the same or opposite side, frequently tachycardia, tremor, increase metabolism and enlargement of the thyroid precede exophthalmos. When exophthalmos is early, other evidences of Grave's disease may still be hard to find. The exophthalmos varies in severity in the course of the illness, and this variation does not necessarily correspond with changes in the severity of the other symptoms. At the menstrual period, and during physical, and still more during mental excitement, exophthalmos is more marked. The amount may be moderate throughout the entire course of the disease, and the sign is mild or absent when the disease develops after the thirty fifth year. Many of these are cases of secondary Grave's disease,

the incidence of which is relatively higher at this period. In these the exophthalmos affects one eye, or both unequally. In primary cases the exophthalmos may be extreme, giving cause for anxiety regarding the integrity of the eyeball. In such cases the cornea is continuously exposed because the eyelids cannot be closed. The cornea becomes congested and tends to ulcerate. Panophthalmos may result, with loss of the eyeball. According to Von Graefe and Jessop, this complication occurs more frequently in men.

Ophthalmic examination shows dilatation of the retinal arteries and occasionally arterial pulsation.

(8-22) Von Graefe's lid sign is present in 14 to 55% of the cases of exophthalmic goiter. Normally the upper lid covers the same ratio of the cornea in all movements of the globe, and no portion of sclerotic is visible at the upper corneal margin. The presence of the Von Graefe sign is detected in the following manner: An object is held before the patient's eyes and he is directed to follow its movements without altering the position of his head. An object is then slowly moved downward, when it will be observed the upper lid lags in following the cornea downward, and in consequence a rim of sclerotic at the upper portion of the cornea will become exposed.

Numerous theories, without practical agreement, have been advanced to explain the symptom, the most tenable perhaps being that the irritation of the sympathetic

produces a spastic contraction of the musculus tarsalis superioris.

(22) Stellwag's sign consists of a diminished frequency of winking. Normally the function of winking distributes the lachrymal fluid over the cornea, bathes it, clears the dust, and prevents the corneal layer from drying. Winking takes place normally three to ten times per minute; in Grave's disease it may not take place more than once in several minutes. Interference with this corneal protection function exposes the cornea to irritation and infection. This symptom occurs in 30 to 50% of cases.

(22-35) Dalrymple's sign consists in retraction of the upper eyelid and a wider palpebral fissure. When Stellwag's and Dalrymple's signs are both present, there is a staring effect. Dalrymple's sign is also present in hysteria, tetanus and orbital tumors.

These three signs have been regarded by one group of writers as due to the increased tone of the involuntary muscle fibers of the upper eyelid supplied by the sympathetic. The muscle fibers are sometimes described as the involuntary part of the levator palpebrae superioris, and sometimes as branch fibers from the muscle described by Landstrom. Another group regard the muscle concerned as the levator palpebrae superioris, which has its nerve supply from the parasympathetic fibers accompanying the oculomotor nerve.

Moebius's sign consists in absence of weakness of the movements of convergence, which occur normally when looking at near objects. Even when this act is successfully performed by the subject of exophthalmic goiter, there is evidence of the need for unusual effort, and convergence is not well maintained. In health, convergence of the eyes on an approaching object continues, until it arrives three and one half inches from the eyes. Landstrom has suggested that this sign is due to action of the fibers of the protractor bulbi, which lie on the temporal side of the eyeball, opposing that of the internal rectus. This sign also occurs in neuroasthenia conditions.

(35) Kocher's sign consists in a momentary retraction of the eyelids, when the eyes begin to focus on a near object.

(35) Enroth refers to edema of the eyelids as an early sign of Graves disease. It may be an early sign of the disease. At first the edema may be limited to the upper eyelids, though this edema is hard and firm, its degree varies with the time of day, it usually is most marked in the morning. It differs considerably from the flacid edema of the lower lids found in subjects with nephritis and heart disease. Enroth states that this edema is often observed in women menstruating and may be due to a functional disturbance of the thyroid gland.

Slight evidence of any one or more of the above eye

signs is a valuable aid to a diagnosis in exophthalmic goiter. Well known as they are, they are not infrequently overlooked, when such aids to diagnosis are required, for example in cases where exophthalmos and the thyroid is not enlarged enough to attract attention.

(c) Cardio-vascular symptoms. (3-8-10-21-24-25-35)

The cardiovascular disorders of exophthalmic goiter are numerous and important. As part of a state of autonomic imbalance, functional heart symptoms may precede the onset of exophthalmic goiter and remain after clinical recovery has occurred. (10) Chaiari pointed out that constitutional cardiovascular anomalies such as cardiopptosis and fragile arteries, as well as vasomotor instability, may determine the intensity of the cardiac symptoms. Others have also stated that the severity of the cardiac symptoms, occurring in a proportion of the cases, is due to a constitutional cardiac peculiarity. (35) Tachycardia is usually an early sign, and there may be a lengthy early period during which there is little further evidence of the disease. During complete rest, the rate may approach the normal, but some trivial incident, remark or emotion may increase the rate to 160 or more and the return to the former rate is much delayed. During this early phase, the condition is not easily identified as a thyroidal disorder, and the inadequate diagnosis of cardiovascular neurosis, of unknown origin, may unfortunately

be made. In practically all uncomplicated cases, tachycardia is present thru out the entire course of the disease. It is one of the cardinal signs on which considerable reliance may usually be placed, in judging of the severity and progress of the cases. In these, tachycardia tends to vary directly with the severity of the hyperthyroidism. ⁽³⁵⁾ An important exception to this rule is that when the heart is previously damaged by some other cause, great variations in rate may occur in consequence of the effect of this primary damage. There are also a few cases of exophthalmic goiter in which the heart rate is only slightly increased, although the other signs are well marked. In at least some of these cases, the natural rate of the heart during the period of good health has been subnormal. In others, chiefly chronic cases with myocardial degeneration, the pulse rate may appear to be about normal or even slower than normal, owing to the large number of undetected extra systoles or to feeble systoles when the auricles are fibrillating. The true ventricular rate may nevertheless still be excessive, as may be proved by auscultation or by graphic records.

(35) In old standing cases, paroxysmal tachycardia may occur; according to Bamberger, this form depends on disturbance of the central nervous mechanism. The sudden onset and cessation is in all respects similiar

to attacks of paroxysmal tachycardia in nongoiterous cases, and these are known to be characterized by a series of extra systoles of auricular or ventricular type. Palpitation and precordial discomfort are common. The occurrence of tachycardia and palpitation, without discoverable cause, suggests the possibility of hyperthyroidism. The breathing is panting, especially on going upstairs. The apex of the heart is displaced outwards, and this is the visual finding even in early cases. The apical impulse is pounding, due to an increased strength of the systole. Further dilatation with hypertrophy occurs as the sequel of the prolonged over-action, so that the apex may later be found in the axilla. In some cases this gradual extension of the cardiac area does not appear to occur. In the large vessels of the neck, excessive pulsation is a feature associated with a feeling of throbbing there and in the thorax, an aneurysm may be wrongly be diagnosed. Sometimes the throbbing is felt all over the body, and the pulsations in the cervical vessels may cause rhythmic movements of the head. Pulsation of the liver or spleen may also occur. Excessive pulsation of the abdominal aorta is often the cause of discomfort and gastric symptoms. Capillaries and veins may show pulsations. The local blood flow in the hands may be greatly increased. A thrill may be felt over the heart, especially during exacerbations in emaciated subjects, and when, cardiac hypertrophy and dilatation exist.

(8) Most authorities hold that the tachycardia of Basedow's disease results from stimulation of the cardio-accelerator centers in the cervical sympathetic ganglia by some sympathomimetic substance having an action similar to that of epinephrin. Thus considered, it is apparent that both the cardiac and ocular symptoms may well arise from the same or closely related sources.

(10) The cause of the dilatation, hypertrophy and insufficiency is due to the tremendous dilatation of the arteries and veins of the thyroid short circuit the blood flowing to the neck and increase the load on the heart in the same manner as do arteriovenous aneurysms. Also the heightened oxygen consumption causes an increase minute volume flow of the blood, which may be from twenty five to sixty per cent greater than normal.

(35) The heart sounds are usually accentuated and murmurs are not uncommon. The murmur usually accompanies the first sound. The chief causes of this murmur are the excessive rapidity and force of the blood stream. Later owing to myocardial degeneration, sound tends to become less intense. A diastolic murmur is a rare finding. In many cases where murmurs are present they give a history of rheumatic fever, or syphilis or other infectious diseases.

Blood pressure. The systolic blood pressure at

first is high, 140 to 180 mm. Hg., while the diastolic pressure is not correspondingly increased, or, what is more frequent, is diminished. The most characteristic change is the consequent increase of the pulse pressure. ~~It is difficult to determine because of the very gradual fading of the loud sound.~~ ^{Not infrequently the diastolic pressure} is difficult to determine because of the very gradual fading of the loud sound. In the latter stages of severe cases, degenerative changes in the myocardium render the heart unfit to maintain the ~~fairly~~ high systolic pressure, and a fall may proceed until the systolic pressure is below the estimated normal for the patient's age. A fall in the systolic and pulse pressure also occurs during remissions or permanent diminution of the hyperthyroidism, with general improvement in the symptoms. The blood pressure, in cases where there has been a great deal of degenerative changes and arrhythmia, is difficult to measure.

(35) Sinus arrhythmia, auricular and ventricular extra systoles, auricular fibrillation, both transient and permanent, auricular flutter, and delayed conductivity are by no means uncommon. Auricular fibrillation was present in 13% of P.D. White's and Aub's cases. Both fibrillation and flutter may be paroxysmal. The cause of the auricular fibrillation is not definitely known, but it is thought that it is due to prolonged overwork of the heart, or due to toxic action of excessive or otherwise normal thyroid function. Hyperthyroidism is now regarded as one of the common causes

of auricular fibrillation. The thyroïdal cause is nevertheless very frequently overlooked, because the thyroid is in many cases quite inconspicuous, although it is the seat of severe chronic disease. A history of rheumatism or sore throats may further distract attention from the thyroïdal cause. Auricular fibrillation is usually not present when the patient first comes under observation, it is also uncommon in cases occurring after the thirty fifth year which are secondary Grave's disease. ~~That~~ ⁽³⁴⁾ Congestive heart failure caused by hyperthyroidism was observed by B. E. Hamilton. The physical signs were due to inadequate propulsive action of the heart; consisting of orthopnea, rales, cough, haemoptysis, enlarged liver, edema, venous congestion. Hamilton points out that all cases of dyspnea, tachycardia, and cyanosis are not necessarily due to the failure of the heart to do its work. In a percentage of cases with fast heart and dyspnea, terminating in death, with fast heart and dyspnea, the lungs were clear and liver small and he concludes that the cause is directly due to toxic substance of the thyroid.

(d) Respiratory system. (16-35)

(35) There may be a feeling of dyspnea in the earliest phases of the disease, before the true nature of the condition has declared itself. Usually the

symptom is present when the patient first comes under observation. It may be slight and the objective signs may be lacking. In some patients no complaint of dyspnea is made, but it is noticed that the alae nasi are distended or respiratory rate is increased. The patient may state that he gets short of breath on walking or he may be confined to bed because of the shortness of breath. In most cases the breathing is shallow and rapid and there is evidence of feebleness in the voluntary effort to breath deeply.

Some patients complain of a feeling of constriction in the throat when an enlarged thyroid, extending down behind the sternum, causes actual flattening or narrowing of the trachea. Huskiness of the voice is common. The most frequent cause is defective adduction of the cords. Aphonia sometimes occurs. Coughing is seldomly really troublesome. Rarely there is bronchorrhoea. Haemoptysis is a recurring symptom in a few patients, in whom all positive evidence of tuberculosis may be lacking. In most instances, it appears to be due to the special capillary strain characteristic of the disease.

(16) The hyperpnea and dyspnea are due to the increased rate of oxidation caused by the increased metabolic rate. An increase in pulmonary ventilation roughly paralleling the basal metabolism can be demonstrated

readily by metabolic tests on thyrotoxic patients.

(e) Skin.

(35) The skin is usually thin and more transparent which is due to the deficiency of subcutaneous fat. For this reason, it can be pinched up in folds no thicker than those of a fine glove. It is softer, warmer, and more intensely injected than normal. The vasomotor instability is well shown by the patches of hyperemia and of pallor of the skin of the face, neck, and upper part of the sternal region. Later in the disease there is a permanent capillary dilatation in the skin of the face and neck. The skin is hypersensitive and dermographia is common. Hyperidrosis is practically constant, and accounts for a diminished resistance to the electrical current. As a result of disuse of the occipito-frontalis muscle, the furrows of the forehead are absent or faintly marked. Pigmentation, leucoderma, alopecia, ~~edema~~ or petechiae are occasionally present. Pigmentation is especially common on the upper eyelids in men, but is not infrequently present in women. General pigmentation is a striking feature in the groups of chronic cases with cardiac decompensation. Edema may be circumscribed or general. Edema may be a terminal sign of myocardial degeneration.

(f) Nervous system. (4-8-23-30-35)

(35) Nervousness is the earliest symptom in

many cases and often the highest centers are involved.

(4) The mental change may have various forms, and which of these is assumed will very largely depend on the antecedent mental constitution and the nature of the psychic impressions, which cause the mental reactions. The intensity of the mental change will depend on the same factors and on the metabolic, vascular, and cerebral changes, directly or indirectly caused by "hyperthyroidism." Subjects are anxious minded, irritable, easily disposed to tears, depressed by fears, exalted, or otherwise emotional. Headache, vertigo, mental fatigue, and insomnia are often complained of, as in neurasthenia. There is excitability and restlessness which many times is quite severe.

(35-23) The change in the mental disposition sometimes results in a change of habit and bearing. They may become the shut in type and this is brought on by the feeling that their appearance has been changed. It is not uncommon to see more severe mental changes, such as deliriums, delusions, hallucinations and melancholia.

It is by no means proved that these symptoms are always or ever solely due to the action of the toxemia of hyperthyroidism on the cerebral cells. Their relation to hyperthyroidism may be that they are an effect of various cardio-vascular disorders, characteristic of exophthalmic goiter, upon the cerebral circulation. Many patients give a history of mental

strain over a long period of time, and not infrequent, there are coincident chronic focal infections causing toxemia.

All or any of these may be a factor in producing the mental symptoms, but more work is required before the actual cause is determined.

(8) Tremor of the outstretched fingers is one of the most constant signs. The tremor is fine, rhythmical, and rapid, about 8-10 per second. They are intensified by emotion, and may be sufficient to prevent finely co-ordinated movements, such as sewing. It is believed the tremor of exophthalmic goiter is a disturbance of muscle tonus, resulting from over stimulation of the sympathetic innervation and this stimulation of the sympathetic being due to some unknown circulating sympathomimetic toxin.

(g) Metabolism. (11-12-13-35-37)

(35) The percentage of cases of exophthalmic goiter having increase metabolic rates differ in different clinics, but in most of the clinics ninety percent of more of the cases show a basal metabolic rate above plus 20.

(11) The oxygen consumption and the formation of carbon dioxide may be greater than in acute fevers, diabetes or leukemias. The fact that pyrexia is uncommon and hyperpyrexia extremely so, is due to the

remarkable balanced hypertonus in the autonomic nervous system. If this were not so hyperpyrexia would occur. If this balance is disturbed by the injection of atropine, fever occurs immediately. The mean temperature tends to be subnormal, although occasionally rises above normal are not very infrequent and a terminal rise in fatal cases is common.

According to Faltan the increase of the fundamental exchange is possibly due to the violent increase of tonus in the whole vegetative nervous system.

(13) During natural sleep or sleep induced by morphine, and after abolition of the tremors by hyoscine, the increased oxygen consumption is maintained. The minimum metabolism after a standard fasting period and during rest, i.e. the fundamental exchange or basal metabolic rate, was also found to be increased, the carbon dioxide production and oxygen consumption being greatly increased.

(1275) Extraordinary emaciation may occur largely in consequence of increased katabolism. Kocher found emaciation in 88% of his cases. Emaciation increases with exacerbations of hyperthyroidism and diminishes with remissions. Some patients remain fat and a very few become fat. The emaciation is intensified by the additional katabolism due to restlessness, by defective ingestion greatly emphasised during periods

of anorexia, and by excessive excretion particularly when there is diarrhea.

(35) In consequence of the increase metabolism, the heat production in very severe cases ^{show an increase of 75% above normal to the} fifty per cent or more. There is a definite parallelism between the severity of clinical manifestations of hyperthyroidism and the activity of basal metabolism. The state of the basal metabolism may consequently be used as a criterion in estimating the severity and progress of the cases. Single observations of the basal metabolic rate are practically worthless because the patient is not accustomed to the method. (35) A series of observations are important, and aid to diagnosis. Boothby and Sandeford's analysis of 6200 cases of thyroid disease, showed that 98% of exophthalmic goiters show an increase of more than ten per cent above average normal values. There was a small percentage of cases presenting all the usual signs of exophthalmic goiter except the increase of metabolism. Two per cent have a basal metabolic rate within ten per cent, of the normal, and seven per cent are within fifteen per cent.

(37) The blood pressure and pulse rate are important in uncomplicated cases of exophthalmic goiter because there is a certain definite relation to the basal metabolism. There seems to be a corresponding rise in pulse pressure and pulse rate when the basal meta-

bolism is increased. Due to this relationship Reads formula has been used to obtain the metabolic rate.

(37) BMR equals $.75 (P.R. \text{ plus } .74 P.P.) \text{ minus } 72$

By substituting actual basal pulse rate and pulse pressure readings in the formula the basal metabolic rate is obtained within ten per cent of its correct value in slightly over half the cases.

It has been found by experimental work that the minute volume output of the heart is increased in proportion to the increase of metabolism and then after thyroidectomy the systolic output per beat of the heart is decreased.

(h) Gastro intestinal symptoms. (8-21-25-35)

(35) Under favorable conditions the functions of the alimentary tract are performed in an approximately normal manner in the majority of cases.

There may be dysphagia present and thirst is sometimes a prominent symptom. Anorexia is not uncommon in acute cases and sometimes present in chronic cases.

In the most typical cases there is usually a large amount of food consumed, more than a person who is in good health and engaged in hard work, and hunger may be severe. This above symptom is often present with a loss of weight and is probably due to the increased metabolism.

(25) Vomiting may be a very grave symptom and may be unrelated to meals or may follow every meal.

Nausea and discomfort may or may not accompany the vomiting. Some authorities believe these symptoms are due to increased peristalsis while others say that the violent pulsations of the aorta contribute to the cause of nausea after meals.

(8) Diarrhea or chronic constipation are characteristic of many cases. The diarrhea however is the more constant symptom and some patients may have twenty stools a day. The diarrhea is thought to be due to the increased peristalsis and increased intestinal secretion. The constipation may be due to a faulty innervation or there may be an over stimulation of the sympathetic nervous system.

(35) Fatty stools containing undigested meat fibers are fairly common. There are two hypotheses as to the cause: (1) They are due to a functional disorder of the pancreas. (2) They are due to the disorder of the autonomic nervous system resulting in increased peristalsis, whereby the contents are hurried along so that the opportunity for absorption is limited.

In some cases abdominal pain may be severe and it is some times very difficult to rule out an acute abdomen.

(35) X'ray examinations show a rapid transit of the opaque meal thru the gastro intestinal tract. This hypermotility is thought to be due to dominance of the

parasympathetic tone.

Perspiration and warm skin.

(16) These two symptoms are quite common in cases of exophthalmic goiter. The part it plays in fever *+ Exoph. Goiter,* in both there is an increased heat production. The amount of sweating is closely proportional to the increased heat production. The increased metabolic rate causes an increase in heat production which in turn brings about a peripheral dilatation of blood vessels and perspiration.

(i) Muscle and joint changes.

(35) Rheumatoid arthritis is present in a very small percentage of cases of exophthalmic goiter and the cause is unknown.

In many cases the occipito frontalis muscle cannot voluntarily be brought in to use and weak quadriceps extensor contraction is characteristic. (14) The quadriceps test for myasthenia is carried out by having the patient sitting in a chair and have them hold the leg out at right angles to the body. They can rarely maintain the leg in this position for more than twenty or thirty seconds, while in normal individuals without thyroid disturbance, the leg can be extended for one minute.

Dr Plummer tested this condition by having the patient step from the floor up on a chair and in

patients with thyroid disturbance, there is a weakness and pain in the quadriceps.

The cause of this muscle weakness is probably due to the increased metabolic rate.

(27) The fingers and toe nails are often partly and irregularly separated from the nail bed, with occasionally a turning up of the outer edges of the nail. This condition is rarely seen except in cases of exophthalmic goiter.

(j) Urinary findings.

(35) The total output of urine may be above normal but not usually so, the fluid excreted by the kidneys being restricted by hyperhidrosis. In ten per cent there is albuminuria, with or without casts. Nephritis is uncommon. Frequency of micturition, and discomfort or actual pain on micturition, are fairly common symptoms, and are probably due to high concentration, high acidity, and hypertonus of the parasympathetics. Intermittent glycosuria occurs frequently. F. Schulze states that it is found in twenty five per cent of all cases. Bram in eighty five per cent of his own cases. While the blood sugar tends to be higher than normal in exophthalmic goiter, a lowering of the kidney threshold for sugar, or more frequently a lag in the mechanism for restoring the glucose of the blood to normal, are partly explanations of the frequency and intermittence of glycosuria in this disease. On the whole, the efficiency of the

mechanism shows the endocrine function of the pancreas to be in a fairly balanced state of hyperactivity.

The administration of thyroid substance in exophthalmic goiter may cause glycosuria as in normal people. The glycosuria of exophthalmic goiter does not appear to depend on interference with the oxidation of carbohydrates. Acetone and diacetic are present in the urine in the more severe cases. Indican is not found in the urine.

(k) Blood findings. (15-35)

There is no characteristic change in number, form or size of the red cells. The hemoglobin is usually normal.

In typical cases of exophthalmic goiter, leucopenia and mononucleosis are almost constant; in atypical forms, these are found less frequent. The mononucleosis is more constant than the leucopenia. The increase of lymphocytes and large mononuclears is relative, and is chiefly due to absolute reduction of the neutrophil polymorphs.

In Eason's series of cases, the total white count averaged under five thousand per cm. The differential count varied greatly. The average polymorphonuclear count was fifty; small lymphocytes, thirty one; large lymphocytes fifteen and five tenths; transitional eight; masts two tenths eosinophils two; basophils three hundredths.

There is no definite relation between the degree of lymphocytosis and the severity of the symptoms. As neither leucopenia nor mononucleosis occurs with absolute constancy, and as both also occur in simple goiter, myxoedema, and generally in pathological states dependent on alterations in the internal glandular secretions, they have no pathognomonic value in differential diagnosis.

The blood coagulates more slowly than normal blood.

Hyperglycemia is not uncommon, but the fasting blood is more frequently normal. This increased blood sugar is thought by many to be due to the rapid absorption from the intestine. While others think it is purely on a basis of a hyperactive sympathetic nervous system.

(1) Thymus.

(35) If the onset of the disease is in early adult life, the thymus is constantly enlarged in fatal cases that are examined post mortem. If the onset occurs after the thirty fifth year, the thymus is no longer a factor, clinically or pathologically.

(m) Genital system.

(35) Although many cases of exophthalmic goiter occur before the twentieth year, in only a small percentage of these cases is the onset so early as the first year of menstrual life. The suggestion has been made

that tachycardia and palpitation, sometimes occurring at puberty, is due to slight hyperthyroidism. According to some observers, a history of delayed puberty or of habitually small menstrual flow is frequent in those suffering from exophthalmic goiter, but many writers believe there is no evidence to show that a state of genital infantilism is characteristic. At the onset of the disease the duration and quantity of the menstrual flow is usually lessened, and complete amenorrhea of many months duration is not uncommon. During the course of the disease the symptoms are usually intensified at each menstrual epoch. This may be an ovarian disturbance basis.

(35) During pregnancy there is a general remission of the symptoms of exophthalmic goiter. It rarely develops during pregnancy, but when it does the symptoms are very severe. The primary cases that arise during climacteric are few, and many do not show the typical grouping of signs and symptoms. In old standing cases atrophy of the genitals and mammary glands are not uncommon. In men impotency may occur.

Reviewing the records of various clinics will show in what percentage of cases the various symptoms occur.

(18) A study of 1036 cases of exophthalmic goiter in the Mayo clinic. (Boothby)

Age (years)	36
Duration of goiter, (years)	4
Duration of symptoms "	1.5
Age at onset of symptoms.	36
Cardiac decompensation per cent.	42
Exophthalmos per cent.	61
Thrills " "	53
Bruit " "	80
Glycosuria " "	1.
Blood pressure systolic average	146
Diastolic " "	74
Pulse pressure " "	70
Pulse rate " "	119
Basal metabolism " "	Pos +50
Clinical diagnosis correct per cent	98

(32) A study of 500 cases by A. S. Graham. These patients come to the clinic with the following complaints.

Nervousness.	53%
Palpitation.	30%
Loss of weight.	26%
Presence of goiter	24%
Weakness	20%
General debility	10%
Stomach trouble	8%
Dyspnea	7%
Edema effecting legs	6%
Mental irritability	4%
Exophthalmos	3%
General anascara	3%
Chronic headache	3%
Diarrhea	3%
Choking sensation	2%
Rapid growth of goiter of long standing	2%
Dizziness	1%
Insomnia	1%
Substernal pain	1%

(32) Symptoms present in the 500 cases.

Nervousness	96%
Tremor	96%
Loss of strength	94%
Dilatation of heart	33%
Decompensation	50%
Auricular fibrillation	12%
Nausea, vomiting and diarrhea appearing at crisis	11%
Exophthalmos	41%
Goiter	74%
Substernal goiter	8%
Tonsillar infection present	50%

The average age of admission 38 years.

20% in third decade.

30% in fourth decade.

25% in fifth decade.

15% in sixth decade.

Ratio of men to women, one to five.

(35) Kessel, Lieb and Hyman.

28% of cases - One or more eye signs.

20% " " - Tremor.

84% " " - Tachycardia and goiter.

10% " " - Tachycardia goiter and tremor.

11% " " - Tachycardia, goiter, tremor
and exophthalmos.

(16) Massachusetts General Hospital last one hundred
and fifty unselected consecutive cases.

Tachycardia	100%
Nervous instability occurred in	99%
Tachycardia	98%
Tremor	94%
Goiter	91%
Palpitation	84%
Loss of weight	83%
Exophthalmos	81%
Dyspnea	81%
Thyroid bruit	81%
Asthenia	78%
Increased sweating	66%
Increased appetite	63%
Von Graefe sign	35%
Moefurs sign	29%
Diarrhea	25%
Pressure symptoms	

(29) 4000 cases by Bram.

Increased B. M. R. in	99.5%
Afebrile heart in	99%
Thyroid enlargement in	81%
Exophthalmos in	88%

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