An Account of Graves' Disease, with a critical inquiry into the Nature of the disease.

This is presented by Thomas Anderson Glover MB CM
with a view to obtaining the degree of Doctor of Medicine

April 1897
The photograph represents a girl who came under my care here nearly two years ago. It was only recently that I was able to obtain a photograph. I regret that I was unable to get one showing better the characteristic symptoms, but it brings out very strikingly the enormity
waste of tissue that is such a marked feature of the disease.
I shall not give a full account of the case, but mention a few of the more important points of interest.

Age at present—nearly 18 years. The patient first developing the disease at the age of 15 years.

Family History. Father is a drunkard and he mother is very nervous.


Recovery from this was followed by enlargement of right then left lobe of Thyroid, then Bosph Helmos, then persistent headaches. Von Graefes and Sheillvas's signs are absent.

There is marked general muscular tremor, and the patient is off suddenly and without any feeling of faintness to lose the power of balancing herself and falls flat on the ground.

One or two other important changes I allude to later.
I have endeavoured in this Thesis to present an account of Graves' Disease, along with any observations that a study of the literature upon the subject which I could obtain has enabled me to make.

Articles on Graves' Disease are numbered by hundreds, and it has been impossible for me to consult any but the more important in the English language. I give a list of books, etc. I have consulted, and drawn upon.

1. Grainger Stewart & Leeson  
   Clinical Notes on Graves Disease  
   Edinburgh Hospital Reports, Vol.1 p.187  
   Bulbas Lesions in Graves Disease, Vol.11 p.275
2. Murray. 20th Century of Medical Prac. Vol.10  
4. Elder. Principles of Pract. of Med. 1892  
5. Graves. A System of Clinical Medicine  
8. Taylor. Practice of Medicine
Various Medical Annals.
Also to many articles in various issues of the
British Medical Journal, and its Epitome
I am indebted.
The more important are:
"Thyroid Feeding in Epithelialic Syndrome"
by Dr. David Owen. Oct 10th, 1896.
"Remarks on Progress in Epithelialic Syndrome"
by Dr. Williamson. Nov 17th, 1896.
Here are also valuable articles on the Thyroid
by Robert Hutchinson. Jan 23rd, 1897.
and Victor Horsley, December 5th, 1896.
Reference is also made to Dr. Byron Bramwell's
article on Thyroid Feeding in Myxedema in:
Edinburgh Hospital Reports, Vol. 77.

All quotations from any other authors than
those above stated, are not particularly
referred to have been derived from one or
other of the above works.
Erythematous Goitre or Graves Disease, with various synonyms in various languages, is a disease characterised by great prominence of the eye, palpitation, muscular tremors and enlargement of the thyroid gland.

One of the first cases described was that by Caleb Miller Parry of Bath, but Graves of Dublin gave us the first real picture of the disease and first got near both real significance. No name has yet been invented which fairly meet all the requirements of the case, but either of the names above mentioned serves well enough for purposes of identification so by one or other name I shall allude to it in future.

Frequency of occurrence of the disease.

We can hardly describe the disease as common or of frequent occurrence, but nowadays very many more cases are met with of at all events reported, than was the case in Graves' day. Certainly means of making known cases in one's practice are more to hand than formerly but when one compares Graves' three cases
with the record of any physician of equal standing in our day one hardly can help seeing that the disease is becoming alarmingly more frequent. Also it is probably more frequent than is ordinarily supposed, for doubtless many slight and evanescent forms of the disease may pass unnoticed, or be mistaken for ordinary anaemia.

Relative frequency in the sexes.

It is found that women are more usually affected than men. This is only what might have been expected when one considers the more nervous, emotional constitution of women and the obvious relationship borne by the thyroid to the menstrual function.

Taking the cases recorded by over twenty different observers (nearly five hundred cases) I find 5:7 men to 4:26 women, or 2 men to 15 women, approximately.
Age of Occurrence.

It is commonly supposed that the disease chiefly recurs among young females, and to a great extent this is so, but it is far from being solely a disease of female youth. Grange's, Stewart's, and Gibbons' cases ranged in age from 20 to 46 years. Among Williamson's cases were persons whose ages were 39, 49, 44, 44, 46, 40, and 50 years. The disease has been observed in people over 60 years (Stoke quoted by Tagge) and also in children of 14, 7, and 2 years. Probably it would be more correct to assign no age limit for the disease though cases occurring after fifty years of age and in persons under fourteen might rightly be termed rare.

Distribution.

Ordinary goitre can be assigned as a rule to various localities, Derbyshire or Yorkshire neck, and as Balyle says, "in the sunless valleys where the cretins dwell," but we cannot
allocate Grave's Disease to any particular districts. It had not, however, been noted among uncivilised peoples, and, except perhaps not among native of India. Not can it be said to occur particularly in any given class of the community being most particularly a disease of individuals.

Occurrence Among Animals. This has been observed in certain rare instances. Rodot reported a case of a cow affected. The disease has also been noted in horses, a four year old horse was seen to be affected after a gallop, and died at the end of a month.

Hereditary. Grave's Disease does not appear as a rule to be directly inherited, but there are a sufficient number of cases recorded to show that there may be a family tendency to the disease. An instance is recorded of it in a boy aged 8, whose mother also is said to have
been affected.

Murray quotes the case of a hysterical woman, out of whose ten children eight suffered from Gravel Disease in varying degree and one of these had four children affected.

Kenzie mentions six pairs of sisters who were affected.

In some families there is a tendency to goitrous affections; one member of a family may be myxedematous, while another suffer from Gravel Disease (Maurie).

Wells mentions the case of a man suffering from Erythralmic Goitre who had an uncle and brother who were affected with ordinary Goitre.

Erythralmic Goitre also appears in families with a tendency to Chorea, Epilepsy, Hysteria, and Insanity.

Dilamine gives a good example of this associated tendency. Out of six generations of a family, the disease appeared in four generations, various forms of nervous disease occurring in all six generations.
Origin.

The disease may set in gradually, first one or other of the symptoms showing itself, the others following in a train, or the onset may be very sudden. Very generally a shock mental or physical is responsible for the first appearance of the disease.

Trouseau mentions the case of a lady, who having one might been crying for a long time on account of her father's death, "suddenly felt her eyes swell and lift up her eyelids," while at the same time she had copious epistaxis, violent palpitation of the heart, and throbbing and enlargement of the thyroid; four days later the nature of the case was recognized. Here we have a case in which a definite shock is quickly followed by the symptoms we call Graves' disease.

Grainger, Stewart, and Gilson cite several cases. In one case, a man, who had apparently suffered from Syphilis, but showing no signs of Graves' Disease, fell
A distance of thirty feet, when he commenced to suffer from chronic diarrhoea, other more marked symptoms of Gravis' Disease setting in after some months.
Here we have what may be called a predisposing cause of Gravis' Disease, and the latter setting in gradually, after a definite shock.
C. Todd, Brit Med. Journal July 25th, 1876, reports a case, the patient attributing his trouble to a fall from a window, the symptoms setting in gradually.
A fright in the puerperal state was the exciting cause in another of Grainger, Stewart and Gibson's case, the symptoms setting in gradually.
Peripheral Irritation may be either an exciting or predisposing cause of the disease.
A very interesting case is recorded by Grainger Stewart and Gibson, where successful treatment of a hypertrophic condition of the mucous membrane of the nasal pharynx was followed by a marked diminution of the symptoms of Gravis' Disease.
W. de Havilland Bell in his Egyptian Lectures.
for 1896 (British Medical Journal Feb 28th) alludes to the connection between intranasal changes and ophthalmic goitre, and gives several cases. In two cases relief from ophthalmic goitre followed treatment of the intranasal changes, in one case the course of the disease was not apparently modified.

In one case in which T. Felix Simon removed nasal polypi, unilateral incomplete Grave's Disease followed. An attack of Grave's Disease lasting three months followed removal of the turbinate body with the gall万千瓦-centery by W. A. S. Charley.

Grave's disease may supervene in a person the subject of ordinary parenchymatous goitre. Rheumatism is a predisposing cause, and may be the initial cause.

Brislowe gives cold as the exciting cause in one of his cases.

Dr. Shadwell in the National Review for February 1897 on the 'Hidden Dangers of Cycling' mentions a case within his knowledge where a girl developed the disease as the result of a rather long ride which she preferred herself able to do without difficulty.
Symptoms.

These are divided into
Primary and Secondary.

The primary or cardinal symptoms are:
- Enlargement of the thyroid: Goitre
- Prominence of eyeballs: Exophthalmos
- Rapid beating of the heart, and a fine muscular tremor.

The secondary symptoms affect most of
the systems of the body.

Perhaps in this paper it will be better
as for me it will be easier to describe
the symptoms as they affect the various
systems, after the manner of Edinburgh

Alimentary System.

In many cases, we
get disturbance of the gastro intestinal tract.
Diarrhoea is one of the most frequent of
these symptoms. It is occasionally
very severe and paroxysmal in character.
Trevesian calls these paroxysmal attacks
of diarrhea, Enteric Crisis. Cases in which
death has occurred in consequence of profuse
diarrhoea are recorded by Color and by
Paroxysmal vomiting—Gastric Crisis—is also a frequent symptom, and has proved fatal (Brit. Med. J., Feb. 16, 1897, p. 337). Haematemesis, melena, tachypnoea, and pica are also seen.

The diarrhoea is said to be of nervous origin, and comparable to other well-known symptoms, such as excessive sweating, polyuria, and profuse bronchial secretion, but on post-mortem examination of two fatal cases Grainger, Stewart, and Gibson found extensive cataract of the alimentary canal.

Pica may be taken as showing the lowered mental and physical condition of the patient, just as it is seen sometimes in a bad form in badly cared for children, and to a slighter degree in the too often anaemic working girls of our large towns.

Haemopoietic System.

This is always affected.

Anaemia is always present to a certain extent, though, as a rule, it is not so very pronounced as might have been expected.
Thyroid Gland.

Some observers have stated that occasional cases occur in which there is no enlargement of this gland. Without denying any statement on the subject, I consider it difficult to say so positively and possibly constant observation of the gland both before and after a patient became afflicted might have revealed some enlargement.

The size of the gland varies; it may be only slightly enlarged or may be very prominent, though it rarely reaches the large size seen in endemic goiter. In one case, however, reported by T. Wilks in Guys Hospital Reports 1840, the left lobe was found after death to extend down into the chest and alter the shape of the trachea.

The swelling of the gland is rarely found symmetrical; generally one lobe is more enlarged than the other, most usually the right, though Crango, Stewart, and Gibson found the left lobe more commonly to be the earliest and chief seat of the enlargement.
Yeo (Brit. Med. Journal 1894, p. 320) records a case in which for some time only the left eye was prominent while the enlargement of the Thyroid was limited to the right side and when hypophthalmos developed on the right side the left lobe became enlarged. The enlargement is by no means constant but changes with emotion or excitement.

Mann (Transact Med. Soc. London Vol. 1887) says the enlargement of the Thyroid may be present for years before other symptoms appear. The enlargement is due in the earliest stage to over-stimulation and thereafter hyperemia causing increased growth both of glandular tissue and stroma.

The intimate connection of the Thyroid with the disease will be discussed later.

Thymus Gland.

The Thymus is stated to be often found hypertrophied in Graves' disease. Paget mentions that in a post-mortem performed on a patient who died in Guy's Hospital the thymus gland was four inches long and had a thickness of three quarters
of an inch. The patient was over twenty years of age.

Dr. Rose Bradford (Brit. Med. Journal, Feb. 6th, 1891) mentioned four cases in which the thymus was found abnormally large, but states that it ought to be remembered that an enlarged thymus was found in lymphadenoma, leucocytocemia and Addisonian disease, though Jeffrey (Le Progres Medical 1894, p. 205) asserts that such condition of the thymus occurs exclusively in lymphatico-malacic goitre. Certainly it is significant that lymphatico-malacic goitre does not usually appear until a period of life at which the thymus normally disappears.

Dr. David Owen (B.M. J., Oct. 10th, 1896) considers this revival of the thymus to be compensatory in character and presents several arguments in support of his theory.

The evidence of many observers certainly goes to show that the thymus and thyroid glands have an antagonistic effect to each other on body metabolism.
The spleen also may be found affected in the course of the disease. Prof. Wood, Philadelphia, quoted by Owen, states that he found splenic extract beneficial in a case of epithelialic Goitre, and doubtless there may be some very intimate connection between the ductless glands. In only one of Grainger-Stewart's Gibson's cases was any enlargement of the spleen found, and that was in a patient who had suffered from malaria in India.

Circulatory System. The subjective phenomena of faintness and giddiness are very often the first symptoms to attract the patient's attention and force them to consult a medical man.

Precordial pain is often complained of, and on the slightest provocation, or no provocation, many patients suffer to an extreme degree from palpitation.

Cardiac dyspnoea sometimes occurs. Tachycardia is one of the primary symptoms of the disease. The number of beats may
reach 150 to 200 per minute.

In early uncomplicated cases there are no murmurs, and the sounds of the heart are clear and ringing, being sometime audible at some distance from the patient. Sometimes however, and at a later stage generally always, the sounds are blurred and murmurs are present.

Eulenburg (quoted by Grainge, Stewart, & Gibson) states that cases have occurred in which there was neither tachycardia nor palpitation. Most observers state that there is hypertrophy of the heart, and it certainly seems reasonable that this should occur. In a case of Grainge, Stewart, and Gibson, the heart weighed fifteen ounces. Faggie states that in autopsies performed at Guy's Hospital, the heart only weighed nine a ten ounces, but he admits that a degree of relative hypertrophy may have been present.

The heart as a rule undergoes dilatation from muscular failure, but it probably depends on the nutritive possibilities of the individual heart which of the two conditions occur.
Oedema, as a result of the heart mischief, is often fortuitous, either in the lower extremities, pleural or peritoneal cavities, and it has been observed in the eyelids (Sower). In a few cases solid oedema has been seen, somewhat resembling the supraclavicular swellings seen in Myxoeidema, and has led to the conclusion that the two diseases may coexist. There is great pulsation in the Carotids, and the Thyroid gland may be felt pulsating. The beats of the radial arteries are not unduly forcible, and there may be extreme irregularity of the pulse (Grange, Stewart Gibson, Bender and others). Arterial tension seems to be moderate, and in most cases the arteries are poorly filled. Although there may be no murmurs audible in the cardiac region, murmurs may be heard over many of the arteries, produced in many cases partly by the pressure of the stethoscope. Enlargement of the renal vessels has been observed, and exaggerated pulsation also (Sowers).
Flushing and burning pulse alternately is a common symptom, and a cachexia is easily produced in most cases. Palpation of the liver has been noted by Leber.

Venous phase is common throughout the body.

Valvular disease of the heart has been found, probably of independent origin. Epistaxis. The occurrence of haemorrhage from the nose has been recorded by Trouseau, de Haviland Hall and others. As also the occurrence of haemorrhage from other regions.

Faintness may be caused by an altered state of the circulation due to deficient force of ventricular systole.

The palpitation may be brought about by errors of diet or anything tending in any way to produce excitement. Dyspnoea is due to deficient action of the right side of the heart.
Tachycardia is best explained by an over-excited condition of the accelerator nerves of the heart.
Other explanations suggested are:
A diminished activity of the inhibitory influences to which the heart is subjected in health.
A change in intraventricular pressure from alteration of the circulation within the vessels.

Respiratory System.

Severe nervous dyspnea is sometimes seen also severe paroxysmal coughing, Laryngeal Crisis.
Fatal Asphyxia has been noted as a termination of the disease.
There may be profuse sputum secretion comparable to the excessive sweating and polyuria seen.
Bronchitis may occur in long standing cases, due to cardiac embarrassment.
Pneumonia and Pleurisy may occur as complications.
Urinary System.

Polyuria is frequently seen, is comparable to the excessive sweating, such a common symptom, and due to various motor influences.

Albinuria has also been observed. Granger Stewart and Gibson, however, consider that in not a few instances it would now be referred to the category of functional albuminuria.

Possibly the patient is predisposed to albuminuria, and more than ordinarily liable to pass albuminous urine on exertion and after certain diets.

Albunin is also occurs.

Bettman (Brit. Med. Journal, Epidemiac March 6th, 1879) relates a case where Diabetes Mellitus and Graves' Disease were found in the same person, a woman aged fifty-four, and he states that the symptoms of Graves' Disease became less as the sugar disappeared from the urine.

Diabetes was also present in one of Granger, Stewart and Gibson's cases, and though the association of the two diseases is
very rare, it goes some way to prove Trainghi Stewart Gibson's suggestion that kidney mischief when present in Graves' disease might be referred to some change—functional for choice—in the floor of the fourth ventricle, though it does not necessarily disprove that the kidney change may be due to vaso-motor influences.

Integumentary System

Diseases of the skin, which in Europe at all events are regarded as rather rare, occur not infrequently in the course of Graves' disease. These are Leuco-dermia, Melanoderma, and Sclero-derma, and occurring in Graves' disease must be regarded as very interesting since they are diseases of nervous origin.

Leboir (quoted by Moris Diseases of the Skin) has in some cases found changes in the nerves supplying the whitened patches of skin in Leuco-dermia.
and, as showing how nervous excitement may affect the pigment of the body.

Sir James Paget mentions the case of a lady subject to nervous headaches who found on the mornings after an attack that a patch of her hair had gone quite white, gradually returning to its normal colour.

Frequent perspiration is a common and distressing symptom, a patient sitting still suddenly breaking into a profuse sweat, due no doubt to vasomotor influence.

Addison's disease and sympathetic hyperplasia have been observed in the same patient.

There may be great changes in the cutaneous appendages.

The hair on the scalp becomes scanty and may disappear, as also from the axillae and pubes.

The character of the hair also changes, becoming dry and ragged.

As a rule, the loss is general, but it may be confined to one side of the body only.
The nails also share in the change, becoming thin, weak and brittle, sometimes indeed being represented only by a soft paper-like film (Stewart and Gibson). In the case of my own mentioned at the beginning, the nails of both hands became brittle, split longitudinally and came out, new nail growing very thin, and this coming out in its turn. Sometimes both hands are equally affected, sometimes one more than the other, sometimes individual nails are worse than the rest and occasionally the corresponding nails of opposite sides are correspondingly affected. A corrugated appearance of the nail with a yellowish opacity is sometimes seen (Stewart and Gibson). Germain Lee has observed atrophy of the eyelashes.

It seems to me that these cutaneous changes illustrate remarkably the excessively rapid rate of tissue waste — the compression of the life of the tissue into a short period of time.
which to my mind is Graves' Disease.

Reproductive System.

Amenorrhoea is generally considered to be a most unusual feature of the disease, in women, but Graniger Stewart and Gibson narrate a case in which menstruation went on regularly, and Russell Reynolds found menstruation to be the rule with a large majority of his patients. There may be a leucorrhoeal discharge. The amenorrhoea may be partly accounted for by the anaemia, but more probably it is due to the upsetting of some balance between the Thyroid and the Ovaries.

Great wasting, in fact, total atrophy of the mammae may occur, as in the case at the beginning where only the nipple is to be seen or felt. In the male sex, impotence has been observed by Trouseau and Graniger Stewart and Gibson.
Nervous System.

The nervous system shows many striking changes. Temperature, febrile attacks are common, and local irritation or mental excitement may cause a rise in temperature totally at variance with the exciting cause, and there may be a rise in temperature without any ascertainable cause.

Hyperaesthesia is a general symptom. Subjective luminous phenomena are described by Saleziowitz, and auditory symptoms by Grant, Stewart, and Gibson. General nervousness is always present. Headache is often unilateral, great irritability of the temper, impairment of memory, and sleeplessness is a common and painful symptom.

Hysteria is very common, almost any symptom of hysteria may arise. There may be localized or general convulsive seizures of an epileptic, choreic, or ketanic type. Various nervous diseases occur as complications.
Muscular Tremors.

Very fine muscular tremors form a cardinal symptom of this disease. Probably they are always present at one time or another. This tremor may come on early, but usually does not appear till other symptoms have been present for some time.

It may be present on both sides of the body, may be only unilateral, or may even be confined to one limb.

It is a very fine tremor; about 8 to the second. It may be seen by making the patient extend a hand. It affects the whole hand, not individual fingers.

Sudden giving way of the legs due to a loss of coordination is a common symptom.

A patient standing or walking will suddenly fall without warning or without any previous feeling of faintness.
Neither the superficial nor deep reflexes present constant changes.

In a good many cases, there is a diminution of electrical resistance. It is not however always so, and is sometimes met with in health, and is probably due to the moisture in the skin, even when actual perspiration is not visible.

Exophthalmos.

This is another cardinal symptom of the disease, and generally a most unmistakable one. There are all degrees of prominence of the eyes, from the case in which the patient merely has a staring expression, to a case in which exophthalmos was so marked that dislocation of the eye took place. Some observers state that exophthalmos may be entirely absent, but I am inclined to think, as with reported absence of any enlargement of the
Thyroid gland, that constant observation of the patient both before and during her illness would have revealed some prominence.

It is not uncommon to find one eye more prominent than the other, and occasionally the exophthalmos is confined to one side entirely. Dilatation of the pupil has been noted though von Graefe did not observe it once in two hundred cases.

Myopia has been suggested as its cause. Sometimes patients notice muscle.

Defective convergence of the eyes has been observed.

When there is very marked protrusion of the eyes they may suffer from exposure, and sloughing of the cornea is stated to have occurred.

Von Graefe described a very important symptom — delayed descent of the eyelids when the patient looks down, without moving the head. Sometimes the descent is altogether
delayed, sometimes in a jerky sort of way. Ramsay (Glasgow Med. Journ. Aug. 1881) notes a case in which the upper eyelid followed the first part of the downward movement of the eye, and then remained stationary while the eye looked still further downward, till after a few seconds a spasmodic retraction of the lids took place which brought the white sclerotic into view.

The presence of von Graefes symptom is by no means invariable. Mannheim and Russell Reynolds found it absent in a good many of their cases.

Sharksy found the symptom present in fourteen out of five hundred and thirteen persons; none of whom had hyperkalemic Goitre.

Von Graefe considered that the symptom was due to spasmodic contraction of the involuntary muscular fibres of Miller, which aid the Levator Palpebrae Superioris in raising the lid, and which receive
Their nerve supply from the cervical sympathetic.

Stellwag's sign is persistent retraction of the upper eyelid, due to an increase in the natural tonic contraction of the elevator of the upper lid which is always in action while the eyes are open. When present it increases the staring expression.

It may occur either with or without von Graefe's symptom.

Retraction of the lower lid has seldom been seen.

Bristowe gives an account of a most remarkable case in which there was Ophthalmoplegia Externa.

There is a slowness of movement sometimes observed in the ocular globes, the patient when directed to look at anything, turning the eyes languidly to
The spot.
This probably only occurs in long-standing cases, and is due to tiredness of the scalar muscles owing to their being continually stretched, or to fatty degeneration of these muscles.

A considerable degree of wasting is present.
Richard (P. M. Journal. Epilepsy for January 18th, 1896) narrates a case in which, without apparent cause, a patient would lose eight or nine pounds in the course of a few weeks without any alteration in his general condition. Richard ascribed it to hypothyroidism and adduced much evidence in support of his suggestion.

With regard to definite explanation of the nervous phenomena, we are met at the outset by not finding definite or consistent results on post-mortem examination, in a great many cases results being negative.
The exophthalmos has been attributed to an overgrowth of fat in the orbit but though the natural fat in the orbit has been found increased that explanation can hardly be suitable as in most cases the eye appear normal after death which they hardly could do if their prominence had been due to a physical cause pushing them forward.

Also been supposed to be due to regarded intra-cranial circulation, also to contraction of Müllers non striated orbital muscle, but none of these explanations appear to me to meet the requirements of the case.

A toxic action by something on certain parts of the central nervous system would meet all the requirements of the case, whether or not such toxic action is present I will discuss later.
Complications.

Persons suffering from gothalmic goitre are, from their debilitated condition, peculiarly liable to suffer from some intercurrent disease, and particularly from various nervous disorders. Influenza, Pleurisy, Pneumonia and Rheumatism often occur. Epilepsy and Hysteria are very common.

Locomotor Ataxy.

Jeffroy (quoted by Murray) has observed seven cases in which Locomotor Ataxy and Graves' Disease were present in the same individual.

St. John, Stewart, Gibson, and Balch have also noticed symptoms of Locomotor Ataxy in Graves' Disease.

Paralysis Agitans (Mobius), Chorea (Sauthier), Dysthy (Dreyfus Briaree), Thomas' Disease (Raymond) have all complicated the disease, as have Arthritis (Hendy, Mande).

Osteomalacia (Krepper).

Unilateral cases of gangrene of superintendent have been seen by Towers, Collins, and Rablpea.
Nature and Pathology of Graves Disease.

The multiplicity and variety of the symptoms of this disease have all tended to produce erroneous ideas as to its nature and it is only lately that we seem to be getting a clearer idea as to the fundamental features of the disease.

No one now considers that Graves' disease is a disease of the heart. Doubtless the heart is affected, but that only follows in the train of symptoms, it (the affection of the heart) does not form the starting-point of the symptoms.

Not in any theory that it might be due to organic disorder of the nervous system tenable.

Doubtless organic changes of certain parts of the nervous system would account for all the primary symptoms of the disease, but
we do not or very rarely get such changes, and we do get the symptoms. Many and careful examinations have been made of parts of the nervous system from cases of Graves' disease, and the results were mostly negative, and such changes were found were stated by Hale White to be no more than would have been found on post mortem examination of specimens taken from a number of cases at random. Filchner's experiments and those of Dandaji and Bienfait show that some of the symptoms of Graves' disease might occur as a result of interference with the normal action of the nerve centers in the medulla oblongata, and Mannheim records a case of Bulbar Apoplexy in which the symptoms of Graves' disease soon appeared, the symptoms disappearing on absorption of the effused blood took place. This case is of great value
and shows us where the seat of nervous change would be, but it proves nothing.
Müller and others have found no signs of disease in this part of the nervous system in cases examined by them, and Motiers states that as a rule no lesions of the medulla are found.
Granger, Stewart, Gibson allude to a lesion of the medulla they found in one of their cases (Edin. Med. Rep. 1881).

Put briefly, in the face of the many negative results found on examination we cannot argue any change in the nervous system to be the cause of Atrophalthamic Götte.
Professor Greenfield, Bradshaw Lecture 1878 pointed out that the changes in the nervous system found in Atrophalthamic Götte resemble the changes found in Leukence and Rabies and like them may be secondary.
Thyroid Theory

It seems to me most reasonable at present to assume that the disease is due to excessive action on the part of the Thyroid Gland whereby an excessive amount of secretion is absorbed into the system, with possibly some special action upon the nerve centres in the medulla oblongata and elsewhere.

Regarding the functions of the Thyroid we possess a great deal of evidence, the difficulty with regard to it consists in drawing a logical conclusion from that evidence that shall fit in with what is seen in disease connected with the Thyroid. Within the limits of this paper I need hardly go into details of all the experiments made in connection with the Thyroid.

It has been proved without doubt that the Thyroid has great influence on tissue metabolism, and that
That influence is in the direction of
promoting a healthy action of
the body, a stimulation of the whole
system, and more in connection with
some parts of the body than others.
A study of Dr. Byrom Bramwell's cases
of Myxoedema (Edin Hosp. Reports Vol. 31)
shows that at once.
In Myxoedema we have a deficient
action of the Thyroid Gland, and, in
consequence, in the more marked
forms of the disease, we have a
state of suspension of nearly
all the functions of the body, a
kind of living death.
Treat the myxoedematous patient with
what is lacking in her own person
— Thyroid Gland —, and we see a
reaction at once commencing,
tissue as good as dead, is call off,
a torpid brain begins to think,
a being without heat is warmed, and
a dull heart begins to beat.
Carry the process still further
and we see that the same agent
Thyroid gland— if given in doses greater than required to produce the above effects produces tissue change at a still greater rate. Béclère gives a remarkable instance of this.

A woman, aged 31, suffering from Myxedema, took by mistake ninety-two (92) grammes of thyroid extract in eleven days. The symptoms which developed were, tachycardia, rapid respiration, ophthalmos, brilliancy of the eye, transient tremor of the arms, rise of temperature, insomnia, polyuria, glycosuria, albuminuria, and partial paraplegia.

In other words, the person who formerly suffered from Myxedema then suffered from ophthalmic Gotthe or Hyperthyroidism. Her symptoms being obviously due to the thyroid extract.

The case recorded by Mannheim showed the parts of the nervous system involved, but it only proved their disease of the parts affected.
could cause the symptoms we call Gravis' Disease, it did not prove that the disease, Erythralmic Goitre is disease of those parts.

Bickell is not a solitary case. In one of Byron Bramwell's cases of Myxedema a patient had received too much Thyroid Extract and symptoms of Thyroidism followed.

A marked feature of the treatment of Myxedema by Thyroid Extract is the loss of weight which follows treatment, a hastening of the processes of tissue metabolism seen also very commonly in Gravis' Disease. In his address on the Pathology of Erythralmic Goitre to the British Medical Association meeting at Carlisle, Prof. Murray said: "A considerable number of cases have now been recorded in which owing to the development of fibrosis gradually leading to loss of function of the Thyroid Gland, the symptoms of Erythralmic Goitre have been..."
replaced by those of Myxedema.
We have seen how we could cause
Grave's disease to occur in a person
suffering from Myxedema, by
giving an excess of thyroid gland,
and now we see that we get
Myxedema following Ectothalmic Goitre
in cases where the active area of
the thyroid gland has become less.
O'Byrom Bramwell gives the case
of a lady who suffered from
Ectothalmic Goitre and afterwards
from Myxedema, and as above
stated such case are far from
uncommon.
Such cases ought to be borne in mind
when one is considering how best
to treat a case of Grave's Disease.
Cases are mentioned too, where
Myxedema and Ectothalmic Goitre
appeared to co-exist, probably they
are cases showing the transition
stage from the latter disease to the
former, and are in no way out of
keeping with what has been said.
W. Walter Edmunds, B.M., M.A., M.A. (1896) mentioned, as being against the
thyroid secretion view, the fact that
thyroid feeding in Graves' disease
does not act so injuriously
as we would a priori expect, but
may there not be deficient absorption
of thyroid material introduced
into the system by the mouth.

With regard to the part played by
the thymus gland in this disease
there has lately been much discussion
but no definite conclusions have
been arrived at beyond the
universal agreement that the
presence of a revived or hypertrophied
thymus would appear to be an
effort of nature to antagonize the
rapid waste of tissue produced by
the action of the thyroid.

There would appear to be some, as
yet not exactly known connection
between the various ductless glands.
Is the change in the thyroid gland absolutely the starting point of the disease?

I consider that it is the first visible starting point of the disease, but that it first of all receives some nervous impulse such as might be supplied by a shock, so that one might argue, that prior to the commencement of Graves' disease proper there had been a functional change in the nervous system.

One of the cases mentioned by Graves, was that of a lady who had been in a "nervous" state for three months before any other symptoms were noticed.

No theory concerning the nature of Joseph Baume's disease has yet been advanced which could not be opposed and with a certain amount of success by opponents, but it seems to me, far too little
If anything has been said about the nature and temperament of persons affected, and far too little made of their temperament as a very important factor in relation to the initial stages of the disease.

Theory says, to a large extent, humanity might be divided for the purposes of practical medical work, according to constitutional peculiarities, and every one in practice readily recognizes certain 'constitutions.' May we not add another to the number of these constitutions, and speak of a Thyroid Constitution. I have not sufficient experience to enable me to lay down hard and fast laws for the recognition of such a constitution, but, arguing from analogy, from a study of other constitutions, and from a study of this disease, I see nothing improbable in the existence of a peculiar constitution in certain people, whereby
on the slightest provocation such
nervous impulse is given to the Thyroid
Gland as to cause excessive action of it
and with excessive action the train of
symptoms known as Graves' Disease.
We have a sanguineous constitution,
a nervous constitution, a malarial
constitution, a rheumatic constitution
and so on, and, in a man of this,
The rheumatic constitution, we may
find that he has not suffered from
Rheumatism, and again with the
malarial constitution, we may not
recognize it except in persons who
have suffered from Malaria, so with
Graves' Disease. We might not
recognize a Thyroid constitution till a
person suffered from epithelialioid
or we might recognize the constitution
in a person who had not suffered
from the disease, and never might.
It seems to me difficult to explain
The presence of the disease on any
other grounds than that there exists
a class of people in whom any shock
any upsetting of the nervous balance will upset the normal action of the Thyroid. For do I necessarily argue that such upsetting of the action of the Thyroid is always in the direction of excessive action. Out of a large number of cases of Myxoedema, very many will be found to have commenced after causes similar to what might have produced other diseases. Given causes produce certain effects; but to enable that dictum to be quite accurate in medical practice we have to acknowledge the existence of certain predispositions.

Allow a person with his system "run down" to be exposed to infection, and we expect him to suffer from the results of exposure, should immunity not have been previously obtained. Let a person to sleep in a wet field all night, and we expect certain effects to follow. It may be Rheumatism or it may be an affection of the lungs, and so on, making due allowance for his constitution.
As I have said, given causes are, making due allowance for constitution, expected to produce certain effects, and to my mind, apart from the existence of a predisposing constitution it is difficult to explain the onset of Gravis Disease at all.

Hundreds of people every day are exposed to what is recognized as the chief primary exciting cause of Gravis Disease, yet how few of them suffer from it even in a remote degree, and where no appreciable exciting cause can be found to explain the onset of the disease it is perhaps because we are unable to comprehend the inwardness of mental processes in many natures.
Morbid Anatomy.

The principal changes found, of any interest or direct bearing upon the disease, are those found in the Thyroid Gland, and, occasionally in the Thymus Gland, and parts of the Nervous System.

Thyroid Gland. The principal changes found in the Thyroid are, an increase in the amount of the secreting surface of the gland, with, of course, enlargement of the gland as a whole. The number of colloid is largely increased; usually the lining epithelium is changed in character. Instead of being cubical, the cells are increased in size and columnar in type.

At the Brit. Med. Assoc. meeting at Edinburgh, Prof. Murray and others agreed that there was less colloid substance to be seen than in health. The gland stroma does not appear as a rule to be much increased in amount.
Thyroid Gland.

The presence of this gland in any number of cases of Graves' disease must be looked upon as of great interest. Apart from its mere presence, however, the gland as found in Graves' disease does not appear to differ in structure from a normal gland.

Nervous System.

As I have stated before, negative results of examinations of the nervous system are so frequent as to compel us to look elsewhere for an explanation of the symptoms of the disease, but interesting cases are met with, where changes have been found. In one of Graves, Stewart and Schimica's cases, was found a small haemorrhage of recent date in the floor of the fourth ventricle, and in the underlying nervous tissue they found a large number of colloid bodies, caused by the pressure. The haemorrhage on the nervous tissue. In the same paper (St. John's Hospital Report, vol ii) an excellent account of Bulbodysies is given.
Diagnosis

This is of course a matter of no difficulty in any pronounced case of the disease. But in any very slight case, and such cases are very numerous, the existence of Ophthalmic Goitre might be very readily overlooked. Any case of supposed ordinary anaemia in which the usual remedies have not succeeded should be carefully examined for one or other of the symptoms of Grave's Disease.

Prognosis.

With regard to the termination of cases of Grave's Disease, it is difficult to speak. Some cases last a long time, while others terminate very quickly. The immediate cause of the disease, severity of onset, age, sex, family history, and personal surroundings, must all be looked at.
Mackenzie quoting Moore, gave a case of recovery in two days, other cases are recorded in which recovery took place in twelve days, and a month. Death, however, may ensue as rapidly. Mannheim mentions a death at the end of the third day, and other cases with death at the end of a few weeks.
The majority of cases of Erysipelas Gritre run a very chronic course, cases lasting as long as fourteen, seventeen and twenty years being recorded. Certainly if one could see his way to giving a favourable prognosis in any given case I believe it would be of great service to the patient.
Statistics of hospital cases do not throw much light on the ultimate termination of Graves disease but I Willianman, Manchester traced the histories of a good many cases with the following results (A.M.J. Nov. 7 1876).
Result in thirty-two cases.

<table>
<thead>
<tr>
<th>Cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal Termination</td>
</tr>
<tr>
<td>Recovery</td>
</tr>
</tbody>
</table>

Recovery, almost complete.
(Durations of disease in years 7, 11, 7, 62.) 2

Considerable improvement.
(Durations of disease in years 8, 11, 7, 62.) (2)

Only slight improvement.
(Durations of disease in years 7, 64, 5, 27, 17, 174.) 18

Conditions much the same.
(Durations of disease in years 9, 72, 37, 22.) (2)

Patient still alive at the end of 7 years, condition not known. 1

Total. 32

---

"Hall White followed up twelve people who had been under treatment at Guy's Hospital and found that there were 10 well, after illness of 2, 3, 5, 18 years. 4. Much better. 1. Dead. 12."
The process of recovery is gradual, some cases will show an improvement in cardiac symptoms, but with Eiphthalmmie and Thyroid enlargement much the same, while in other cases the Eiphthalmmie will disappear, the other symptoms remaining.

Recovery from Eiphthalmmie Goitre, as I have mentioned, is occasionally followed by Myxedema.

Mode of Fatal Termination.

A great majority of cases appear to die from some intercurrent disease. The debilitated condition in which patients suffering from Graves' disease usually are, rendering them very liable to such disorders as Influenza, Pneumonia, and Bronchitis, all of which have proved fatal in cases of Eiphthalmmie Goitre. Phthisis was a cause of death in one patient in Royal Infirmary, Edinburgh, Pneumonic fever has been the cause
of death in a good many cases, and
heart disease from antecedent rheumatism.
The cause in a good many more.
The various nervous diseases which complicate
Grave's disease are also responsible for a
number of deaths.
When we come to consider the cause of death,
as from the disease proper, we find
that failure of the heart is a very
frequent cause of death, death being
preceded in many cases by severe attacks
of palpitation and breathlessness.
Death also occurs from exhaustion,
resulting from diarrhoea and vomiting.
The direct effects of the goitre may cause
death. Brustow mentions a case in
which death was due to the goitre
displacing and compressing the trachea.
Deaths from operative and electrical
treatment are also recorded.
Treatment.

The different methods of treatment which have been adopted in Graves' Disease may be divided into the following groups:
1. Medicinal.
2. Electrical.
3. Surgical.
4. Local.
5. By Animal Extracts.

Medicinal. I think that by this time every one must be convinced that any attempt to cure Graves' Disease by medicinal agents alone is irrational and useless, although at various times various drugs have been said to be of service.


It is given in 20-gr. doses three or four times daily, and is said to diminish the size of enlarged thyroid glands.

Iron and quinine given alternately each for three weeks at a time are said to have done good probably by acting as a tonic.
Among other drugs that have been used either for the cure of the disease or the relief of its symptoms are:


2. Electrical. Treatment by electricity has so far as I can see, very little to recommend it. The application of a current to the closed eyelids has been recommended as tending to diminish the puffiness. I fail to see how it could do so. Galvanising the sympathetic nerves has also been tried.

A method of treatment by electricity mentioned by Murray is this. The anode, with a diameter of three inches is well moistened with a warm solution of salt in water and placed on the back of the neck over the seventh.
cervical vertebra.
The cathode measuring one and a half inches in diameter is moved up and down along the line of the anterior border of the sterno-mastoid first on the one side of the neck and then on the other.
A current of two or three milliamperes should be employed for six minutes at a time three times daily.

Surgical.
I can see the rationale of operative treatment in Gravner disease, but I think that cases for operation must be selected with extreme care. Look at it this way! Is the thyroid gland the seat of the mischief? If so, then by an artificial diminution of its area we may hope for some improvement. If not, there remains the hope that the thyroid may in time become, as was
Exhausted, and a natural cure result; this is by no means infrequent; in fact, it has been stated the patient may ultimately become myxedematous through the thyroid becoming fibrosed. Therefore cases for operation must be selected with supreme care; in view of the fact that all operations on the thyroid gland are of a dangerous nature. Operative treatment however is sometimes a matter of necessity, not choice. When the enlargement of the thyroid becomes so great as to cause dysphonia by mechanical pressure, part of the thyroid must be removed in order to give relief.

Jacobsen in his book 'The Operations of January 1891' reports three operations, but in neither case with any striking success, and in the first, a distinct failure. Murray states that tapping, and if necessary, draining any cysts that are present produces good results. Ligation of the arteries of the thyroid to promote atrophy of the gland has been tried.
Ecthyrepsy.

This is the operation for exposing the enlarged thyroid and fixing it in the wound, then leaving it to shrink under an aseptic dressing.

Buchan says that the most suitable cases for operation are those in which there was an ordinary goitre previous to the onset of Ecthyreptic Goitre.

With regard to the advisability of operation, every case must stand on its own merits. Where atrophy is threatened, or where there is excessive thyrotoxicosis, or where the heart seems to give indications of not lasting, or where we are unable to afford relief from any pressing symptoms in view of what has been said about the Thyroid, I think there is every justification for removing a part of it.
Local.

In ordinary goitre, diminution of the size of the thyroid is said to be obtained by rubbing red ointment of mercury ointment into the skin over the thyroid and then allowing it to dry by exposure to the sun, and this has been done in Graves' Disease with some benefit.

Injection into the thyroid of ethereal solution of iodiform has also been tried.

By Animal Extracts:

Prof. Wood (Philadelphia) is reported to have obtained good results in the treatment of Graves' Disease by administering Splenic Extract, but the reasons for its administration do not seem very clear. Thymus Extract. This has now received a very fair trial, and numerous reports of cases have been published in which it was tried.
gland may be of not guilty known, but it seems to have some effect on counterbalancing waste of tissue and to that extent may be of service in this disease. Dr. Herbert MacAlpine (26th Oct. 1897) who has tried it in twenty cases has concluded that that in all that can be claimed for it.

General. A method of treatment which embraces all the above when necessary seems to be to be best adopted for a disease the exact nature of which we do not yet know. The first thing to be done is to order the patient to rest and to prescribe a suitable diet, light and nourishing keeping in mind the tendency to diarrhoea and vomiting. Any mental strain remove if possible. Search for any source of peripheral irritation and remove these if possible. If the case be not an extreme one give a favourable prognosis as a part of treatment.
Bromide of Potassium is the best sedative where the patient suffers from insomnia, and I mix it freely with the rest cardiac agent. As a tonic, and for anaemia I found the following combination useful and well borne. Absorbinate of Iron and Soda with Myronia in the form of Bi Palatins (Oppenheimer). Great benefit may be derived by a stay in a pleasant company at a seaside place with a fairly high altitude. Where there is much wasting give Extract of Thymus gland.

Any affection of the eyes that may supervene must be suitably attended to. Where pain in the precordial region is complained of, reliefs may be experienced by the application of ice-bags.

Give defensible stimulants for the relief of Dyspnoea.

Where all methods of treatment have failed to relieve, or the heart is beginning to threaten dilatation and the patient does not appear likely to stand the post-lager illness before natural cure, surgical treatment is indicated.