THE VALUE OF OPERATIVE PROCEDURES
ON THE THYROID GLAND IN GRAVES' DISEASE.

THESIS
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by
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INTRODUCTION.

The comparative merits of medical and surgical treatment of Graves' disease have been much discussed of recent years — in fact ever since the theory that the disease was a condition of Hyperthyroidism was first put forward.

I have always been interested in the study of enlargements of the thyroid gland. During my early student days I suffered from exophthalmic goitre which was successfully cured by operation. This tended to make me have a strong bias in favour of operative treatment of this disease. But latterly the care of these cases in private practice has taught me to realize the value of medical treatment. I know of no disease in which it is more necessary for the physician and surgeon to realize the need for each other's help.

Although commonly known as Graves' disease, the peculiar symptoms which characterize the disease were first pointed out by Parry in 1786. Little notice was taken of them until 1835. Graves again called attention to them and his name is now given to the disease. Basedow in 1840 also described the disease and it is often known as Basedow's disease, especially in Germany.
What is exophthalmic goitre? If simple enlargements of the thyroid gland are excluded and cases of thyroiditis and "malignant goitre" omitted, there still remains a large group of cases with symptoms of thyroid intoxication. The term "hyperthyroidism" is frequently used in the same sense as "thyroid intoxication". Among the cases with symptoms of intoxication there are those with diffusely enlarged vascular goitres and the classical picture of Graves' disease and there are those in which the symptoms of intoxication appear after perhaps years during which a simple goitre has been present. The disease is one that is fairly evenly distributed over the country. According to Berry exophthalmic goitre is rare in places where ordinary goitre is common and certainly is often found to exist in places where ordinary goitre is unknown. But some localities furnish more cases than others. Chester, Lancashire and the West of Scotland produced the cases which came under my observation. A peculiar feature of the disease in these parts of England is the absence of exophthalmos. Why this should be so is not definitely known. There are two views concerning the origin of exophthalmic goitre, first, that it is of nervous origin, second that it is due to a disturbed thyroid function. There are
many facts which tend to support the first view. Barie, Mendel and others observed Graves' syndrome in tabes and considered the cause of it was a lesion of the solitary bundle which is connected with the ninth cranial nerve in the medulla. The disease has been observed in cases of paresis and Parkinson's disease.

It has been shown in the cat that repeated stimulation of the sympathetic nerves to the thyroid brings about symptoms of hypersecretion. The sympathetic system can be stimulated in various ways among others by substances elaborated by the suprarenal glands and by toxins formed in the alimentary canal. Mosconi calls the thyroid the "gland of emotion". The basal metabolism in Graves' disease is greatly increased, this is due to an increased activity on the part of the sympathetic system.

The second view regarding the origin of Graves' disease is the endocrine one. Klose fed dogs with thyroid secretion from a case of Graves' disease, and, the result was the production of fever, tremors, sweatings tachycardia and exophthalmos. In Graves' disease the susceptibility to thyroid extracts is often so great that the smallest doses of thyroid may provoke accidents.
The difficulty of readily explaining the part played by a disturbed thyroid gland in Graves' disease led people to wonder if other endocrine glands played any part in the causation. When the adrenals produce a thyroid overactivity, it is probably through the sympathetic system. Goetsch has shown an accentuation of the symptom group of this disease from a hypodermic injection of \( \frac{1}{2} \) a mg of adrenalin demonstrating a reciprocal action of the thyroid and adrenals. It has been shown that after an injection of thyroglobin extracted from the thyroid gland adrenalin increases still more the arterial pressure.

The role of the pituitary is uncertain outside of acromegaly and gigantism. Operations on the pituitary or on the thyroid produce a reciprocal pathological effect. When the overactivity of the thyroid gland is checked by surgery the symptoms are usually benefited. Remembering that in Graves' disease there are two pathological conditions the sympathicotonia and hyperthyroidism one wonders which of the two can be considered the primary factor. The reciprocal influence of both is well known.

Many observers consider Graves' syndrome due primarily to the effects of a toxic substance originating in the thyroid and irritating the sympathetic system; secondarily mention has been made
of some of the many organic nervous diseases, in which Graves' disease develops. These facts tend to prove that the symptoms are the result of a permanent irritation of the Vasodilator nerves situated in the cervical sympathetic nerve and as the Vasodilators of the head and heart have their deep origin in the medulla, there lies the explanation. The sympathetic nerve sends its filaments to the bottom of the orbit and to the thyroid and cardiac plexuses. With a permanent irritation of the Vasodilators coming from its centre there is a constant afflux of a considerable amount of blood to the thyroid and retrobulbar vessels. It seems, therefore, that disorder of the sympathetic nerve is the immediate cause of Graves' disease. The more sensitive the sympathetic nerve the more easily caused is this condition.

MORBID ANATOMY AND PATHOLOGY.

The following changes are found in the thyroid in cases of Graves' disease. The gland is usually symmetrically enlarged, but only to a slight extent as compared with the enlargement found in parenchymatous goitre. Sometimes the enlargement is hardly noticeable and each lobe seldom exceeds in size a goose's egg. The surface is smooth and
the vessels covering it are enlarged and tortuous though not to the same extent as in a parenchymatous goitre of corresponding size. The cut surface appears solid and homogenous. No vessel can be made out and no colloid is visible. On microscopic examination of an ordinary stained section the most noticeable feature is the absence of the ordinary round vesicle filled with such colloid as is found in the normal thyroid. Instead of these is seen a collection of branched or stellate vesicles arranged irregularly.

The colloid material is very much reduced in quantity and may be absent altogether, instead of a single layer of cubical cells lining the vesicle, as in the normal gland.

There is found a marked proliferation of cells into the interior of the vesicle forming as it were papillae. The cells themselves are more columnar in shape and have a large vesicular nucleus situated peripherally, where the cell stains more darkly than elsewhere. What there is of colloid material is retracted and granular: in the smaller vesicles it is absent altogether. Between the vesicles there is an increased amount of interstitial tissue and a certain amount of lymphocyte infiltration
These changes represent a state of considerable physiological activity and resemble those found in cases of compensatory hypertrophy after partial thyroidectomy.

In addition to the changes found in the thyroid there are often degenerative changes found in the heart, blood vessels, liver, kidneys, muscles, mucous and serous membranes, such as are usually found in toxaemic conditions. The fatty tissue in the orbit is increased in amount. According to Kocher, swelling of the lymphatic glands in the neighbourhood of the thyroid is a constant feature. Some authorities have found evidence of hyperaemia in the medulla oblongata and small haemorrhages in the floor of the fourth ventricle, but these are by no means constant.
SIGNS AND SYMPTOMS.

The signs and symptoms of Graves' disease may now be considered under the following heads:-

1. Cardiac Symptoms. The commonest of these symptoms for which the patient seeks advice is Palpitation. The excess of thyrotoxin in the body produces an increased basal metabolism, this increases the work of the heart with the result that the pulse rate is increased. The volume of the pulse is large because of the increased outflow from the left ventricle. This eventually leads to hypertrophy and dilatation of the heart. The heart's action may remain rhythmic. Further hypertrophy and dilatation occur which may terminate in heart failure. The heart's action may become arrhythmic and the usual disorder of rhythm occurring in hypertrophy is auricular fibrillation. Systolic murmurs are heard at the apex and often at the base. The "bruit de diable" is a fairly constant sign of this disease. It is said that the heart sounds have been heard at a distance of four feet from the patient (Graves). Attacks of acute dilatation may occur. The blood pressure is of unfavourable prognosis. Owing to the cardio-vascular disturbance there is a general state of congestion. The patient complains of a constant feeling of heat.
2. **The Thyroid Gland.** It is enlarged usually to a moderate extent but in severe cases the enlargement may be scarcely noticeable. The gland may be firm to the touch presenting a granular feeling to the palpating hand. On account of the irregularity due to hyperplasia at other times, it feels soft and almost cystic. The superior thyroid artery can often be felt pulsating much more vigorously than in the normal gland. The whole gland may show an expansile pulsation. Frequently as a result of increased vascularity a soft blowing systolic murmur can be heard over the gland and a thrill can be felt on palpation.

3. **Eye Signs.** A most striking feature of this disease is the condition of *exophthalmos* it presents. This gives a peculiar "terrified" expression to the face. The *exophthalmos* is usually bilateral but occasionally it is unilateral. The degree of *exophthalmos* varies a great deal sometimes, being so extreme that the eyeball is displaced from the socket. There are various signs connected with the eye changes.

(a) There is an increased width of the palpebral fissure accompanied by infrequent winking caused by spasm or retraction of the upper lid.
10.

This is one of the earliest signs and is nearly always present. It is known as Stellwag's sign.

(b) There is a marked lagging of the upper lid when the patient looks down. This is Von Graefe's sign; it is not so constant as Stellwag's sign. It is not peculiar to Graves' disease.

(c) There is a want of co-ordination between the movements of the lid and those of the eyeball on looking upwards, Kocher's sign, Lagophthalmos.

(d) On looking upwards with the head held down the forehead is not wrinkled as it is normally. This is known as Joffroy's sign.

(e) There is a weakness of convergence of the two eyes on looking at a near object; Moebius' sign.

The reflexes of the pupil to light and accomodation are natural and beyond some unusual amount of pulsation in the retinal vessels nothing abnormal is seen with the ophthalmoscope.

4. Nervous System. The most characteristic of these is a fine tremor 7 - 10 to the second, involuntary, and most noticeable in the hands, but also to be observed in the arms, legs, tongue, lips and more rarely over the whole body. The psychic state of the patient is well known, one might contrast
the "everted" personality of the Base douran patient to the "inverted" or shut in personality of the myxodemic. People suffering from exophthalmic goitre exhibit a restlessness and an overalertness, also marked apprehensiveness and anxiety often they are irritable and have fits of temper. In very severe cases mental symptoms may take the form of an active delirium, in others there is deep depression.

5. Changes in the Skin. The skin is moist and the patient perspires freely, particularly in the hands and under the arms. The hair falls out and is often prematurely grey. The nails crack and become striated longitudinally. The teeth become brittle. Pigmentary changes are common, but much bronzing shows that diseased suprarenals are a complication. Sometimes well defined areas of leucoderma are seen on the neck. In long standing cases where the thyroid seems to have become exhausted the skin acquires a myxoedematous condition. Owing to the moisture in the skin its electrical resistance is much diminished.

6. Metabolism. It is certain that a maintained increase in the basal metabolism is the fundamental symptom of exophthalmic goitre. All the symptoms of exophthalmic goitre increase or decrease as the
metabolism varies. In severe cases the oxygen consumption is increased to as much as 50% to 70% above the normal. The amount of urea excreted in the urine is increased. In a very severe case the patient loses weight very quickly. This is due to the rapid oxidation of the tissue and the burning up of the patient's own tissue protein. Therefore the basal metabolism as shown by the calorimeter is greatly increased. There is a lowered tolerance for glucose — that is to say the amount of glucose which can be given without causing glycosuria is less than average. Hence glycosuria is frequently present.

7. **Changes in the Blood.** The red cells and the percentage of haemoglobin are about normal or slightly reduced. The polymorphonuclear leucocytes are diminished and the lymphocytes increased often to double the normal amount. The eosinophiles are usually diminished. The diagnosis of a typical case when the cardinal symptoms are well marked presents no difficulty. Cases of Graves' disease occurring in men above middle age are rarely diagnosed because of the sex of the patient and the ill defined swelling of the thyroid gland.

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COURSE AND PROGNOSIS.

The course of exophthalmic goitre is fairly typical. The well known work of Plummer has shown that at an average of nine months from onset there is an acute exacerbation of the symptoms which more or less prostrate the patient. About this time the gastro-intestinal symptoms develop. The crisis reaches a climax, then improvement sets in. The patient then has ups and downs for an average of about 2 years from the time of onset when there is a second crisis, which is not usually so severe as the first from the lesser degree of toxicity the patient very rarely dies at this time. The cardiac dilatation during the first crisis is about \( \frac{1}{2} '' \) and at the second crisis is about \( 1\frac{1}{2} '' \). As a rule the disease runs a chronic course, but if left untreated it slowly progresses and probably the ultimate condition, if no complications supervene, would be one of myxoedema. Under suitable treatment some patients apparently recover but the large majority seem to improve for a time then relapse again. Pneumonia bronchitis and cardiac disease seem to account for about half of the fatal cases. If the disease develops suddenly the outlook is very grave.

A peculiar form of the disease sometimes manifests itself as acute exacerbations brought on
by catarrh or influenza or angina. All the symptoms increase in severity and death may result in 48 hours or less from overexertion of the heart. The heart becomes enormously dilated and its action very irregular. The temperature goes up to 104 or 105 and there is much dyspnoea, albuminuria, and oedema. The patient becomes delirious and finally dies from coma, a similar course is sometimes observed after operation especially if it has been performed under a general anaesthetic.

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ILLUSTRATIVE CASES.

Case 1. R.A., male, age 34, miner.

He complained of a swelling in the neck, and that the least excitement put him into a "useless state of trembling", and that he had lost confidence in himself.

Water Supply. He had lived at Dunkeld and Rosewell. At Dunkeld the water was got from Loch Ordie. The houses were supplied by communal taps in the street. Buckets were filled and then used as needed. At Rosewell the water was also supplied by communal taps, he did not know where it came from, but he declared it was very dirty and brown coloured.

Family History. The mother and father were both alive and well and there was nothing to suggest any previous nervous trouble.

Personal History. He had no gastric trouble, his habits were simple, he was a moderate smoker and teetotaller.

Previous Illnesses. He had had measles and whooping cough in youth. There had always been a tendency for rheumatism to manifest itself by frequent sore throats.

Emotional Factors. In June 1922 the patient was very badly cut about the scalp and his left hand badly hurt by a fall of rocks in the pit. He was off work for 16 months. In November 1924 his head was
badly bruised by another pit accident and he was off work for 1 month. In February 1925 his head was cut by a falling stone from the pit head and he was off work for 1 week. He felt he had lost confidence in himself after his first injury; after the second he was always in a state of apprehension. After the last he was too frightened to go down the pit and when he did he was pouring with sweat through nervousness.

Symptoms. Patient stated that his eyes got sore and ran with tears after no exertion. Bright lights troubled him. The least exertion made him shake so much that he was unable to shave himself.

On Examination. The thyroid was enlarged, the right side was much more enlarged than the left. The skin over it was freely moveable. The surface was uniform and there were no nodules to be made out. There was a slight tenderness on the right side. At times there was difficulty in swallowing.

Eye Signs. Von Graefe and Stellwag's were negative. Moebius was positive. Joffroy's was negative. The wink reflex was rather increased. There was no exophthalmos. The pupils were equal and reacted to light and accommodation. There was no pigmentation of the lids. There was marked tremor of the lids when the eyes were closed for inspection.
Cardio-vascular System

The patient felt his heart throbbing and heard it beating when excited. The heart was not enlarged B.P. 120/70 T 97. There was marked throbbing of the aorta.

Treatment.

He was put on acid sodium phosphate, grs XX and sodium salicylate grs X t.i.d. with chloral and bromides at night to ensure sleep. After he had settled down and become somewhat less nervous he was sent to have his teeth extracted. The lower jaw was cleared out on the 11.6.25 and the upper jaw on a fortnight later. He was sent to the Eye Department and found to have a slight degree of myopic astigmatism and after this his headaches and sore eyes improved. He was allowed up after one month in bed and continued to improve slowly, becoming steadier and less nervous, the basal metabolic rate still remained below normal and his weight did not alter appreciably. After three months in hospital he was sent home greatly improved.

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Case II, Mrs I.H., age 42, housewife.

Water Supply. Native of Fife. The water supply where the patient lived was well known to be hard and limy.

Heredity. There was no history of goitre in the patient's family, nor of nervous disease.

Personal History. The patient always had a good appetite, she did not eat much but had no intense likes or dislikes. She ate much vegetables cooked and uncooked, also salads and fruit. She gave no history of any previous illnesses or accidents.

Symptoms. She first complained of nervousness and an abnormal fullness of her neck of about 2 years duration. She also sweated a great deal. About 10 months ago the nervousness increased so much that she was not fit for her work and she was sent for advice. She noticed also that she had been losing weight.

State on Examination. The skin was rather sallow and had been becoming browner of late. The gland was moderately enlarged the left side somewhat more than the right, the isthmus was clearly defined, there was transmitted pulsation on either side, no dilated veins or other morbid appearance. Sometimes there was difficulty in swallowing, but she never had any attacks of choking. There was no dullness under
the shernum. Both eyes were prominent and the palpebral fissure was wider than normal, pupils equal and active, rather large, Stellwag's sign and Moebius' were negative.

Cardio-vascular System. The pulse rate was 104. She had one attack of palpitation. She was always conscious of her heart's action. There were systolic murmurs heard over all areas of the heart.

Nervous Symptoms. Fine rapid tremors were present in the fingers - they became course and spread to the arms, legs and head when the patient became excited. She was very excitable, profuse perspiration and flushing was noticed when she was being examined. The patient had suffered from constipation all her life.

Faeces. Total fats 41% (of which 52% are split fats).

Blood. The Wassermann reaction was negative. Fasting sugar .115%. Sugar curve - high and prolonged, 50 grms given over 1 gm excreted in 2 hours. Still above renal threshold then.

Basal Metabolic Rate.

| 31 :7 :25 | 70% |
| 13 :8 :25 | 65% |
| 26 :8 :25 | 40% |
The patient was admitted for operation but as she was not in a fit condition for it she was transferred to the medical side. She was ordered rest in bed for 2 months and she was given Lugol’s solution of iodine M 5 t.i.d. This did not seem to affect the progress. Improvement was steady, as the following table shows:

<table>
<thead>
<tr>
<th>Week in Hospital</th>
<th>B.M.R.</th>
<th>Pulse Rate x Pulse Pressure x 1000</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>-</td>
<td>8.36</td>
<td>7st.3¹/₂lbs.</td>
</tr>
<tr>
<td>2.</td>
<td>+ 10%</td>
<td>6.73</td>
<td>7st.3¹/₂lbs.</td>
</tr>
<tr>
<td>3.</td>
<td>-</td>
<td>6.33</td>
<td>7st.7lbs.</td>
</tr>
<tr>
<td>4.</td>
<td>+ 65%</td>
<td>7.9</td>
<td>7st.8¹/₂lbs.</td>
</tr>
<tr>
<td>5.</td>
<td>+ 40%</td>
<td>7.28</td>
<td>7st.13lbs.</td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td>6.93</td>
<td>8st.2lbs.</td>
</tr>
</tbody>
</table>

After 6 weeks rest the patient was seen by a surgeon. Her mitral stenosis was considered to be a contra indication to general anaesthesia although compensation was fully established, but it was considered justifiable to operate under local anaesthesia.

Operation. The neck and superficial tissues were infiltrated with ½ % Xeroacaine. The sterno mastoids were also infiltrated and the cervical plexus via Barun’s point. A curved incision was made across the neck from right to left and the skin flaps reflected upwards
21.

and downwards. The fascia was divided and the sternal head of the sterno hyoid muscle cut. The branches of the anterior jugular vein which was ligatured were clamped and cut. The capsule of the thyroid was adherent to the gland tissue in a marked way as though X ray therapy had been given. The anterior part of the right lobe was then shelled free of the capsule and cut away, leaving a portion of normal tissue in the posterior bed. The superior and inferior thyroid vessels were clamped and ligated at the same point. The left lobe was untouched. Haemostasis having been thoroughly secured the structures cut were sutured together in the reverse order and the skin closed with silk worm gut and Michael clips.

The condition was fairly satisfactory that evening. Next day the pulse was very rapid (200-) but quite regular, i.e. acute hyperthyroidism had set in. She was given digitalis. She remained semi-conscious and died at 4 p.m.

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Case III, M.B., age 21, female, single waitress.

In the winter of 1923 she noticed that her eyes were protruding. At this time she was nervous, run down, easily tired and suffered from palpitation; the protrusion of the eyes came on suddenly after she had had a bad fright, having been disturbed by burglars one night. The swelling in her neck got worse and she left her work to go home to rest. After some months she had improved greatly till an attack of influenza after which the disease got worse and she came to the Infirmary.

History. Patient had lived at Orkney till she was 16 years of age. Here the water supply was hard. Patient lived on a farm which had a private supply derived from a quarry. After she was 16 she lived in Edinburgh where the water supply is protected and filtered.

Family History. There is no history of goitre or nervous disease in her family.

Personal History. The patient drank a lot of milk; not much fruit, plenty of fresh vegetables, and said she always took a lot of tea.

Previous Illnesses. She had had measles very severely at 12 years of age and influenza very badly in 1923 when she had been 3 weeks in bed and since
then had not felt well. Her upper teeth were decayed and had been removed. There was no history of nose, throat, or ear trouble and she was otherwise perfectly healthy except for constipation, which had troubled her for about 2 years (ever since the goitre had started).

On examination thyroid gland. There was a large bilateral swelling in the front of the neck, size of a large egg, on each side and extending up on each side of the thyroid cartilage. On palpation the enlargement was smooth and was of soft consistency.

The Eyes. There was marked exophthalmos equal in both eyes. The upper lid was retracted and pigmented and lagged behind on looking down. There was no weakness of convergence. Pupils reacted to light accommodation.

Cardio-vascular System. Pulse was regular in time and force. The rate was 110 and the tension was good.

Heart. On inspection pulsation could be seen over a large area internal to the left nipple and covering the 3rd, 4th and 5th interspaces, tremor of the intercostal muscles could also be seen. On percussion the heart was enlarged to the right. The blood pressure was systolic 132, diastolic 62.
The Blood. The Wassermann reaction was negative. Glucose tolerance test. After 50 gms of glucose there was no glycosuria. Curve a little high and fell slowly. Basal metabolic rate was +55%.

This was a fairly severe case of exophthalmic goitre at a relatively early stage and she was seen in consultation with a surgeon who thought that medical treatment was advisable in the first instance.

She was given complete rest and after a week of investigation was put on insulin 5 units t.i.d. Soon this was increased to 10 units. She stood this very well for a week and then developed very red and painful areas round the sites of injection. To combat this 15 gms of glucose were given orally one hour before insulin, as it was thought that the reaction was a manifestation of hypoglycaemia. This certainly improved the condition and after the dose had been increased to 30 gms cleared it up entirely. The patient was also given acid sodium phosphate grs XX t.i.d. The basal metabolic rate at this time was still +62%. The insulin and glucose were continued for another month and were well borne. The weight increased slightly (5 lbs) and the pulse remained fairly steady at 100. During this time the basal metabolic rate was +39%. On the 28th June unsulin and glucose were stopped and potassium iodide gr I
b.i.d. begun. It was given for 7 days. The pulse rose to 20, then fell to 90. The pulse pressure fell to 70 and the basal metabolic rate to -12%. Insulin and glucose were recommended, 10 units and 30 gms b.i.d. The pulse fell to 80 with the basal metabolic rate at +27%. During the next week the pulse fell to 100 but the basal metabolic rate was still +31%. On 29th July the basal metabolic rate was +52, pulse pressure 80, pulse rate 100. Insulin and glucose stopped. Lugol's solution of iodine M 5 t.i.d. was begun and the patient gained 3 lbs in 4 days. The dose had to be reduced as patient developed an iodine rash, still she gained 4 lbs during the next week. On the 13th August, 1925, she was transferred to a convalescent home for prolonged rest.
Case IV, M.F., age 44.

She came first under my notice with a month's history of headache and giddiness, necessitating her leaving off her work of ironing. She had been in bed on and off for a few days at this time during this period.

Examination revealed well marked exophthalmos, general enlargement of the thyroid and a pulse of 112. Von Graefe's sign was present and there were fine tremors in both hands. She perspired freely and her weight was 7 st. 1 lb. The urine contained no albumin but Fehling's solution was reduced.

She was kept in bed and treated with general tonics while ice was applied to the thyroid. By the middle of August there was a noticeable diminution in the amount of exophthalmos, but otherwise there was no change. At times she complained of precordial pain and a systolic murmur could be heard at the apex. She had electric baths twice a week. This treatment was continued till June when her weight was 7 st 2½ lbs. Her pulse rate varied between 132-110 and her temperature was usually subnormal.

It was now decided to try the effect of operation. Accordingly on June 11th the left lobe
of the thyroid was removed under a local anaesthetic. After the operation she vomited a good deal and her temperature was 100 for 2 days. She was given plenty of water to drink and had no further discomfort. The wound healed perfectly and she was allowed to get up on July 1st. On the 8th July it was noticed that the exophthalmos was less and the eyes were not so staring as they had been. Von Graefe's sign was still present and also fine tremors and the pulse rate was 110. By the end of the month her general condition seemed much improved and she was sent to a convalescent home for a month. Her weight was 7 st 10 lbs when she went and 7 st 12 lbs at the end of her time there. The tachycardia remained unchanged and Von Graefe's sign was always to be obtained. Her voice was weak and there was diminution in the tremors. She was seen again on Nov ember 11th. She said she felt 10 years younger. There was still some swelling on the right side, but very little exophthalmos. She chiefly complained of weakness and swelling of the feet and ankles. Her pulse was 130 and her weight was 9 st 2 lbs in her clothes.

When last seen in December of that year her weight was 9 st 5 lbs in her clothes. Her voice was stronger, there was still some slight exophthalmos and Von Graefe's sign was still present. Her pulse rate
was 120. Though able to do her work, she said she soon got tired and would soon have to give it up altogether.
Case V, M.C., female, age 49, domestic servant.

She complained of nervousness of many years duration and weakness of about 2 weeks duration. History. 10 years ago the patient had been in Leith Hospital, where she was told she had exophthalmic goitre. She improved and put on a fair amount of weight after her discharge from Hospital she went out to Canada and while in Edmonton had an operation performed, – the partial thyroidectomy. The scar is still visible and fits in with history. After she returned from Canada she became much more self-conscious than before and used to imagine that people were talking about her and eventually got into the habit of making accusations against comparative strangers. She also had frequent emotional outbursts. After one very bad one she was sent to Hospital.

State on Examination. She was a small woman, well nourished with well marked exophthalmos and scarcely able to stand. The thyroid was not enlarged but there was visible pulsation in the carotids. There was a transverse scar just above the sternum. The thyroid gland was only just palpable.

Eyes. There was well marked exophthalmos and the pupils were equal, circular and reacted well. Von Graefe's sign was positive, also Stellwags Moebius and
Joffroy's. Tremor was not at all well marked.  

**Cardio-vascular System.** Pulse 120, regular in time and force, apex beat was in the fifth interspace, 4" out. Sounds were closed in the mitral area and soft systolic murmurs were present in all other areas.  

**Nervous System.** Intelligence was below average. Memory was deficient. Patient was very emotional and excessively affectionate in her manner. She was always declaring that someone had told her such and such a thing was going to happen (e.g. the Queen was coming to see her or that she was going to die).  

**Progress.** She was so restless and talked so incessantly a lot of nonsense disturbing everyone that she was transferred to the ward for early mental cases, not long afterwards she had to be certified as of unsound mind.  

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Case VI, E.E., age 18, machinist, first seen in May 1925.

She said she first noticed her eyes being prominent about 1 year ago. At the same time she suffered from palpitations and shortness of breath and was in a general condition of nervousness. In August 1924 she had noticed a swelling in her neck which had commenced on the right side. In October her voice became affected so that she could no longer sing. Since then she said she had been gradually getting worse.

On examination she was found to be a fat healthy looking girl. Her eyes were very prominent. Stellwags and Von Graefe's signs were both present, but the latter was not well marked. There was some brown pigmentation about the neck and the thyroid was much enlarged especially on the right side, the circumference of the neck being 15½ inches. There was some difficulty in deglutition. She was very nervous and had well marked tremors in the hands. Her pulse was 80. The heart was slightly dilated and there was a systolic murmur at the apex. The urine contained no albumin and did not reduce Fehling's solution. After a week's rest in bed as the obstruction to deglutition seemed to be getting worse it was decided to operate. A partial thyroidectomy was
therefore performed under novocaine and adrenalin, 2 hypodermic injections of morphia (\(\frac{3}{4}\) gr) having been given. The dissection proved difficult owing to the many large and aberrant vessels and there was considerable bleeding. The thyroid was found to extend behind the oesophagus. The patient bore the operation well. Her pulse which was before the operation 100 went up to 140 afterwards. She made a rapid and uninterrupted recovery. On July 26th the scar on the neck was quite healed and decidedly smaller than it had been. Her pulse rate was 96. The eyes were less prominent and her general condition satisfactory.
Case VII, J.W., male, single, age 29.

He complained of being nervous all his life. This had been most noticeable to others. Life in the army, especially in the trenches, tended to make this worse. He also complained of sore eyes for some years. His vision became blurred after a long day's reading or writing. He had noticed his eyes becoming prominent; this had been getting worse lately.

Water Supply. Patient declares that when he was in the army he did not exercise enough caution concerning his drinking water. The water in Alloa where he lived at home was soft.

Heredity. There was no history of goitre. The mother was of a somewhat nervous temperament and occasionally had difficulty with her speech. The father, two brothers and one sister were all alive and well.

Personal Habits. He was a moderate drinker and smoker. He was very fond of drinking tea. He ate a good amount of fruit, bread, scones, and cooked vegetables.

Previous Infections. He gave a history of measles, mumps, colds in the head and frequent sore throats. His appetite was poor and his bowels were constipated.

On Examination. There was a slight visible enlargement of the thyroid. On palpitation the enlargement was uniform and symmetrical. There were no nodules. On auscultation there was a soft systolic murmur just audible. The gland moved freely on swallowing.
There was no dysphagia or dyspnoea.

Eyes. There was slight bilateral exophthalmos. Von Graefe's sign was present, also Stellwag's. The pupils were equal circular and slightly dilated. There was slight brown pigmentation of the eyelids.

Cardio-vascular System. The pulse varied from 90–100 per minute and there were slight recurrent attacks of palpitation. The apex beat was in its normal position, fairly forcible, localised and there was no thrill. There was a soft mitral systolic murmur which was not propagated.

Nervous System. There was a fine tremor of the tongue and there was also the characteristic tremor of the fingers.

Gastro-Intestinal System. His appetite was poor. Bowels were constipated. Stool 18% fat of which 33% was fatty acid. He was treated medically as a fairly mild case of exophthalmic goitre, being given tinct Belladonna, acid sodium phosphate, insulin and glucose. This did not have the expected effect on his weight, although he complained of hypoglycaemic symptoms before the insulin was accompanied by glucose. His appearance and general state improved but he did not lose all his tremors or exophthalmos. The blood pressure rose steadily but the pulse pressure did not alter appreciably. The basal metabolic rate fell
and this may possibly be attributed to the long course of insulin. During the next month insulin was stopped and he was put on to liq. arsenicalis M III t.i.d. He improved greatly and left the hospital soon after.
Case VIII, R.F., age 30, typist, was admitted to the Royal Infirmary in December 1924 with the following history.

She first noticed her neck swollen about May. She consulted her own doctor who prescribed thyroid tabloids and later on medicine, the nature of which was not stated. This treatment did not reduce the size of the gland, but the patient lost about 14 lbs in weight and had to leave off taking the medicine. Then she began to suffer from palpitation and in consequence she was obliged to give up playing hockey and later on cycling. She said she had never been troubled with palpitation before taking the tabloids. For some months she had noticed that her hands became very shaky when she was tired. In September she had to give up work altogether. She then saw a second doctor who prescribed rest in bed. She found, however, that she lost a stone in weight in a fortnight, so she got up again. She then went into the country and spent her time in gardening and was much improved. Later on she saw her doctor again and on his advice decided to go into the infirmary.

On admission she was found to be very nervous. Her pulse rate varied from 80 - 140. There was slight exophthalmos, a fine tremor of the hands
and both lobes and isthmus of the thyroid were enlarged. Von Graefe's sign was present but not well marked. She perspired very freely. One week after admission the right lobe of the thyroid was removed under local anaesthesia, extensive infiltration of the tissues with 5% novocain solution and a little general anaesthesia just to keep the patient quiet. After operation the pulse rate was 120 and remained so till 3 days later when it fell to 96. The stitches were taken out on the 8th day after operation and the wound was perfectly healed by the 12th day. It was then found that the tremors had practically gone and that the perspiration was not so profuse. Her voice which had been weaker was better and her speech was not so hurried. Her eyes were more natural in appearance and the average pulse rate was slower, on January 1st she was discharged improved.

Nearly 2 years later on reporting at hospital she declared that the operation had been a complete success in every way. When she had left the hospital she weighed about 6 stone. She had then gone to South Devon for 3 months, during which time her appetite increased and her weight went up to 9 stone. In answer to further questions she said
she could now play hockey and cycle as well as ever. Her voice is quite natural and her hands are no longer shaky. She does not suffer from palpitation and does not perspire more than other people. In short she considers herself completely cured.
Case IX, M.R., age 19, was admitted to hospital in November 1924. She had noticed a swelling in her neck for about 1 year, also some prominence of the eyes. She suffered from breathlessness and tremors during the same period. The swelling was not increasing in size and her average pulse rate was 124.

For 6 months she was ordered rest and given general medicinal treatment, but showed no signs of improvement at all. Operation was, therefore, proposed and on May 10th 1925. The superior and inferior thyroid arteries were tied on the right side. A local anaesthetic novocaine and adrenalin was employed to start with, but early in the operation Chloroform was given as the anaesthesia had not extended to the lower part of the incision. After the operation the pulse was 140. On the 19th May her condition was described as follows: "Feels much better, hands less tremulous, exophthalmos about the same, pulse about the same, marked pulsation in the carotids, especially on the right side. Von Graefe's sign present. The apex beat was $\frac{1}{2}$ outside the nipple line and the impulse was forcible. No murmur could be heard at the apex, but there was a systolic
murmur audible over the wound and also over the pulmonary valves. On June 1st she was discharged from hospital relieved. There was then a slight discharge from the wound and her pulse rate was 100. On September 6th she was again admitted to hospital, saying she had noticed an improvement in her general health since the operation and had put on flesh.

The following note described her condition on 15th September: "Eyes a little prominent (about as before), very little swelling in the neck.

Heart. Apex 5 inches from the middle line, impulse very forcible, shakes the whole chest and causes retraction of the right nipple. No murmur. Hands still very tremulous. Pulse 120. She cannot do more than a very little work. She was discharged on the 17th and advised to come up later for a further operation. This was performed on November 24th, the superior and inferior thyroid arteries on the left side being tied under general anaesthesia. During the operation the pulse rate rose to 136 and on the 25th it was 126 and on the 26th 106. On December 2nd the stitches were removed and the wound was quite healed by the 9th. The pulse rate was then 100. On May 29th she was once more admitted to the hospital, she looked fairly well, but a considerable degree of exophthalmos had reappeared. She said she had lost
3 lbs in weight during the previous 3 months. There
was marked tremor of the hands, her pulse was 124,
and the precordial pulsation was as well marked as
before. As the improvement obtained by ligaturing
the arteries was obviously not being maintained, it
was not thought advisable to take further measures.
Accordingly on June 1st a partial thyroidectomy was
performed, the left lobe of the thyroid being excised.
She bore the operation well in spite of some venous
bleeding. A week after the operation the pulse rate
had dropped to 100 and her general condition was
satisfactory. On June 28th she was discharged
"improved", her weight steadily increasing. On July
24th she reported. She was much better and had
gained 1½ lbs in weight. Her eyes were only slightly
prominent. She sometimes had palpitations and she
got short of breath if she got very excited. Her
hands were still shaky, but less so than they were.
She has had no further illness but she says she can
do no work.
Case X, J.B., age 20, kitchenmaid, had noticed a swelling in her neck for 2 years. For 6 months previous to her coming under treatment, she had suffered from palpitation, tremors and had lost weight rapidly. When seen in July 1925 she was a fairly well nourished girl. Exophthalmos was well marked. Her pulse rate was very variable, being very rapid on any excitement and about normal when she was at rest in bed. Tremors were very noticeable in the hands and she was subject to disagreeable flushings. There was a very large goitre. The heart’s apex beat was in the fifth space in the nipple line rather forcible but no murmurs could be heard.

Rest in bed and medicinal treatment failed to produce any noticeable improvement so it was decided to try operation. On July 17th the right lobe of the thyroid was removed in two portions under general anaesthesia. The wound was drained. On recovering from the anaesthetic the patient was in a state of wild excitement: the pulse rate rose to 200. The symptoms of apparent acute thyroidism were quite uncontrollable and increased. She vomited several times during the night and oxygen was administered. The wound discharged freely. Her condition remained the same until the afternoon of the 19th. Her face became flushed and the breathing irregular.
The pulse rate was hardly able to be counted at the wrist and the right side of the heart became greatly dilated. At 6 p.m., 50 hours after the operation, she died.

Case XI, A.S., age 40, nurse, was admitted to Hospital in January 1924. For 2 years she had suffered from anaemia, palpitation, and sleeplessness, for which she had been taking trional, paraldehyde and chloralamide. She had noticed a swelling in her neck for a month and had been losing weight for 6 months. A few days previous to her admission, she had been suffering from vomiting.

On examination, she was seen to be a thin, dark-skinned woman. There was no exophthalmos but some slight nystagmus. Von Graefe's and Stellwag's signs were present but Moebius' sign was not. There was a swelling in the situation of the thyroid and a fine tremor in the hands. Her breathing was rapid and her pulse irregular. A thrill could be felt at the base of the heart and in the vessels of the neck. No murmur could be heard at the apex, but there was a systolic murmur at the left base well heard.

Early in February some bronzing of the skin was noticed in various parts of the body. Throughout the month she steadily lost ground. A systolic
murmur developed at the apex. The right lobe of the thyroid showed more enlargement and there was some slight exophthalmos. Her weight was steadily decreasing. Owing to the very definite pigmentation of the skin and to a positive result to a Tuberculin Reaction Test, and also to the presence of glycosuria it was suggested that the case might be one of Addison's Disease. Two other physicians were asked to see her, they were not disposed to agree to this idea and the case was considered one of Graves' disease.

Up till March she was treated with digatilis arsenic malt and cod liver oil. She was then given X ray treatment, short exposures over the thyroid daily for one week and then a rest for 3 weeks. She began to improve slightly. She remained in hospital till September when she was discharged as cured. Her pulse was 96. The pigmentation had gone and there was very little, if any, exophthalmos. I have been unable to trace her further history.

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Case XII, E.M., female, age 40, was admitted to hospital on the 11th July 1924 with the following history.

She had noticed a swelling in her neck for 9 years, which had decreased during the last month. In January 1924 she had had quinsy. She felt so weak afterwards that she had stayed in bed till the end of March. In April she was up for a few days and did two days' work. She then developed great weakness and breathlessness and had pains in the chest and abdomen and was quite unable to do anything.

On examination she was found to be very thin and wasted. Her pulse rate was 106 and she was very short of breath. Exophthalmos was marked and Von Graebe's sign was present, also Joffroy's sign. There was a fairly large goitre, the right lobe being larger than the left. The skin over it and the eyelids were pigmented. The jugular veins were distended, and the goitre pulsated visibly; the right border of the heart was $2\frac{1}{2}$ inches to the right of the middle line, and the apex beat could be felt in the axilla. There was a loud systolic murmur at the apex and rales could be heard all over the lungs. There were no well marked tremors. From July 14th – 22nd she suffered from much diarrhoea and vomiting.
On July 21st the following note of her condition was made: "She has repeated weak cough, she has had one attack of well marked dyspnoea and several smaller ones. The thyroid is enlarging down behind the sternum or perhaps the thymus. She is losing weight and is a very awkward case for there is danger of having to do a tracheotomy in a hurry. The lesser risk for her would be to tie some arteries if possible the inferior thyroid on each side."

On July 25th she was very restless and had increased difficulty in breathing. Her pulse was 108 and very weak. She was obviously too weak to undergo any operation and on July 29th she died.

A post-mortem examination was made on the following day; the thyroid was found to be uniformly enlarged and no cysts could be found. It weighed 3 ozs. and extended a little below the level of the manubrium sterni. It was firmly adherent to the outer aspect of the trachea. The thymus was very enlarged. The heart was dilated and the lungs and other organs all showed signs of chronic congestion.

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Case XIII, A.P., aet 30, married, was first seen in April 1925. She had noticed a swelling in the neck for some months and for a long time she had felt "shaky and nervous". She had palpitations and shortness of breath on the slightest exertion. On examination she was found to have a slight amount of exophthalmos. Von Graefe's sign was present. The thyroid was obviously but not markedly enlarged and a thrill could be felt over it. Her pulse rate was 120, well marked tremors were present in the hands. The urine was not normal. A fair degree of anaemia was present. She was ordered to bed and put on light nourishing food for three weeks. She was then allowed to get up for an hour or two during the day time. All this time she was taking a mixture containing Arsenic Belladonna and Potassium Bromide, but with very little good result. She was then sent away for a change of air and returned after 3 weeks feeling better. She was now allowed to go about her ordinary household duties and was only seen at intervals of some weeks, when she had what she called "attacks of faintness", but which seemed to be more of the nature of hysterical attacks lasting 2 – 3 days. These usually yielded to treatment with bromides quite easily. Her pulse rate was very erratic, being often hardly countable and usually irregular. The thyroid remained enlarged
and no alteration was noticed in the tremors.

In October it was decided to try the effect of treatment with thymus gland extract, $2\frac{1}{2}$ grains were given twice a day to commence with and after one week this was increased to 5 grains twice a day; at the same time the thyroid was painted with iodine 3 times a week. This treatment was continued very satisfactorily and when last seen the thyroid was decidedly smaller than it had been, the exophthalmos was hardly noticeable. The pulse rate was 96. She said she had felt much better than she had done for a long time and was able to do her household duties quite comfortably. She no longer felt "done for" as soon as she went for a walk. She had not had one of her attacks for more than 3 months. She was, however, still nervous and there were well marked tremors in the fingers. During the last year she gained 12 lbs in weight.
Case XIV, M.R., aet 20, housemaid, was first seen on July 9th 1924. She complained of a swelling in her neck and that her hands were shaky. Five years previously she had had a severe fright on hearing that her mistress' daughter had been killed on the railway. This had been followed by a nervous breakdown. She noticed at the time that she had some prominence of her eyes, but it had diminished since. For 2 years she had been wasting and during the last year had noticed the tremors in her hands and the swelling in her neck and also a certain amount of shortness of breath and pain in the side on exerting herself at all. For the last month her hair had been coming out in large quantities. She also gave a history of diarrhoea and nausea during the last few months and said she perspired rather freely.

On examination she was found to be a healthy looking very excitable girl. She talked very rapidly. Her temperature was 99.6° and her pulse rate 144. The skin on her neck was rather dark and had the appearance of being sunburnt. The pulsation in the carotids was very noticeable. There was some prominence of the left eye, but very little if any of the right. Both Moebius' and Joffroy's signs were present, but Von Graefe's could not be obtained. The thyroid was
moderately and equally enlarged on the two sides, a systolic thrill could be felt over it. Fine tremors were easily visible in the hands. The apex beat was in the fifth space, $5\frac{1}{2}$ inches from the middle line and was very forcible. The area of cardiac dullness extended one inch to the right of the sternum. There were no added sounds; the urine contained no sugar or albumin. A blood count showed 4,785,000 red cells, 5,600 white, of which 38% were lymphocytes and 54% poly morphs, haemoglobin 76% and colour index .8. Her blood pressure was 105 and her weight 8 st 1 lb. She was ordered complete rest and put on a light diet and given thyroidectin gr V t.i.d.

Very little improvement resulted and on August 6th her condition is noted as follows:

"She feels better but has no appetite. Thyroid is still very swollen but quite soft. Perspires much less. Left eye is still prominent, skin less pigmented. Tremors still present and quite noticeable when she is asleep. Weight 6 st 10½ lbs, showing loss of 1 st 4½ lbs in a month. Pulse rapid and thready. B.P. 85. There is marked pulsation all over the left side of the chest, extending into the axilla and seen best in the 3rd space. There is no enlargement of the auricle to the right of the sternum."
The heart sounds are both loud and there is a slight systolic murmur heard at the apex."

As thyroidectomy did no good it was decided to give it up and try adrenalin. Accordingly on August 7th she was given 10 minims of a 1 m 1000 solution intramuscularly at 7 p.m. During that evening she complained of a choking sensation in the throat and had some palpitation.

Her pulse rate was 124. The injections were combined twice a day at 10 a.m. and 7 p.m. till August 19th when she refused to have any more, saying they made her feel sick, made her heart bad, and gave her pain on the top of the head. Her blood pressure was taken before and after the injections. It varied from 110 - 115 before and rose to 160 - 165 after them. She lost another 1 lb. in weight. On August 21st she was given 740 of the adrenalin solution by the mouth. Before taking it her blood pressure was 110, 10 minutes afterwards it was the same, 20 minutes afterwards she vomited and had pain in the epigastrium, 70 minutes later her blood pressure was 100. It was obviously no good persevering with adrenalin so that was stopped and she was given a course of X-ray treatment. Her heart at this time was seen to be very little enlarged to the right, but very greatly to the left, outwards and upwards into the 3rd space.
Pulsation could be seen in the second left interspace which was alternate with the contraction of the ventricle. Before starting this treatment her average pulse rate was 120 and she was losing weight. After a few days of treatment she began to show signs of improvement and her average pulse rate dropped to 108 while she put on \( \frac{1}{2} \) lb in weight in a week. This treatment was kept up till December when she suddenly developed Scarlet Fever and had to be sent to a Fever Hospital. Her weight was then 6 st 6 lbs.

Some months after when she reported at hospital the swelling in her neck was a little larger. She has no protrusion of the eyes and only suffers from palpitation and shortness of breath, when she hurries. Her hands are still shaky at times. Her weight was 9 st 2 lbs, a stone more than when she came under notice first. She says she feels perfectly well and has had no further treatment. She is now married and can do her household work quite well.
Case XV, aet 33, schoolmistress, applied for treatment August 8th 1924, complaining of palpitations, pain in the right side, a swelling in the throat. She said that she had been quite well until June of that year when she noticed she was getting thinner and had palpitation on the slightest exertion and some pain in the right side. In August 1923 she saw a doctor who gave her some tablets and she said the more she took the worse she became. In September 1923 she first noticed the swelling in her neck which had been steadily getting larger since. She had suffered from indigestion for 18 months and was troubled with shaky hands. She also perspired more than she used to. There was an indefinite history of muscular rheumatism, also a very definite one of constipation.

On examination she was found to be a very nervous woman. Her hair was prematurely grey, her tongue furred and tremulous. There was no exophthalmos and Von Graefe's sign was not present. The thyroid was slightly enlarged on the right side and soft and tender to the touch. The pulse rate was 140 and there was a fine tremor in the hands. The urine contained no sugar or albumin. Her weight was 6 st 11 lbs. She was ordered rest in bed and given ordinary tonic treatment. The tremors in the tongue and hands got
less and the attacks of palpitation less frequent. Instead of having one every hour she only had about two per day. Her pulse rate averaged 120. Otherwise there was not much change and her weight remained about the same. She remained in bed till September 1926 and was then allowed to get up. When seen in the middle of October her condition was much the same, but her weight had gone up and was then 7 st 21 lbs. Tonic treatment combined with plenty of fresh air was continued. She was seen about a year later, the swelling in her neck was about the same, she seldom now had palpitations. Her hands shook only when she got fatugued. At times she perspires a good deal. Her weight has gone up 2 stones. She considers herself "much better" and can do her work quite comfortably. She has required no further treatment.

.............
Case XVI, M.T., aet 33, married, was first seen on November 8th 1924. She had been quite well until 17 months previously when her first child was born. Her mother died a week before the birth of the child and this worried her a good deal. She began to get nervous and suffered from trembling of the hands and legs. In March she went to the Women's Hospital Whitehouse Lane, for weakness and nervousness. While there, it was noticed that her eyes were becoming prominent and that her neck was swollen. She was treated with rest and X rays. She left in May and since that date has been troubled with palpitations, shortness of breath, fainting attacks, and increased perspiration. For 3 weeks she was troubled with vomiting 3 or 4 times a day, but this passed off.

Her eyes were very prominent. Stellwag's, Von Graefe's, Joffroy's and Moebius' signs were all present. The thyroid was much enlarged, soft and rather tender to the touch, and there was well marked pulsation over it. The circumference of her neck was 14½". Her pulse was 104 and regular. There were tremors in her fingers and a slight systolic murmur could be heard at the Pulmonary Base. She was ordered rest in bed and put on tonics till December 4th. Under this treatment the pulse rate slowed down to 88, the eyes became less prominent, and did not feel "so tight". The tremors became less and the circumference of the neck went
down to 14". She was then given Thyroidectin grs V t.i.d. in addition to tonics and this was continued throughout the month. From December 12th to 19th she suffered with a severe attack of gollicular tonsillitis, but after recovering from this, she was much in the same state as before. Her general condition was improving and she was putting on weight. Writing in October of the next year she says she is in about the same condition as she was when seen in December. Her weight is about the same, she still perspires a lot and suffers from palpitation and shortness of breath. Her hands are not quite so shaky but she still feels "nervous". There has been no alteration in the swelling in the neck or the eyes.

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Case 17, A.B., aet 25, came under treatment on July 24th 1924 with the following history:

She had been perfectly well until one month previously except for anaemia. She then noticed a lump in her neck and some prominence of her eyes. She became very nervous, sweated a good deal, had palpitations very badly and was very short of breath. She always felt faint on getting up in the morning.

On examination she was found to be an anaemic girl. Her eyes were prominent and the lids were swollen. Stellwag's, Von Graefe's, Kocher's Moebius' signs were all present. The thyroid was enlarged, especially the isthmus and right lobe. Her pulse rate was 90. Haemic murmurs could be heard at both bases and along the sternum. A loud systolic bruit could also be heard over the thyroid and a thrill could be felt. Up till August 7th she was treated with sodium phosphate grs XX t.i.d. The pulse rate dropped from 90 - 70 and the palpitations were somewhat less. It was then decided to try the effect of operation. This was carried out on August 10th, under a general anaesthetic. The right inferior thyroid artery was ligatured. The dissection was difficult owing to the net-work of veins and the operation lasted 1 hour. She took the anaesthetic badly and became cyanosed. The pulse rate was 114
during the operation and rose to 160 afterwards. The next day it was 128 and it remained high for 3 days, on 2 occasions reaching 160. The wound healed by first intention and the stitches were removed on August 16th. The pulse rate was then 80.

On August 28th under a general anaesthetic the left inferior thyroid artery was tied. The operation lasted 35 minutes and the patient bore it much better than the previous one. Afterwards, however, the pulse rate rose to 170 and there was hoarseness and difficulty in swallowing, caused no doubt by the bruising of the recurrent laryngeal nerve. At 11 p.m. the same night there was an increase in the pulse rate and respiration rate. She was given adrenalin and stimulants. The wound was opened up and plugged. Three hours later the heart stopped and the patient was dead.

A post-mortem examination revealed some old pleural adhesions and congestion of both lungs at their bases. Beyond this and some patches of atheroma in the aorta nothing abnormal was found.
Case XVIII, G.F., housemaid, aet 20, first noticed a swelling on the right side of her neck in June 1924. This got rapidly larger and was followed by a similar but smaller swelling on the left side. Prominence of the eyes was noticed about the same time, as also, palpitation and tremors in the hands. She began to get nervous and have attacks of flushing.

On examination she was found to be a fairly healthy looking girl and there was no marked anaemia. The thyroid was bilaterally enlarged, the circumference of the neck being $14\frac{1}{2}$ inches. The heart sounds were normal and the pulse rate 112. There was a fine tremor of the hands and the skin was generally moist. Her weight was 8 st 1 lb. For 6 weeks she was treated by rest in bed and various drugs, Pot Iodide, Sodium Phosphate, Belladonna digitalis. In spite of all this no signs of improvement were seen. The circumference of the neck remained the same, the pulse rate varied from 112 - 120 and the weight was decreasing. It was then decided to try operation. A week later, therefore, a partial thyroidectomy was performed under a local anaesthetic. The operation was successfully performed, but the patient died the next day. No post mortem examination was made.
Case IX, R.E., aet 22, governess, was admitted to Hospital on January 31st 1924, complaining of palpitation. Her attention was first called to her condition 3 months previously, when, after reading an article in the Daily Mail, she noticed that she had a very rapid pulse. She consulted a doctor about it and he advised her to go to a hospital. She said she had lost about 8 lbs in weight.

On admission she was a thin highly excitable girl. There was no obvious exophthalmos and the thyroid was not conspicuously enlarged. There was a fine tremor in the fingers and her pulse rate was 120. Her heart was normal and the urine contained no sugar or albumin. Her weight was 7 st 9 lbs. She was put to bed and given the usual tonic treatment, Bromides, Belladonna etc. On 13th February a slight fulness was noticed in the region of the thyroid on the right side and also some slight exophthalmos. The pulse rate varied between 96 and 120, occasionally being as much as 140 if she sat up. She was now given electric baths. On February 20th it was noted that the right lobe of the thyroid was distinctly larger than the left and was tender. The tremors were much more marked in the right hand.

This was repeated on March 2nd, March 5th and March 9th. The pulse rate dropped to 80-88, but otherwise no good resulted, and so the treatment was stopped. Electric
baths were given again and a mixture containing Belladonna and Potassium Bromide. On March 18th she was allowed to get up. The neck was no longer tender and there were no tremors. The pulse rate was 80. Her weight was 7 st 7 lbs, i.e. 2 lbs less than on admission. By March 28th she had regained the lost 2 lbs. and was discharged "relieved". Her average pulse rate since getting up was 96. I have been unable to trace her subsequent history.
Case XX, K.B., aet 32, married, was admitted to the Royal Infirmary on January 1st 1923, complaining of shortness of breath and a swelling in the neck. She gave a history of 10 years "anaemia" and 3½ years wasting. She had noticed the shortness of breath for a year and also some trembling of the hands. She could not say how long the swelling in the neck had been there but it had quite recently become more noticeable.

There was also a history of menorrhagia. On admission she was a pale thin woman with a moist skin. The eyes were somewhat staring and Von Graefe's sign was present. There was a fairly large double goitre. The pulse rate was 120 and a systolic murmur was audible at the pulmonary base. There was a fine tremor in the fingers.

Rest in bed was ordered and she was given a mixture of Belladonna Digitalis and Iron. By March her general condition had greatly improved. She had transient attacks of diarrhoea, but this stopped on leaving off the Digitalis.

On March 11th she was sent to a convalescent home for a month. Her average pulse rate was 80. Writing in October of the next year she says that now she has no swelling in her neck and no prominence of the eyes, her hands are very slightly shaky and she suffers very little from shortness of breath. She has gained 1½ stones in weight and says that her present condition is better in every way. She has required no further treatment of any kind.
SYNOPSIS OF CASES.

The following table shows at a glance the result of various methods of treatment adopted in the 20 cases which form the basis of my thesis.

<table>
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<th>Principal treatment</th>
<th>Result</th>
<th>Remarks</th>
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<tbody>
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<td>Ordinary medical treatment,</td>
<td>greatly improved.</td>
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<tr>
<td>2.</td>
<td>Partial thyroidectomy,</td>
<td>died.</td>
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<tr>
<td>4.</td>
<td>Partial thyroidectomy,</td>
<td>slight improvement.</td>
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<tr>
<td>5.</td>
<td>Ordinary medical treatment,</td>
<td>In statu quo.</td>
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<td>6.</td>
<td>Partial thyroidectomy,</td>
<td>very much improved.</td>
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<td>7.</td>
<td>Insulin Glucose,</td>
<td>&quot; &quot; &quot; &quot;</td>
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<td>8.</td>
<td>Partial thyroidectomy,</td>
<td>cured.</td>
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<td>9.</td>
<td>Ligature of arteries, followed by Partial thyroidectomy,</td>
<td>improved.</td>
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<td>10.</td>
<td>Partial thyroidectomy,</td>
<td>died.</td>
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<td>11.</td>
<td>Medical treatment - X rays,</td>
<td>improved.</td>
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<td>12.</td>
<td>Ordinary medical treatment,</td>
<td>died.</td>
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<tr>
<td>15.</td>
<td>Ordinary medical treatment,</td>
<td>improved.</td>
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<tr>
<td>16.</td>
<td>Ordinary medical treatment,</td>
<td>in statu quo.</td>
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<tr>
<td>17.</td>
<td>Ligature of right and left inferior thyroid arteries,</td>
<td>died.</td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Partial thyroidectomy,</td>
<td>died.</td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>Moebius Antithyroidin Serum,</td>
<td>in statu quo.</td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Ordinary medical treatment,</td>
<td>very much improved.</td>
<td></td>
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</tbody>
</table>
Summarising these results it will be seen that of the 8 cases that were treated surgically, 2 were cured, 1 very much improved, 1 improved, and 4 died; and of the 12 treated by other than surgical methods, 4 were very much improved, 2 much improved, 3 improved, 3 showed no change.

It would now be as well to consider the various forms of treatment under two heads, Medical and Surgical.

Medical.

The disease being obviously one in which the bodily metabolism is increased and being characterised by over-excitability of the heart, it is only natural that simple rest in bed combined with sedatives and heart tonics will be beneficial in all cases. I have most certainly found it so. Improvement is often noticeable after a very few days, especially when a septic focus has just been got rid of. According to Gillies it is a generous estimate to suppose that 25% of the cases get well when treated by rest and drugs only. Dr. Hector Mackenzie gives it as his experience that of the cases treated on broad general medical lines, about 25% make satisfactory recovery, 25% are much improved, but not cured, 25% become chronic invalids and 25% lose their lives from the disease itself. On the other hand, James Berry says: "I
I venture to think that no unbiased or impartial observer can doubt the truth of the assertion that medicinal treatment does nothing to cure the disease. Many cases abort at an early stage and come to an end spontaneously."

He goes on to say that after abundant rest, mental and bodily, the disease does seem to wear itself out and the patient is more or less completely restored to health, provided no secondary degenerations of viscera intervene. He also admits the value of drugs in alleviating symptoms. The most useful drugs for this purpose are undoubtedly Belladonna, Sodium Phosphate, Digitalis Strophanthus Opium, Potassium Bromide, Arsenic and Iron. Much benefit is derived from the use of these in various combinations and they will check the progress of the disease in its earliest stage. When, however, the disease is of long standing, it is doubtful if they do any lasting good and the patient very soon relapses after leaving them off and returning to active life and local applications to the thyroid, ice seems to be most beneficial. I have seen no benefit from electricity and not much from painting with iodine. With regard to X rays, I have not myself seen any cases that have benefited to any great extent. Other writers have, however, recorded permanent cures, e.g. Florence Stoney quotes 14 cures out of a series of 48 cases and 26 others who showed signs of improvement while Rowder reports 17 cures out of 31 cases and 12 others improved. To be of much use the treatment
has to be pushed and then there is the danger of X-ray dermatitis. Of later years iodine has been of value as a therapeutic agent in the treatment of this disease. Iodine has a profound influence in regulating not only the size but the structure of the thyroid gland. Clinically, iodine in hyperthyroidism has brought about some significant changes in the course of a few days the heart has been made to beat much more slowly, sweating was also reduced, and the patient became much less restless. Iodine affects not only the pulse rate but also the whole bodily metabolism. The basal metabolism is greatly reduced after the administration of iodine, but it tends to rise again although not to the previous level. This has been the usual effect of this treatment in exophthalmic goitre, but in some cases there was a different result, but these cases wherein an unsuccessful result has been obtained have been described as cases of toxic adenoma. Professor Mellanby has said that the advantages of iodine therapy were the rapid disappearance of the symptoms, not only, of course, a good thing in itself, but also valuable as a preparation for surgery, an improvement in the condition of the patient during the whole time that the iodine was administered and in some cases a complete recovery. As to these last cases, he admitted that it was quite possible that many of
these people might have recovered without iodine, but on the other hand, he had a strong feeling that iodine had played a part in the recovery. The disadvantages were that in some cases, more particularly cases of toxic adenoma, there were certain definite dangers from the sudden exacerbation of symptoms and that in normal cases, whenever the treatment was stopped, there was exacerbation: and that with iodine treatment there was a possibility of getting asphyxiaion, that is if there were any pressure symptoms in the first place, these would almost certainly be made worse by this form of treatment.

In addition to giving iodine in these cases, he tried to regulate the diet to some extent. The diet includes all the ordinary foodstuffs, with plenty of milk, but he tried to keep the caloric value of the diet low because he had found in animals that the more food they were given the bigger the gland became.

Although quite fully alive to the disadvantages and dangers of iodine treatment, he regarded it as a valuable adjunct in dealing with exophthalmic goitre.

With regard to gland extracts, good results have been obtained. In considering the view that
the disease is due to a perverted action of the thyroid, it seems natural to look for a remedy in the form of some extract that can supply the substance or substances in which the thyroid fails. Dr. George Gibson considered suprarenal extract as almost a specific. Batty records a case treated with ovarian extract which showed some improvement. The modern tendency to treat the disease with insulin produces no improvement in many cases. I have seen good results follow the administration of thymus gland extract but others have found it useless. It is not surprising that an extract which is successful in one case is of no use in another, so much depends upon what substance is lacking in the thyroid secretion and what gland or glands are able to manufacture it in an emergency.

Surgical.

If the symptoms which combine to form Grave's disease are simply caused by an overactivity on the part of the thyroid, it seems only natural to conclude that removal of the right amount of the gland will cure the disease. It is probable though that the condition is due not so much to a simple increase of the normal secretion, but to a perverted secretion, and as one cannot remove the whole gland there is the possibility that the portion left behind may go on secreting an abnormal material and so combine to
produce the symptoms though in a less aggravated form. From my series of cases it will be seen that all that survived the operation were improved to some extent. But it would be as well to consider the published statistics of those who have had a larger experience. The first name that comes naturally to one's mind is Kocher. Recent figures of his are 320 cases operated upon of which 150 were cured, 143 improved, and 22 were unsatisfactory. The mortality was 3 - 4%. C. H. Mayo records a consecutive series of 278 cases operated upon without a single death. Allan Starr's statistics collected from various sources were 190 operations with 23 deaths (12%) 74 cures, and 3 failures. Of the rest 45 were improved and in the remaining 45 the result was doubtful. L. Rehn quotes 61 cases submitted to operation, of these 46 or 75.5 were cured, 6 or 9.8% were improved, 1 relapsed and 8 or 13.1 died of the operation. Bunhill with the experience of 230 operations says the death rate from operation itself is 2 - 4%. With regard to the end results he says that nearly every patient who is free from visceral disease is "almost cured" and after a few weeks or months has been able to live a normal life.
George Murray, of 300 cases he had seen mentioned 10 that were operated on with a mortality of 30%. Needham Green had 3 deaths in 30 cases. Hale White mentions 40 cases of which 26 "did well".

Hector Mackenzie quotes 19 cases operated on at St. Thomas Hospital of which 6 died, 4 were greatly improved, and 4 were slightly improved. Of 8 others operated on him by him, 1 died soon afterwards and none of the others were cured though all said they were improved.

It will be noticed that the results obtained vary considerably. A great deal depends upon the type of case operated upon and the skill of the operator. Until recently it was the practice only to operate on cases after a long course of medical treatment had proved unsatisfactory, but during later years operation has been carried out earlier while the patient is more fit to withstand the shock. It is possible that a large number of cases operated on thus early and claimed as "cures" would have done equally well under medical treatment. On the whole, looking at the question impartially and judging from my own experience of the disease and from the published statistics of others, I am inclined to agree with Dr. Hector Mackenzie when he says "were it not for the considerable risk to life
from the operation I should not hesitate to recommend it as the most rational and most practical method of treatment of the disease. In the milder forms however, there is a good prospect of recovery under medical treatment and there does not seem so much more to be gained by operation to warrant the incurring risk of a fatal result. The risk of death from the operation is so high in acute and severe cases as to render it doubtfully justifiable of the various forms of medical treatment, as I have already said I am inclined to think that the best results are to be expected from a mixed extract of the Ductless Glands combined with rest and tonics.

As Murray says - "the treatment of exophthalmic goitre will become more satisfactory as we acquire more adequate methods of checking the abnormal flow of secretion when it is to be hoped that surgical means will become unnecessary."
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