REPORT and COMMENTARY

on

A SERIES OF CASES OF

GOITRE.

Presented in competition

for

THE PATTISON PRIZE IN

CLINICAL SURGERY.

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by

JAMES PATRICK.
PREFACE.

The remarkable physiology of the thyroid gland, the peculiar features of goitre and the specialised nature of its surgical treatment, has prompted me to adopt this study.

Throughout the commentary I have used the word 'goitre' in its original and widest sense which includes every form of thyroid enlargement, toxic or non-toxic, benign or malignant. The name "exophthalmic goitre" I have avoided, for obviously case 2 is as worthy of the title as is case 4. For the same reason most other titles are to be condemned and hence for want of a better I have employed the term "Graves' disease".

The cases cover all the common and important varieties of 'surgical goitres' and therefore I have made little remark of other types and have confined my attention to an investigation and comparison of those which are alone included in the report.

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SIX CASES OF GOITRE

treated in

SURGICAL WARDS

7 and 8

of the

EDINBURGH ROYAL INFIRMARY.
CASE 1.

Mrs. M.A., aged 46, widow, para 4.

Occupation. Housewife.

Admitted. 4th May, 1931.

Complaint. Swelling in front of neck.

Duration, 21 years.

History. The patient first noticed a swelling on the right side of her neck in 1910 (i.e. at the age of 25). The swelling then was about the size of a walnut, moved upwards on swallowing and was of soft consistence and quite painless. At that time she was of rather a nervous temperament. There was no preceding infection such as tonsillitis or sore throats and she would not admit of any exciting cause such as worry or mental disturbance of any kind. The patient, however, seemed reticent when questioned about the latter and as this was two years prior to her marriage, it seems likely, in the absence of other evidence, that some such cause was present.

From that time the swelling gradually increased in size but still appeared to be solely confined to the right side. In 1913, after the birth of her first baby, she noticed that a similar, but apparently smaller, swelling had made its appearance on the left side of her neck.

Up till this time the goitre, for such it undoubtedly
was, had shown a steady, though slow, increase in size. At her menstrual periods she did not observe any alteration in its size but as it grew she believes that she became more readily excitable. She never experienced any palpitation, sweating or loss of weight, but up till 1913 she became more easily fatigued and was inclined to be irritable. Her appetite was good but she does not think that it was increased; she had no vomiting or diarrhoea nor any difficulty in swallowing. No tremor of the fingers was evident to her at that time and her attention had not been drawn to any protrusion of the eyeballs. She recollects that the palms of her hands were inclined to be constantly moist but she had no particular intolerance of hot weather nor desire for cold. There was no dyspnoea nor sense of constriction of the air passage and she had never suffered from chronic cough.

After she had recovered from her first confinement in 1913, the goitre which was then bilateral and a marked disfigurement, slowly decreased in size and correspondingly her emotional instability lessened in degree. In 1925 her husband died and the shock caused a temporary increase in the size of the goitre but in a few months this slowly subsided and since then the thyroid swelling seems to have maintained its size, and certainly there has been no further enlargement.

At present any excitement or exposure to cold produces
a feeling of constriction over her windpipe and she tends to become breathless on exertion. She now feels the cold rather badly and welcomes the onset of warm weather. Her hair is coarser than formerly and her skin dry in contrast to her condition in 1910.

Of the treatment previously adopted, she has little knowledge but she has had a variety of medicines and amongst other drugs iodine has been given. Pending her admission to hospital she was prescribed thyroid extract and has taken 3-5 grs. of thyroid gland tablets daily with much benefit.

Previous Health: Nil. to note.
Social History: Nil. to note.
Family History: No history of goitre in the family nor in any relations.

Physical Examination. Patient is a well-nourished, well-coloured, healthy-looking woman, but inclined to be stout. She appears to be of a placid nature and is in no way upset on this, her first day, in hospital. There is an obvious bilateral swelling in the lower half of the front of the neck.

The skin is moderately moist and warm and shows no particular thickening. There is no tremor of the outstretched fingers and no suggestion of exophthalmos.
Local Examination.

Inspection: There is a marked swelling in the neck in the region of the thyroid gland. The swelling is more obvious on the right than on the left side but it is otherwise of a uniform nature, apparently involving the isthmus as well as either lateral lobe. The swelling moves upwards on swallowing.

Palpation: The goitre is firm and freely mobile and on account of some slight variation in its consistence, it gives one the impression that it has a lobulated structure. Either lobe extends some distance behind sterno-mastoid muscle but the upper poles can be readily enough defined. On the right side the fingers can be slipped between the lower pole and the upper border of the sternum and clavicle but on the left side, even when the patient is made to swallow, the lower pole cannot be defined: it appears to extend well down within the thoracic aperture on the left side.

The goitre is entirely painless and no thrill can be felt nor bruit heard on auscultation over it: the cervical lymph glands are not enlarged.

Eye signs: (vide Case 4) all negative.

Circulatory System.

Pulse: rate 74; regular in time and force; of good volume; vessel wall palpable and slightly thickened; blood pressure 148/100.
Heart: Nothing abnormal detected: sounds pure.
Other Systems: nothing abnormal found.
Special Investigations.
Basal Metabolic Rate (Douglas Bag Method) + 18.
Geotsch's Test: negative (see commentary).
Provisional Diagnosis: Simple diffuse colloid goitre with a slight degree of myxoedema.
Preoperative treatment. The patient was admitted only 24 hours before operation and was immediately put to bed and given the usual dose of castor oil. That evening 1 gr. luminal and 2 minums of Lugol's Soln. was given. On the morning of operation the routine soap and water enema was given to clear out the lower bowel.

Note that in this case where no hyperthyroidism was present, no special preoperative treatment, such as will subsequently be described, was carried out.
Anaesthetic: Scopolamine and morphine combined with local anaesthesia:
1 hour before operation - H.I. Scop. 1/100 gr. : morph. ½ gr.
20 minutes " " - H.I. Scop. 1/200 gr. : morph. 1/6 gr.
Immediately after the second injection was given, the patient was taken along to the operating theatre and there placed on the table with a small sand-pillow between the shoulders and the head-rest lowered, thus making the front of the neck as prominent and accessible as possible. The whole of the neck having been previously cleaned and painted with tincture of
iodine, a rubber cap was put on and the hair tucked out of the way; the neck was again painted with tincture of iodine and the patient's hands and legs fixed in straps lest she attempt any movement during the operation. Sterile towels were then adjusted over the patient and table, leaving only the operation area in the front of the neck exposed. With these preliminaries, the patient, now well under the scopolamine-morphine narcosis, was allowed to lie for about 15 minutes in perfect quietness until the operator was ready to begin.

The first step was the administration of the local anaesthetic, ½% kerocain containing no adrenalin being the substance used.

**Stage 1.**

**Infiltration of skin.** A preliminary wheal was made over the goitre, using a short hypodermic needle, then with a long flexible Braun's needle attached to a 20 cc. syringe, the skin over the left side of the neck as far back as the goitre extended, was infiltrated. The brawny induration caused by the injected fluid opened up the subcutaneous tissues and the spreading margin of this induration was allowed to precede the point of the needle. The right side was similarly infiltrated and the skin upwards as far as the hyoid bone and downwards towards the sternum likewise treated (fig. 4).

**Stage 2.**

**Block anaesthesia.**

(a) **Sensory nerves.** The supra-clavicular nerves
and the cutaneous colli nerve which supply the skin of the front of the neck all emerge through the deep fascia on either side at a point close to the middle of the posterior border of sterno-mastoid muscle (fig. 1), and at this point on the right side a hypodermic needle was inserted (not more than \( \frac{1}{2} \) inch deep) and 20 c.cs. of the \( \frac{1}{2}\% \) kerocain injected.

(b) **Upper part of deep cervical plexus.** On the same side a point is taken at the junction of the upper and middle thirds of the posterior border of sterno-mastoid muscle (exactly opposite the angle of the jaw). At this point a long straight needle was inserted and passed inwards and backwards until it could be felt striking against the transverse process of the second cervical vertebra. The needle was then withdrawn slightly and again passed inwards, this time in a more anterior plane (fig. 3). The point of the needle now lay close to the upper part of the cervical plexus and 20 c.cs. of the kerocain solution was then injected, and the needle withdrawn.

The operator now passed round to the left side and repeated this block anaesthesia of the superficial and deep cervical nerves. Throughout this procedure the patient remained asleep and was not disturbed in any way.

**Operation.** The local anaesthetic having been injected, fresh sterile towels were placed over the chin. A "collar"
SITES OF LOCAL INFILTRATION
incision (i.e. in the line of the skin folds) was made over
the prominent part of the swelling - about the junction of
the lower and middle thirds of the median line of the neck.
This incision was purely subcutaneous and did not divide
platysma. The skin edges were then carefully reflected up-
wards and downwards respectively and retained with skin
forceps. At this point there was considerable oozing of
blood and so all the small bleeding vessels were caught with
artery forceps and ligated with linen thread wound on a
shuttle. Sterile towels wrung out in warm saline were
then applied round the skin edges to prevent any possible
contamination of the wound from the skin surface. Platysma
was then divided in the line of the skin incision and
reflected as separate flaps, the wound being then held open
with small retractors. The superficial veins of the
neck were thus exposed and in turn each was caught in two
pairs of forceps and divided between. With a sharp knife
the dissection was continued until the fascia covering the
pretracheal muscles, sterno-hyoid and sterno-thyroid, was
stripped off. As the dissection proceeded any small vessels
cut through were caught with forceps and ligated with fine
linen thread.

Next the fascia in the midline between the two sterno-
hyoid muscles was carefully incised right up as far as the
hyoid bone. The pretracheal muscles were then retracted to
either side, using a Macdonald's dissector in separating the muscles from the lobes of the thyroid. In doing this it was important to get the proper line of separation between the outer and the true capsule and not enter the gland, else considerable bleeding would have occurred. It was not found necessary to do a partial transverse division of the pretracheal muscles as sufficient access was obtained by holding back the muscles with a retractor. The forefinger was introduced and swept round the right lobe and the latter drawn partly out of the wound. A strong catgut ligature was passed through the lobe which could thus be readily steadied and controlled without trauma, the ends of the catgut being held in artery forceps. The middle thyroid vein was then seen and secured in two places with forceps. The upper pole of the right lobe was defined and a Cleveland's pedicle needle passed round it, withdrawing a strong catgut ligature which was firmly tied so as to include the upper part of the glandular pole as well as the superior thyroid vessels.

The right upper pole was then divided with the cautery below the ligature and the remainder of that lobe divided slowly and cautiously with the cautery, leaving only a thin shell of thyroid tissue posteriorly. The isthmus was likewise divided, again attempting to leave a tiny posterior shell of tissue behind so that the trachea would not suffer any irritation
The freed right lobe was now held in a warm towel and an attempt made to dislocate the left lobe. It was found, however, that it passed down behind the sternum and it was only with some little difficulty that it was gently drawn upwards into the wound; but in spite of the traction, and pressure on the trachea the patient remained asleep. As before, the left middle thyroid vein was ligated and the upper pole defined and ligated with a pedicle needle and catgut. The left lobe was separated with the cautery, again leaving only a thin shell of thyroid tissue behind. All bleeding points were caught in forceps and ligated with fine linen thread and a final examination made for any further tiny points of haemorrhage.

The pretracheal muscles were then allowed to fall together again and united in the middle line by three interrupted stitches of fine catgut. A rubber-dam drain was inserted between two of these stitches and passed down to the thyroid space. Platysma was united, except in the middle line, with a fine continuous catgut stitch, the drain emerging through the small central space. The skin edges were brought together and united by means of five fine, interrupted silkworm-gut stitches beginning at either end of the wound; the middle stitch passed through and secured the rubber drain which was then cut short close to the skin surface. Finally the skin edges were carefully approximated and Michel's clips introduced.
A figure-of-eight gauze bandage was put on over the neck and upper half of chest. Seen immediately after the operation, the patient was of a good colour, pulse 86, and sound asleep.

Post-operative treatment. For the first 12 hours the patient was kept flat in bed with her head between sandbags and that evening the head was propped up on a pillow. Rectal glucose salines were given 4 hourly for the first 36 hours but nothing by mouth. On the second morning Lugol's soln. was first given by mouth, beginning with 2 m. b.i.d. and gradually increasing the dose to 5 m. b.i.d. but the third day the pulse had fallen to 72 and as it continued to fall thyroid extract was given 2 gr. b.i.d. There was no post operative vomiting.

The other details of the treatment were similar to those given fully in Case 2, but as this was a non-toxic goitre the same rigorous treatment was unnecessary.

Progress: The patient made a rapid recovery and was discharged on 19th May 1931 with the wound soundly healed and in satisfactory general condition.

Daily B.M.R. Chart: see commentary.

PATHOLOGY.

Naked-eye appearance of gland. Both lobes have a smooth exterior. The left lobe which extended into the thorax,
CASE 1.

Showing "colloid" acini and multiple haemorrhages.
is about the size of a tennis ball; the right lobe is about half that size. The gland is of soft consistence but in parts feels lobulated.

Cut Surface is of an amber, gelatinous, finely honey-comb appearance. There are numerous brownish flecks of haemorrhage and fine septa give a faint suggestion of lobulation.

Microscopic: Low power: (fig. 5) Many of the acini are dilated and of irregular shape; in some the walls have broken down allowing adjacent acini to unite in minute cyst formation. A few small spurs of epithelium can be seen projecting into some of the acini; an evidence of former hyperplasia. The acini are filled with a homogeneous colloid which, however, is not deeply stained.

High power: (fig. 6) The epithelial cells are of low cuboidal type, the nuclei which are darkly stained, almost filling the cells. The stroma is increased in amount and fibrous, but in some parts it seems to have undergone a hyaline degeneration. There are numerous small haemorrhages, and the vessels are few, many of them showing degenerative changes of a hyaline nature in their walls. In one area an aggregation of regenerating acini can be seen; these are smaller than normal, the cells are basophilic and the nuclei frequently hyperchromatic indicating active cell division. Some small solid clumps
CASE 1.

Showing area of regenerating acini.
of epithelium are also present. The interstitial tissue in this area has a diffuse hyaline appearance and frequently the remains of degenerated acini can be seen (fig. 6).

"Diffuse colloid goitre with areas of regenerating acini".

Reported 18th July 1931: In excellent health, wound well healed: no recurrence of goitre.
CASE 2.

Mrs. A.D. aged 37, married, para 7.

Occupation: Housewife.

Admitted: 8th Feb. 1931.

Complaint: Swelling in front of neck.

Duration - 2 years.

History: Up to 2 years ago the patient was perfectly well but 2 or 3 months after the birth of a still-born child, she noticed a slight swelling on the right side of her neck. This gradually increased in size and two months ago she noticed that a similar swelling had also made its appearance on the left side.

Before the first swelling became obvious to her she readily became breathless on exertion. She has always been of rather a nervous disposition but has become more so since the onset of the present illness. When the swelling first appeared she had occasional palpitation and, as the months passed, this has become more frequent and comes on even on mild exertion. Formerly she was quite stout but in the past 3 years her weight has gradually fallen and she is now very much thinner. Her appetite on the contrary has increased. She never has any difficulty in swallowing and never vomits; her vowels move 2 or 3 times a day. She has observed a tremor in her hands for the past 18 months and her attention...
has been drawn to some degree of bulging of the eyeballs. She perspires readily and her palms are constantly moist; she is more comfortable in cold than in warm weather.

In March 1930 she had some hoarseness of the voice which persisted for about two months and then gradually wore off but for the last two months this disability has again returned. She never experiences any pain or feeling of constriction of the throat and is not subject to sore throats or cough.

Since their onset, her symptoms have not steadily progressed. At times she has felt much better than at others and during the past two months her health has decidedly improved. The goitre, however, does not appear to have shown any corresponding remissions in size.

At present a feeling of tiredness and palpitation are her chief worries.

Previous Health. Nil. to note.

Family History: One sister had a "swelling in the neck" which persisted for 5 or 6 years and then subsided.

Social History: Nil to note.

Physical Examination. The patient is a well-built woman but is now thin and pale and there is some degree of exophthalmos. There is a slight rhythmical tremor of both outstretched hands, more marked in the left, and she seems generally nervous. The skin is moist and warm.
Local Examination: There is a fullness in the neck, most obvious on the right side, and on either side rapid carotid pulsation is evident. The swelling moves vertically on deglutition.

Palpation: The swelling is definitely located in the thyroid gland but no thrill can be felt. The gland is nodular; three firm nodules can be felt in the right lobe and two similar ones in the left; a solitary nodule occupies the region of the isthmus. In size the nodules vary from a pea to a marble: they are firm but not unduly hard; the other parts of the enlarged gland feel lobulated but are of a softer consistence. The gland is not adherent to the surrounding structures and the skin is freely movable over its surface. The left lobe extends further backwards and downwards than the right but the lower pole can be defined lying just above the upper thoracic aperture. No bruit can be heard on auscultation over the gland.

Circulatory System. The heart is slightly enlarged, the apex beat lying in the 6th intercostal space in the midclavicular line. Heart sounds pure.

Pulse. Rate 120, regular in time and force; good volume; vessel wall not palpable: blood pressure 145/90.

Other Systems: nothing abnormal found.

Special Investigations.

B.M.R. (Douglas Bag Method) + 61.

X-ray. Posterior mediastinal space on screen examination
Provisional Diagnosis: Toxic adenomatous goitre.

Preoperative Treatment: The patient was admitted to the ward 12 days before operation. She was at once placed in bed in a corner of the ward remote from the door, so that she would experience the minimum of disturbance. On the second day screens were placed at either side of her bed but were not closed in front. On the third morning the screens were closed around her bed so that she thus was completely, though gradually, shut off from all extraneous exciting influences.

Diet: She was told to take abundance of water and was given a good full diet, composed largely of carbohydrate foods, avoiding as far as possible fats and proteins, such as butcher's meat, etc., which are known to stimulate metabolism. On the day before operation she was given only light soup and pudding for dinner and merely tea, bread and butter in the afternoon and a glass of milk for supper. At 6 a.m. on the morning of operation a cup of weak tea was given.

Visitors, etc. No visitors were allowed to see her and most newspapers and books were kept out of her reach. When she came into the ward she was informed that "something would be done for her" and the day of her operation gradually and tactfully revealed. In every way she was thus quietened
and reassured.

Drugs. From the date of admission she was given Lugol's iodine solution, beginning with 2 minums t.i.d. and mounting up daily, one minum to each dose, until 10 m. t.i.d. was being given. This final dose was then maintained up to the day of operation. To further quieten her, luminal gr. 1 was given night and morning as required. As her bowels moved 2 to 3 times per day no purgatives were required but on the day before operation she was given the routine dose of castor oil, followed in the morning by a soap and water enema.

The induction of twilight sleep as part of the pre-operative treatment is fully described in case 1.

Operation. 20th Feb. 1931.

Anaesthetic - Scop. and Morph. + local.

"Subtotal Thyroidectomy" - details same as Case 1.

During the course of the operation the patient had a Scopolamine fit, her whole body and limbs suddenly beginning to tremble. In 30 seconds, however, it passed off as suddenly as it had begun, causing no trouble apart from temporally hindering the progress of the operation. The patient did not even wake up though her breathing for a short time was a little more laboured.

Post-operative treatment: Just after operation the pulse had risen to 136 and the patient was flushed and warm but remained asleep. A figure of eight gauze bandage was put on
over the neck and upper part of the chest and the patient immediately returned to bed. In bed she lay without a pillow and with sand-bags on either side of her head lest any restless jerking might lead to slipping of one of the ligatures. That same evening the head was propped up on a pillow.

For the first 48 hours rectal salines containing 6% glucose were given every four hours, and 30 m. of Lugol's soln. was included in the first saline. On two or three occasions, as the restlessness of the patient demanded it, gr. 1/12 heroin was given.

On the morning of the second day the patient was given sips of warm water by mouth and thereafter a light diet and so on up to a full diet was instituted gradually. As before operation, no visitors or newspapers etc. were permitted for several days. The wound was first dressed on the second day and the drain shortened. The clips and drain were removed on the 4th day and the stitches on the 6th.

A flatus enema was given on the 2nd day; occasionally luminal gr. 1 was administered in the evening if required. Lugol's soln. was commenced by mouth on the 3rd morning beginning with 3 m. t.i.d. and mounting up as before to 5 m. t.i.d. Within 8 days the pulse had dropped from 130 to 72 and so the dose of Lugol was gradually diminished and
completely cut off when she was discharged on 3rd March 1931.
At no time was there any postoperative vomiting.

Progress: excellent; no complications.

Daily B.M.R. Chart: see commentary.

**PATHOLOGY.**

Naked-Eye appearance. The gland is firm and nodular and very vascular.

Cut Surface: shows a conglomeration of nodules of varying size, up to the size of a hazel nut. Many of the nodules, particularly the larger ones, are definitely encapsulated, the smaller ones are less obviously so. The whole surface has a reddish gelatinous appearance but some areas are distinctly solid and fleshy. A number of small cysts about $\frac{1}{4}$ inch in diameter can be seen; these on puncturing let free a small quantity of clear fluid, though in some it is a brownish hue from admixture with blood.

Microscopic Low power. The tissue is made up of numerous nodules separated from one another and encapsulated, by fibrous septa.

High power. The structure of the individual nodules varies considerably. In some the acini are dilated and irregular, the epithelium flattened and the colloid deeply stained with eosin - a typical area of colloid goitre. The interstitial tissue of such parts has an appearance as if the colloid had overflown from the vesicles, though it may
CASE 2.

Pseudo-acinar formation in a nodule.
simply be a hyaline degeneration. There are numerous areas of haemorrhage but the vessels show no marked degenerative changes. Occasional collections of lymphocytes are to be seen.

In some areas of other nodules, there are obvious signs of hyperplasia and activity. In these parts the epithelium is tall columnar and frequently projects as papillary ingrowths into the acinus. In these cells the nucleus is situated towards the free margin and the cytoplasm around it is definitely basophilic and granular and the colloid in the lumen is scanty and feebly stained.

In a few of the nodules the epithelium has taken on a peculiar pseudo-acinar formation (fig. 7). The epithelial cells there are of a very high columnar type; their cytoplasm is basophilic and has a finely granular structure. The nuclei are situated for the most part about the middle of the cell and although the circle of nuclei in each area suggests acinar formation, many show no lumen, the cytoplasm of the cells apparently blending in one common centre. Where a lumen is present it is usually small and contains no colloid. The interacinar lymphatics in these areas are dilated and apparently full of a colourless material and in the centre of one such lobule a cystic myxomatous space can be seen.

There is no evidence of malignancy.
"Adenomatous goitre with pseudo-acinar formation".


2:9:31. Scar from healed sinus to be attended to.
CASE 3.

Mrs. A.B. aged 39, married, para 6.

Occupation: Housewife.

Admitted: 6th March 1931.

Complaint: Swelling in front of neck.

Duration, 22 years.

History: After the birth of her first baby 22 years ago, the patient observed that there was a swelling present in the front of her neck. She could not account for its presence and had no recollection of its gradual growth. Since its first appearance, it has remained unaltered in size but in 1928 she began to be afflicted with dyspnoea on exertion and at times she experienced a choking sensation in the neck.

The patient has always been of a nervous disposition but will not admit that she has become more so of late. She now perspires readily and she has become much thinner during the past year. She becomes breathless even when walking along the level and any attempt to climb a stair or hill results in considerable fatigue and aggravation of her breathlessness.

Her appetite is good but she does not claim that it is excessive; she has no difficulty in swallowing but occasionally vomits. Her bowels are regular and she has
no diarrhoea. She has never been subject to sore throats or tonsillitis, but she has recurrent attacks of bronchitis each winter. On occasions, her face and neck become hot and flushed. She has no particular aversion to warmth though she now prefers coldish weather. There has been no tremor of the hands nor protrusion of the eyes as far as she or her friends have been aware and she has had no hoarseness of her voice.

The above symptoms - describe her present condition and they have only gradually been imposed upon her normal life three years ago.

**Previous Health.** Pneumonia 3 years ago.
Frequent bronchitis.

**Social History.** Nil. to note.

**Family History.** No history of goitre in other members of the family.

**Physical Examination.** Patient is well built though thin and somewhat pale. She does not appear to be unduly emotional; there is no exophthalmos.

**Local examination.**

**Inspection.** There is an irregular swelling apparent in the front of the neck, a little more prominent on the right side than on the left. Carotid pulsation can be seen on both sides and the swelling moves vertically on deglutition.

**Palpation.** Numerous small swellings can be felt throughout the thyroid gland but none of them seem distinct and isolated.
The gland is uniformly affected and the enlargement symmetrical. Both poles of either lobe can be felt, neither extending into the thorax although the left lower pole passes further downwards than the right.

All the 'eye signs' are negative (vide case 4). There is no tremor of the outstretched fingers, but the skin of the palms and of the rest of the body generally is unduly moist and warm.

**Circulatory system.** Pulse: rate 120; regular in time and force and of good volume; vessel wall just palpable; blood pressure 138/94.

**Heart.** Apex beat forcible; left ventricle slightly enlarged; heart sounds pure.

**Other Systems:** Nothing abnormal detected.

**Special Investigations.**

B.M.R. (Douglas bag method) + 51.

**Provisional Diagnosis.** Toxic adenomatous goitre.

**Preoperative treatment:** Rest in bed, screens, Lugol's iodine, etc. Details precisely similar to case 2.

**Operation.** 12th March 1931.

**Anaesthetic** - Scop. and Morph. + local.

"Subtotal Thyroidectomy" - details similar to case 1.

To gain sufficient access to the goitre, the pretracheal muscles had to be divided transversely near their upper part, the divided muscles being subsequently united with interrupted catgut stitches. Throughout the operation the
patient remained asleep and the operation was carried out without interruption.

Post-operative treatment - was in all respects similar to case 2. There was slight post-operative vomiting when sips of warm water were first given on the second morning.

Progress: Excellent; apart from slight post-operative vomiting there were no complications. She was discharged on 19th March 1931, looking very much brighter and better than she was prior to her operation. The wound was soundly healed; pulse rate 72.

Daily B.M.R. Chart: see commentary.

PATHOLOGY.

Naked-eye appearance: The gland is enlarged and firm and seems to be formed of a mass of nodules.

Cut Surface shows the enlargement to be due to a conglomeration of nodules, throughout the thyroid gland - a typical "pudding goitre". The whole surface has a reddish gelatinous appearance and large numbers of small cysts are present which on puncturing are seen to contain a clear viscid fluid, in some cases brown in colour from haemorrhage. Numerous small brownish patches are visible, throughout the gland and occasional yellowish flecks of necrosis can be seen.

Microscopic: Low power. All the nodules are of similar structure and encapsulated in fibrous tissue.
CASE 3.

Showing "colloid" nature of the nodules.
High power (fig. 8) The acini are dilated and well filled with deeply eosin-stained colloid. In some, breaking down of the acinar walls has allowed of minute colloid cyst formation. Occasional infolded twigs of epithelium project into the acini indicating former activity and hyperplasia, but the epithelium now is of a low columnar type. The stroma is of a homogenous hyaline nature but some areas have a more fibrous structure. Areas of haemorrhage are frequent and degeneration and endarteritis is to be seen in many of the vessels. In the fibrous tissue septa, which surround and separate the nodules, compressed islets of thyroid tissue can be seen along with frequent aggregations of lymphocytes. This seems evidence that the nodular formation was possibly the result of the development of these septa within thyroid gland tissue which was originally in complete continuity.

"Adenomatous goitre of the colloid type".

The quiescent structure of this gland seems at variance with the original toxicity found on clinical examination, therefore we must assume that the change has been the result of iodine administration during the preoperative period. (Compare with basal metabolic rate chart included in commentary.)

Reported. 29:4:31. In good health; all signs and symptoms of hyperthyroidism gone.
CASE 4.

Mr. E.F. aged 26, single.

Occupation: Gardener.

Admitted: 30th April 1931.

Complaint: Nervousness and weakness; prominence of the eyes and swelling in the front of the neck.

Duration - 3 years.

History. The patient first began his career in an office but in 1927 he left and started afresh as a gardener. This work, however, caused him a good deal of worry and he soon became very weak and 'run down', lost almost two stone in weight, and had to give up his work and return home. There he rested in bed for a month, gradually recovering. During this illness he was very nervous and easily fatigued and his attention was drawn to a slight exophthalmos and to a fullness of the lower part of the front of the neck. He had no excessive perspiration, however, nor did he feel particularly warm. He had sometimes diarrhoea but no vomiting; his appetite was very good. There was no tremor of the hands nor flushing of the face and he only rarely experienced any tachycardia. He had not been subject to sore throats and had no chronic cough.

Since the onset of his illness in 1927 his eyes have gradually come to protrude more and more but the swelling in the neck has never been very noticable, and it was not
until he visited his doctor in Dec. 1930 for life insurance examination that the association between his general symptoms and his enlarged thyroid was pointed out to him. His symptoms varied from time to time throughout his illness and his weight has fluctuated between 7 and 8 stones.

In February 1931 he was treated in a medical ward but without great success and so an operation was advised.

Previous Health. Enlarged tonsils and adenoids removed at the age of 12. No other illness worthy of note.

Family History. One sister has a goitre but it is entirely symptomless.

An aunt for some time suffered from goitre but after a few years the swelling gradually vanished of its own accord.

His parents, particularly his mother, are very nervous types of individuals.

Social History. Nothing to note.

Physical Examination. The patient is of light build and has a fresh, clear complexion. His whole skin appears to show a faint flush. There is no great loss of subcutaneous fat. He has a slight adenoid facies and there is marked exophthalmos.

Local Examination.

Inspection, shows a uniform, bilateral swelling in the region of the thyroid gland. The enlargement, however, is not excessive, and it might possibly be overlooked at a casual glance. The swelling moves vertically on swallowing.
Palpation: no thrill can be felt over the swelling but it can be definitely defined as being due to a thyroid enlargement. It is uniform and firm in consistence and no nodules can be felt. There is no downward extension of either pole. The cervical lymph glands are slightly enlarged.

No tremor can be observed in the outstretched hands.

"Eye Signs".
Joffroy's Sign - absence of wrinkling of forehead on looking up - positive.
Von Graefe's sign - lagging of upper eyelid on looking downwards - positive.
Stellwag's Sign - widened palpebral fissure - positive.
Moebius' Sign - weakness in convergence for near objects - positive.
Cardiovascular System - Pulse: rate 85; regular in time and force; vessel wall not palpable; blood pressure 124/70.

Heart: left ventricle enlarged slightly. Heart sounds pure.

Other systems: increased dullness over superior mediastinum, probably indicates the presence of an enlarged thymus.

Urine contains a small quantity of sugar.

Special Investigations.

B.M.R. (Douglas Bag method) + 79.
Differential leucocyte count.

Polymorphs 56.6%
Small lymphocytes 29.4%
Large lymphocytes 12.3%
Eosinophils 1.3%
Basiphils 0.3%

i.e. there is a considerable general lymphocytosis and particularly an increase in the large lymphocytes.

Provisional diagnosis - Exophthalmic goitre (Graves' disease) in a comparatively early stage.

Preoperative treatment. In order to get the patient into the best possible state for operation the preoperative period was prolonged for 2 weeks. The treatment was in all respects similar to case 2 (i.e. screens, rest, Lugol, luminal etc.).

Operation. 22nd May, 1931.

Anaesthetic - Scop. and Morph. + local

"Subtotal Thyroidectomy" - details similar to case 1.

The thyroid and the surrounding tissues were exceedingly vascular and a considerable time had to be spent in ligating all the divided vessels so that the operation was more prolonged than usual. Occasionally, at the commencement of the operation, the patient was a little restless, and towards the end of the operation he again woke up and muttered incoherently but it was found possible to complete
it without the use of a general anaesthetic. Although the patient appeared to suffer pain he had no recollection of his experiences when asked about them the following day. Post-operative treatment. For 36 hours after the operation the patient was very ill. His pulse rate rose to 140 per minute and he was very restless. Repeated injections of heroin 1/6th gr. had to given for the first three days. Owing to his restless movements and to the extreme vascularity of the operation area, there was considerable oozing of blood from the wound for the first 24 hours. This, however, was successfully controlled by the injection of 2 ccs. of haemostatic serum. On the 10th day a serum rash, with areas of local oedema, appeared over his body, causing considerable inconvenience and not a little excitement to the patient. The clips were removed on the 4th day but on account of persistent oozing of serum, the drain had to be left in until the 9th day.

The other details of post-operative treatment (lugol's soln. etc.) were similar to case 2.

Progress. Apart from the marked post-operative disturbance and the development of a serum rash everything was satisfactory. There was no post-operative vomiting. He left for convalescence 18 days after operation; his pulse had dropped to 78 and he felt much more able and fitter than
CASE 4.

Showing acinar structure and lymphoid follicles.
before. The exophthalmos remained.

**Daily B.M.R. Chart - see commentary.**

**PATHOLOGY.**

**Naked-eye appearance.** Both lobes show a slight enlargement and the vascularity of the organ is markedly increased. The outer surface appears faintly lobulated but the gland is uniformly firm and feels almost granular.

**Cut surface** is of a general fleshy appearance although some areas seem less solid and more gelatinous. There are no areas of haemorrhage and no cysts.

**Microscopic. Low power.** The appearance of the tissue varies in different areas. Some are typical "colloid" areas with dilated acini and low cuboidal epithelium, in parts projecting as tiny spurs into the acini. The colloid, however, is very poorly stained. Zones of hyperactivity alternate with these "colloid" areas.

**High power (fig. 9).** In the hyperplastic areas the normal acinar shape is distorted by numerous epithelial invaginations. The cells are columnar, the nuclei large and the cytoplasm poorly stained, finely granular and slightly basophilic in reaction. Many of the nuclei display an irregularity in size and abnormal staining qualities which are suggestive of rapid multiplication, but no actual mitotic figures can be seen. The colloid is scanty, poorly stained and tends to have a basophilic reaction. Its absence
adjacent to the lining cells suggests that it is being rapidly absorbed through the epithelium. Occasionally desquamated cells are to be seen lying in the centre of the acini. The interacinar stroma is increased in amount and one of the most characteristic features of the section is the numerous collections of lymphocytes grouped round large epithelioid cells in a typical 'germinal centre' fashion. The blood vessels are very numerous and engorged.

"'Exophthalmic' type of goitre with focal areas of activity and inactivity."

CASE 5.

Mrs. N.N. aged 31, married, para. 2.

Occupation: Housewife.

Admitted: 20th March 1931.

Complaint: Swelling on lower part of front of neck - left side.

Duration 15 years.

History: It was about 15 years ago, in 1916, that a friend first pointed out to her the presence of a small swelling in the front of her neck, a little to the left side. This swelling increased slightly in size over a period of about a year and then remained stationary. She can give no cause for the first appearance of the tumour but it is interesting to note that she was but 16 years of age at the time and that its earliest appearance may have been associated with the onset of the menarché which occurred when she was 15. The swelling caused her no pain nor discomfort and after she was married she observed that the tumour decreased in size during each pregnancy and then slowly resumed its former prominence after the puerperium. This, however, may have been an illusion; possibly the general thyroid enlargement which usually occurs in pregnancy may have only obscured the natural prominence of this stationary tumour.

Her health since the first appearance of the swelling has been perfect and she has never suffered from nervousness,
palpitation, excessive perspiration nor any of the other
signs which we associate with excessive or disturbed
thyroid secretion. In June 1930, however, she believes
that the swelling must have become larger as she then began
to experience a sense of pressure on the left side of her
windpipe, though she had no actual pain. About this time,
too, she noticed that her "knees shook" whenever she ex-
erted herself unduly and she began to have frequent attacks
of palpitation, the palpitation, of late, coming on at
times even when she was lying at rest. Since June 1930
she has also become more emotional and irritable. She
now has frequent diarrhoea but no vomiting or dysphagia
and her appetite though good, has not increased. She
has had no hoarseness of the voice nor cough. There has
been no tremor of the hands nor exophthalmos. In Nov.
1930 she had what she describes as an "attack of nerves",
giving way to fits of weeping without justifiable cause.

These symptoms are worst at her menstrual periods;
she has no dysmenorrhoea.

Previous Health. Nil. to note.

Family History. Nil to note. No history of goitre in any
members of the family.

Physical examination. Patient is thin and lightly built but
healthy looking. She is a little pale but not unduly warm.
There is no exophthalmos.
Local Examination.

Inspection: A swelling can be seen over the region of the left lateral lobe of the thyroid but the right side of the neck is of normal contour. The tumour moves vertically on deglutition.

Palpation. A firm rounded tumour is felt in the region of the left lobe of the thyroid encroaching somewhat on the isthmus. It is painless and not adherent to the perithyroid tissue, and the skin is freely movable over its surface. In size, the tumour is that of a pigeon's egg and of similar shape and its margins are clearly definable. No other swellings are to be felt and the other parts of the thyroid gland are not enlarged.

No bruit is audible on auscultation over the tumour. 'Ege signs' are negative and there is no tremor of the outstretched hands.

Circulatory system. Pulse: rate 84; regular in time and force; vessel wall not palpable; blood pressure 124/82.

Heart: not enlarged; heart sounds pure.

Other systems: nothing abnormal to record.

Special investigations.


Provisional diagnosis. Foetal adenoma of thyroid with some slight degree of toxicity.
Pre-operative treatment. Patient was admitted only 4 days prior to operation as there were but slight signs of toxicity. The usual treatment for such cases was carried out (see case 2) but Lugol's solution was only given up to 4 minums t.i.d.

Operation. 24th March 1931.

Anaesthetic - Scop. and morph. + local.

The preliminary exposure of the thyroid gland was the same as in case 1. The left sternohyoid muscle had to be divided transversely. The left lobe of the gland was then separated and mobilised from the surrounding structures, some difficulty being experienced on account of the presence of numerous adhesions posteriorly. By the usual procedure (vide case 1) the left lobe, containing the solitary tumour, was then removed, leaving but a thin shell of thyroid tissue posteriorly, and the wound closed as before.

Post-operative treatment. The general treatment was similar to case 2. Only 10 minums of Lugol's solution was given in the first rectal saline. On the 3rd day Lugol was first given by mouth commencing with 1 m. t.i.d. and mounting up to 3 m. t.i.d. on the 5th morning. Thereafter the iodine was gradually reduced and the patient was able to commence her convalescence 10 days after the operation.

Progress. After operation the pulse rate rapidly fell from 90 to 72 on the 3rd day. There was no post-operative vomiting and no other complications. She was discharged on
CASE 5.

Showing structure of foetal adenoma.
Note columnar formation of cells round blood sinus.
5th April with the wound soundly healed and in excellent general condition.

Daily B.M.R. Chart - see commentary.

PATHOLOGY.

Naked-eye appearance. The lobe which was partly removed is the site of a single large tumour of about the size and shape of a small hen's egg. The tumour is of firm consistence.

Cut surface. The tumour is surrounded by a capsule which separates it from the normal thyroid tissue. It has a solid, greyish-red, fleshy appearance and numerous tiny blood spaces can be seen. There are no cysts present.

Microscopic: Low power. The section shows an almost undifferentiated mass of cells, fenestrated by numerous large blood spaces. Here and there a small acinus containing deep eosin-stained colloid can be seen.

High power (fig. 10) The epithelial cells are closely packed together and there appears to be little if any intercellular stroma. The nuclei occupy the greater part of the cells and show considerable variation in size. No mitotic figures are evident but some of the nuclei are clearly hyperchromatic. The cytoplasm of the cells is basophilic. Frequently the cells take on a circinate arrangement without actually forming acini, and the few acini which have formed are very small and their lining cells are cuboidal and basophilic though a small amount of
eosin-stained colloid lies in the lumen. The blood spaces form numerous diverticula. Their walls are composed of a single layer of endothelium but in spite of that, no area of haemorrhage can be seen. No doubt the compact nature of the surrounding cellular tissue gives strength to the weak vessel walls. A peculiar feature is the more orderly and columnar nature of the cells around many of the blood spaces, suggestive of some secretory activity of the epithelium there. Throughout the solid masses of epithelial cells occasional fibrous septa can be seen.

"Foetal adenoma showing practically no differentiation".

CASE 6.

Mrs. M.L., aged 63, para. 4.

Occupation: Housewife.

Admitted: 9th Jan. 1930.

Complaint: Swelling on scalp behind right ear.

Duration, 3 months.

History. It was about the end of Sept. 1929 when the patient first observed a swelling, about the size of a hazelnut, situated on the skull behind the right ear. The swelling was painless and caused her no trouble but as it continued to grow she visited her doctor who at first recommended simple excision, but, noticing that it was pulsatile, decided to send her in to the R.I.E. Whenever the patient felt cold the swelling would draw attention to itself by causing some discomfort apparently through a slight temporary enlargement. She had never got a blow on that region of the head.

Previous Health: Nothing to note.

Family History: Nothing to note.

Physical Examination. Patient is a thin, frail, emaciated woman. She looks ill and appears much older than her age. There is a superficial capillary dilatation over the malar bones and the skin is of a faint icteric tinge and muddy.

Local examination.

Inspection. A diffuse, pulsating, swelling of about 2
inches diameter is seen over the posterior part of the right mastoid region; the overlying skin is reddened and congested.

Palpation. The swelling is larger than mere inspection suggests. It is situated over the right half of the occipital bone, above the level of a line drawn through the external auditory meati. Definite expansile pulsation can be felt and although fluctuation can be elicited over the whole of the tumour, it cannot be emptied. No definite margin of the tumour can be felt but the bone in that area is eroded, the sharp edges of the bone being readily felt around the swelling. It is not tender but is so soft that one cannot ascertain whether the skin is attached to it or free.

On auscultation a loud systolic bruit can be heard over the whole of the swelling.

Cardiovascular System. Pulse: rate 90; regular in time and force; both radial arteries of equal volume, vessel walls a little thickened and tortuous; blood pressure 122/78.

Heart: No dilatation; heart sounds pure in all areas.

Nervous System. Reflexes normal; intelligence good; nothing abnormal detected.

Thyroid gland is firm and slightly enlarged particularly in the left lobe.
Other Systems - nothing abnormal detected; no similar swellings elsewhere in the body.

Special investigations.

Wassermann Test - negative.

X-ray of chest - no increase of aortic shadow.

Differential diagnosis is fully considered in the commentary. The chief possibilities are:

1. Aneurysm of occipital artery.
2. Metastasis from a malignant thyroid.
3. Telangiectatic sarcoma of bone.

The swelling was so markedly pulsatile and fluctuating and situated so precisely in the line of the occipital artery that after a brief deliberation, a provisional diagnosis of aneurysm of the occipital artery was made.

Operation. 14th Jan. 1930.

Anaesthetic - chloroform and ether.

A vertical incision was made over the centre of the tumour and deepened until the tumour was exposed. There was considerable haemorrhage and great difficulty was experienced in attempting to control it, all the vessels in that area being enlarged and engorged. After some dissection the occipital artery was found overlying the swelling and entirely free from it. Fusiform or cirsoid aneurysm, therefore, had been the wrong diagnosis. Dissection around the margin of the tumour revealed the sharp edge of the eroded bone and the tumour was obviously in the bone. It
was not considered advisable to remove a portion of the tumour for examination because of the extreme vascularity and the haemorrhage which had already been encountered, but it was presumed that the tumour was a telangiectatic sarcoma ("bone aneurysm"). The association of the swelling with the thyroid enlargement was even then considered unlikely. The wound was thereupon closed with interrupted silk worm gut stitches.

"Exploratory incision of tumour".

Progress. After operation the patient gave cause for considerable anxiety for the first two days. Her pulse was feeble and rapid and she was refusing stimulants. After this, however, she improved and made a satisfactory recovery.

On account of the vascularity of the tumour further attempts at excision were deemed inadvisable and so radium application was given.

Operation. 4th Feb. 1930.

Anaesthetic: Chloroform and ether.

An incision was made in the line of the scar and the tumour once more exposed. Again great trouble was caused by the profuse bleeding from the region of the tumour, even after the application of Horsley's wax to the eroded bone edges. Six 5 Mgm. needles of radium were applied around the periphery of the tumour and the wound closed.
Progress. After 5040 Mgm.-hrs. application the radium needles were removed on 11th Feb. 1930. At the same time the wound was partly opened up and a small portion of the growth removed for microscopic examination. This caused considerable haemorrhage and it was necessary to pack the wound with gauze in order to control the bleeding. The patient was discharged on 18th Feb. to the convalescent home. Already the tumour had begun to diminish in size.

Two days later the pathologist's report on the tumour was obtained. The tissue was similar to that of a hyperplastic thyroid.

It was now clear that this was a secondary spread from a malignant thyroid tumour; the enlargement of the thyroid gland, therefore, was the result of a malignant change although the patient had never complained of any symptoms referable to that organ. The patient was recalled and a careful investigation of the thyroid gland made.

**Inspection** - no obvious enlargement of the gland to be seen.

**Palpation** - The left lobe and adjacent part of the isthmus was slightly enlarged. The tumour was hard and slightly nodular, on the surface. It moved vertically on deglutition and did not appear to be fixed to the surrounding structures and the skin was freely movable over it.

**Diagnosis** of malignant tumour of the thyroid was therefore evident.
Readmitted: 11th March 1930.
Operation: 18th March 1930.

Anaesthetic. Scop. and Morph. + local.

"Total thyroidectomy". The procedure was similar to that described fully in case 1. The pretracheal muscles were divided transversely to obtain adequate access. Both lobes could be readily dislocated from their bed; the tumour, therefore, had not apparently extended beyond the capsule into the surrounding tissues. The parathyroids on the left side were removed with the left lobe but before removing the right lobe, the blood supply from the inferior thyroid artery to the parathyroids, was isolated and the parathyroids on that side carefully preserved.

Post-operative treatment. Following operation the patient was given the usual treatment (vide case 2). In addition owing to the risk of tetany developing, parathyroid extract gr. 1/5th and calcium lactate gr. 5 were given t.i.d.

Progress. The patient made a satisfactory recovery and at no time gave any cause for anxiety. There was no evidence of tetany. She was discharged on 29th March 1930 with the wound well healed and her general condition satisfactory. The secondary tumour of the occipital bone had further decreased in size being now about the size of a walnut though flatter. Slight pulsation was still present. The patient
was accordingly advised to return in 6 weeks for further treatment and in the meantime was instructed to take thyroid extract gr. 5 b.i.d. under the guidance of her doctor.

She did not return until 15th Oct. 1930 when she complained of a swelling on her right side and of a smaller swelling on her back - evidently further thyroid metastases.

Readmitted on 4th May 1931 for further treatment.

Further History. After her discharge from hospital in March 1930 she improved in health. In August 1930 a small swelling appeared close to her spine in the small of her back and grew to the size of a pea and then remained stationary. She felt it pulsating when she lay down but otherwise it caused her no trouble. In the following month a similar swelling appeared on the right side at the lower costal margin. It, too, enlarged, reaching to about the size of an egg.

In March 1931, the occipital tumour which had almost vanished began again to enlarge and has now reached the size of a walnut. It also pulsates and is somewhat painful causing thus a good deal of trouble to the patient.

She is now very easily fatigued and has palpitation at times. Since March 1930 she has been taking thyroid extract
regularly.

Physical Examination. The patient looks ill but not so emaciated and weak as she was before her thyroidectomy a year ago.

Local examination.

1. A pulsatile, slightly tender, swelling, about the size of a walnut, is situated over the occipital bone, slightly to the right of the mid line. The first metastasis is now only represented by a diffuse, slightly elevated, softish area and this other tumour appears to have arisen as a medial extension of the original metastasis.

2. There is a soft pulsatile swelling situated on the right side between the tip of the last rib and the iliac crest. It is about the size of a small hen's egg and is not tender. The skin is easily movable over the tumour.

3. There is a similar, soft, pulsatile swelling about the size of the tip of one's finger, lying a little to the left of the spine of the 3rd lumbar vertebra. It is not adherent to the skin.

Special investigations.

X-ray examination.

Skull: no evidence of metastases in occipital or other bones.

Pelvis: no evidence of metastases.

Spine: extensive destruction of laminae of 3rd and
4th lumbar vertebrae; there is a suspicious area of rarefaction in the spine of 12th thoracic vertebra.

Ribs: no evidence of metastases.

Other bones: no evidence of metastases.


Diagnosis: Thyroid metastases in

(a) occipital bone
(b) 12th rib, right.
(c) laminae of 3rd and 4th lumbar vertebrae.

Operation. 22nd May 1931.

Anaesthetic - chloroform and ether.

(a) metastasis in occipital bone: 9 2Mgm. needles of radium inserted around the growth.

(b) rib metastasis: on incision the tumour appeared to be encapsulated and adherent to the tip of the 12th rib. It was dissected out and removed although great difficulty was experienced in controlling the haemorrhage which resulted.

(c) vertebral metastasis: 7 2Mgm. radium needles were inserted around its periphery.

Progress. The patient made a satisfactory recovery after the operation. The radium needles were removed on 26th May 1931.

Total dosage to occipital metastasis, 1728 Mgm. Hrs.

Total dosage to vertebral metastasis, 1444 Mgm. Hrs.

Discharged on 24th June in fair general health. The two metastatic tumours had already begun to respond to the
Fig. 11.

CASE 6.

Section of primary tumour in thyroid.
radium treatment and were considerably reduced in size. The tumour at the back of her head had now ceased to cause her any pain though pulsation was still present. The wound in the flank was soundly healed. Daily B.M.R. Chart - see commentary.

PATHOLOGY.

Naked-eye appearance of thyroid gland. The enlargement of the gland is confined to the left lobe and isthmus, these parts being stony hard in consistence. Owing to its extreme hardness a saw had to be used to section the gland.

Cut surface has a reddish and grey mottled appearance. There is no nodular encapsulation. Extensive areas of calcification are present and it is to this that the stony hardness was mainly due.

Microscopic Appearance.

Primary tumour: Low power. The tissue has a papilliferous structure. In many parts the cell masses appear solid, suggestive of a medullary type of thyroid tumour, but on the whole, the tissue is adenocarcinomatous in type. Small acini are present throughout most parts of the tumour.

High power (fig. 11). The epithelial cells show great variation in size and shape. Many form pseudo-acini, the nuclei being grouped in a circular fashion but the
CASE 6.

Thyroid gland - almost normal tissue with epithelial cells lying free in stroma.
cytoplasm, which tends to be basophilic, fuses in a common centre. Some true acini, however, are present though they contain little if any true colloid material. Occasionally hyperchromatic nuclei reveal active division but in no part could actual mitosis be seen. There is little stroma present but numerous blood vessels lined by a single endothelial layer can be seen and frequently epithelial cells, lying singly or in pairs in the stroma, are evident, having apparently separated themselves off from the parent papillae. There is no lymphocytic infiltration as in most other types of malignant neoplasms.

Large numbers of cells can be seen invading the capsule and lying in rows along the tissue planes, occasionally forming minute acini. In two places tumour cells can be observed invading the walls of veins.

This invasion of the veins and of the capsule constitute definite evidence of malignancy.

A second section (fig. 12) from a different part of the thyroid, shows fairly normal acini and increase of interacinar stroma. Numerous cells, apparently derived from thyroid epithelium, are lying free in the stroma. They show no evidence of cell division and appear perfectly benign. Probably they are cells which have migrated from the acinar epithelium and may represent a precancerous stage in the development of malignant neoplasia.
Fig. 13.

CASE 6.

Section of metastasis in occipital bone.
Section of occipital metastasis (fig. 13). The metastatic tissue here has entirely departed from the papillary structure of the primary growth. It is of a more adult and benign type. Numerous enlarged acini can be seen lying amidst a fibro-hyaline stroma; the lining epithelium is cuboidal and basophilic and the lumen is almost filled with colloid. Many individual cells of thyroid epithelium lie amidst the connective tissue stroma, occasionally taking on a circinate arrangement or pseudoacinar formation. A few hyperchromatic nuclei are to be seen but on the whole there is little evidence of cell multiplication. There are numerous small haemorrhages from the abundant thin-walled blood vessels but nowhere can the epithelial cells be seen invading the vessel walls as in the primary tumour.

There is no absolute pathological evidence of true malignancy in this secondary tumour.

Section of rib metastasis (fig. 14). The adult acinar formation is even more marked than in the occipital secondary tumour and there is no evidence of a papilliferous structure. The acini show great variation in size and shape and contain only a scanty amount of a thin, poorly-stained colloid. A noticable feature of the epithelium is the enormous proliferation of the nuclei which appear to overlap one another so that practically no cytoplasm can be seen. Practically all
CASE 6.

Section of metastasis in rib.
these nuclei appear as a mere ring; they are apparently deficient in chromatin material. In parts, however, a darker staining nucleus can be seen. Long strings and solid clumps of these abnormal nuclei also lie amidst the interacinar tissue but no associated cell cytoplasm can be made out. The stroma is thin and partly myxomatous and many faint nuclear forms resembling those of the acinar epithelium are enmeshed in it. Blood vessels, lined only by a single endothelial layer, are numerous but there is no sign of vascular invasion by the neoplastic cells. Lymphocytes are singularly absent.

The tumour is sharply delimited by its fibrous capsule, there being not the slightest trace of invasion of the latter.

Conclusions.

(1) The primary tumour is a papilliferous adeno-carcinoma.
(2) The primary tumour is malignant.
(3) The occipital metastasis is not definitely malignant.
(4) The rib metastasis is apparently benign and is of a more adult structure than the metastasis in the occipital bone.
COMMENTARY.
INTRODUCTION.

Of all the ductless glands, the thyroid is the most accessible and has been studied the longest, yet much of its physiology and pathology remains unsolved. Goitre is not uncommon, particularly in women, and their modern social activities render it all the more disfiguring and disturbing. Apart from such aesthetic and social considerations, however, any condition of hyperthyroidism is a serious one, for practically every cell in the body is involved in the increased metabolism and all eventually suffer in varying degree.

GEOGRAPHICAL DISTRIBUTION.

It is well known that goitre is very much more prevalent in certain districts than in others. This applies generally to all goitres but more particularly to the simple colloid goitre (e.g. case 1). It is found in most of the great mountain ranges of the world - the Alps, the Himalaya's and the Andes - but it is by no means confined to such districts, being prevalent in some of the great plains as around the St. Laurence and the Great Lakes. In England its frequent occurrence in the hilly parts of Derbyshire has given it the name of "Derbyshire neck" but peculiarly enough it is unknown in the only true mountainous part of Britain, the Highlands of Scotland.
The other types of goitre in this series of cases are also more prevalent in such goitre areas and Berard and Dunet conclude that, in these endemic parts, from 2.5-4% of all malignant tumours affect the thyroid gland whereas in goitre free areas the percentage falls to 0.4-0.5%. Where goitre is endemic, therefore, malignant tumours of the thyroid occur in greatest numbers.

Throughout the world sporadic cases of every type occur and each one of my series appears to come into this category.

**SEX INCIDENCE.**

One of the most striking facts in the series of cases, which included all admitted to the wards within a period of five months, is that 5 are female and only one male.

The sex incidence of these forms of goitre requiring surgical interference varies in different districts. The closer one approaches the centre of an endemic region the more the proportion increases on the male side and this probably explains De Quervain's figures of 3 females to 1 male. Crile's figures of 5.5 females to 1 male are more closely in accord with the proportion in my cases and with my mental estimate of the sex proportion in the cases admitted to the surgical wards of the R.I.E. during the past three years.
Metabolic studies in men and women suggest that the larger amount of thyroid tissue in the latter may be a reserve available and employed normally for the next generation. The flow and ebb of activity in that and other endocrine glands in the female, during puberty, menstruation and pregnancy, must obviously be greater than in the male, affording great opportunities for the onset of pathological instability. The stimuli which tend to produce overgrowth and hyperfunction are also more numerous and more powerful in women, who are naturally somewhat less stable in both mind and metabolism than are men and these factors taken together would seem sufficient to explain the peculiar preponderance.

**AGE INCIDENCE.**

The maximum age incidence of all cases of goitre coming for surgical treatment is from 30-40 (3 of my 6 cases came within this age period). In the male alone the maximum age incidence is from 20-25 years (vide case 4.).

Taking each type of goitre separately the maximum age periods may be stated:

(a) **diffuse colloid goitre** - first appearance about 20-25th year.

(b) **Grave's disease** - onset 20-25th year.
(c) **adenomatous goitres** - 30-40th year.

(d) **foetal adenoma** - before the age of 20.

(e) **malignant goitre** - 40-65th year.

In regard to age incidence, therefore, all my cases can be taken as being quite characteristic.

**DEVELOPMENT OF THYROID GLAND.**

In the human embryo of six weeks development the thyroid first appears as a small dimple in the floor of the buccopharynx, lying in the midline in front of the second branchial cleft. This depression gradually deepens until it becomes a sac opening by a narrow orifice on the summit of the tuberculum impar. The head of this growing epithelial bud enlarges and becomes bilobed as it travels caudally into the underlying mesoblast and thus it becomes surrounded by a fibro-elastic capsule and is connected by a long hollow stalk (the thyro-glossal duct) with the primitive buccopharynx, the opening there being given the name of the foramen caecum.

About the end of the second month the developing hyoid bone divides the thyro-glossal duct into a cephalic and a caudal portion. The thyro-glossal duct soon atrophies but the primitive bilobed thyroid remains and proliferates and ultimately forms the greater part of the adult gland.

In the structural development of the thyroid gland, a
series of spaces first appear in the solid epithelial mass and Norris carefully points out that these early spaces are not thyroid follicles. Williamson and Pearse regard them as the precursors of the intra-thyroidal lymph system and believe them to arise from the contained mesoblastic element in the thyroid bud. These spaces extend to the periphery of the bud and here they fuse, thus separating the primitive gland from the surrounding fibroblastic tissue. At this stage, therefore, the thyroid may be described as a stalked organ floating in a large lymph space and Williamson emphasises the importance of the simultaneous development of an intra- and extra-thyroidal lymph space.

The epithelium of the thyroid gland is now arranged in the form of long columns of cells running a straight course or coiled and folded on themselves. The vesicles of the gland appear to be formed by the accumulation of colloid material from groups of cells, each cell of the group discharging its colloid into a common centre. The apparent reversion at birth to a solid undifferentiated mass of cells has been proved to be due to a post-mortem desquamation which rapidly occurs, for if the gland is fixed immediately after death, it is seen to be composed of alveoli lined by cuboidal epithelium and containing colloid as in the adult.
ANATOMY OF THYROID GLAND.

The pure anatomical relations of the thyroid gland are too well known to require description here but I shall deal with certain points which are of special importance in reference to the cases.

Position. The two lateral lobes of the thyroid do not occupy symmetrical positions. The right lobe forms the larger mass on the antero-lateral aspect of the trachea and larynx and is appreciably nearer the surface than the left lobe: the left lobe forms the greater mass between the postero-lateral surface of the larynx, trachea and oesophagus. This explains, therefore, why,

(a) a visible or palpable swelling on the right side is so often the first sign of a general enlargement (cases, 1, 2, & 3).

(b) discomfort on the left side or a sense of pressure, dysphagia or choking is frequently the first symptom of a general enlargement.

(c) adenomata or general enlargement of the right lobe appears in the neck above the clavicle while any similar swelling of the left lobe, being prevented from growing forward by the upper margin of the sternum, clavicle and lower insertion of left sterno-mastoid muscle, is more likely to extend deeply into the neck or
down towards the thorax (e.g. case 1).

**Thyroid sheath.** A true sheath surrounds and is adherent to the gland and sends in septa into the parenchyma. Surrounding this is a false capsule formed by the pre-tracheal fascia which binds the gland to the larynx. In operating on the thyroid, the lobes are mobilised by separating the true from the false capsule.

**Blood supply.**

(a) **Superior thyroid arteries,** one on each side, enter the gland at the upper pole of the lateral lobes and are distributed over the anterior and lateral surfaces. They are said to give twigs only to the interstitial tissue septa and in this way resemble the distribution of the hepatic artery in the liver.

(b) **Inferior thyroid arteries,** enter each lobe at its hilum and can be traced to the network of capillaries which surround each vesicle. These, therefore, constitute the functional arterial supply of the thyroid gland. The anastomotic branch with the superior thyroid artery courses up the posterior surface of each lobe and is of interest in relation to the parathyroids.

(c) **Thyroidea ima,** a fifth artery, is present in 10% of cases; it is usually a branch of the innominate artery.

In contrast with the organ which they supply these
arteries are remarkable for their large size.

Lymph drainage. There are two distinct systems of lymphatics emerging from the thyroid gland:

(a) the 'lymphae comites' of the veins (i.e. the lymphatics of the capsule) which pass to the cervical lymph glands.

(b) the lymphatics which begin around the acini and pass downwards, forming the so-called thyro-thymic ligament of Piersol, to end in the thymus gland. The importance of this lymph drainage will be discussed later.

Nerve supply is mainly sympathetic from the middle and inferior cervical ganglia; the sympathetic nerves pass almost entirely along the course of the superior thyroid leash of vessels.

The gland is also supplied by some fibres derived from the pharyngeal branches of the vagus.

Sympathetic stimulation causes an increase of secretion but the fact that the thyroid will continue to function when transplanted into a distant organ, shows that nervous influences are not essential to promote its secretion.

Parathyroids. Most commonly there are but four parathyroids: one behind each lower pole and one behind the centre of each lobe at the level of the cricoid cartilage. They may be partly or completely embedded in the thyroid gland and so
render complete thyroidectomy without parathyroidectomy a
difficult operation. The parathyroids lie just lateral to
the anastomosing branch between the superior and inferior
thyroid arteries and derive their blood supply from that
branch.

**HISTOLOGY.**

The orthodox views on the histology of the thyroid
are that it consists of a framework of connective tissue
enclosing numerous rounded or oval vesicles lined with
cuboidal epithelium. Each epithelial cell contains
numerous mitochondria and a Golgi apparatus which is
generally situated between the cavity of the vesicle and
the nucleus. According to Schafer, Ewing and others no
basement membrane is present but Dunhill, and others of
equal eminence, are quite as certain that a basement
membrane is present. It seems inconceivable that such
diversity of opinion should exist about so simple a
matter. All other glandular epithelium is built upon a
basement membrane and there seems no reason to suppose
that the thyroid should not be similarly constructed. On
the other hand there seems to be greater unanimity in re-
gard to the absence of basement membrane in the thyroid of
certain fish, stimulation in such species causing a diffuse
growth of thyroid epithelium resembling a malignant change; and from comparative anatomy we might argue that the human thyroid, though more orderly might have an evolutionary connection in this absence of any basement membrane.

The matter is an important one, for lack of basement membrane would indicate a special potential mobility on the part of the thyroid epithelium and may explain the malignant and metastasizing nature of many apparently pathologically innocent thyroid tumours. In the sections which I had at my disposal I could not discern a complete basement membrane around any of the acini, though frequently filamentous portions of vascular and lymphatic endothelium could be seen closely simulating a fragmented membrane. I must, therefore, subscribe to Schafer's view that in the thyroid structure basement membrane is non-existent. The capillaries then must be regarded as being in direct contact with the vesicular epithelium.

There are no complete partitions between the epithelial cells and the cytoplasm of one cell is believed to be in direct contact with that of its contiguous cells as in the case of the liver. This peculiarity may in part explain why the cells in a normal thyroid can maintain such cohesion and order when the support of a basement
membrane is lacking.

The vesicles normally contain an eosin-staining iodo-
colloid substance, which is formed within and extruded
from, the lining epithelium. The amount of colloid
accumulated in the acini at any one time varies considerably
and it is usually stated that excessive accumulation of
colloid indicates thyroid inactivity and that deminution
in colloid storage is associated with glandular activity.

An extremely interesting and revolutionary contribution
to our knowledge of the structure of the thyroid gland was
made a few years ago by Scott Williamson. His views are
based on embryology and comparative anatomy as well as on
clinical and laboratory investigation of the adult gland.
According to him the morphological unit of the thyroid is
a lymph sinusoid containing coiled columns of epithelium
which are enmeshed in a basket-work of specialised blood
capillaries. By special staining methods he has shown
the presence of minute canaliculi in the cytoplasm of the
acinar cells and claims that it is through these that
certain of the thyroid secretions pass into the lymphatics.
Groups of gland units form lobules and although true inter-
lobular vessels are present the intralobular vessels are
composed of only a single endothelial layer, so that,
histologically, artery and vein are indistinguishable. The
lymphatic sinusoids drain into intralobular lymphatics which
emerge from the gland at the hilum of each lobe and thence proceed to their termination in thymic tissue. His contention is that the thyroid and thymus cooperate through their common lymph system and from the associated changes in these two organs in toxic goitre there would seem to be considerable truth in his conclusions.

As I shall refer again to this association, a brief account of the changes in the thymus from infancy onwards is necessary.

The metatrophy of the thymus provides three morphological varieties.

(1) a lymphocytic variation,
(2) a granular or lipoidal fat variation,
(3) a vesiculated fat variation.

The latter is the phase commonly found in the adult and this explains the common view that the thymus undergoes a true atrophy in early life.

Much of Williamson's work has been corroborated but certain points have not yet been fully ascertained. Recent microdissection methods seem to show that the thyroid is of globular rather than of tubular arrangement.

**PHYSIOLOGY.**

The functions of the thyroid gland may be summarised:

(a) it controls growth;
(b) it regulates metabolism - of particular importance is its regulation of nitrogen metabolism.
(c) it metabolises iodine, absorbed from the food, into thyroxin, and it is through the medium of this secretion that it controls metabolism;
(d) It is believed to have an antibacterial and antitoxic function, though recent research has failed to establish conclusive proof that this is so.

Here again Williamson and Pearse startled the medical profession with their views on thyroid physiology. Formerly it was believed that the gland secreted thyroxin which was contained in the iodo-colloid of the vesicles and that this filtered off between the epithelial cells and was eventually absorbed into the blood stream. These two workers gave very good reasons for believing that, in addition to iodo-colloid a second secretion is formed from the vesicular epithelium. It has been shown conclusively that iodo-colloid never implicates the lymphatics nor does the thymus or lymph glands of the neck ever contain iodine or thyroxin. There is no doubt, however, that there is present in the lymphatics some secretion which can stimulate lymphocyte production, and this Williamson claims to have traced from the lumen of the acini through the micro-capillary system of the epithelium into the perifollicular lymph spaces and thence down to the thymus. This lymphogenic substance is normally detoxicated in the thymus and is neither similar to, nor a derivative of, iodocolloid and they claim to have shown it to be responsible for the toxic state in Grave's disease and toxic goitre generally. They regard the colloid as something in the nature of a vehicle which, like taurocholate of bile, is in continuous circulation in the body and is only
stored in the vesicles as is the bile in the gall bladder.

**CLASSIFICATION.**

Any classification may be pathological or clinical or a combination of the two. In a work such as this a clinical classification with reference to the pathological condition present is desirable and to correlate the different cases I have made use of Dunhill's recent publications.

The type of goitre and the resulting clinical condition depends on three primary factors:

1. **the stimuli:** they may be normal but excessive; they may result from disturbance in some other endocrine organ such as the ovaries (vide case 5); from lack of iodine, deficiency of manganese or toxic absorption as from tonsillitis; certain psychic states are probably the most powerful stimuli in the development of the toxic types of goitre (c.f. case 2 where the goitre followed a stillbirth and case 3, where the symptoms date from the birth of her first baby).

2. **the thyroid gland:** the gland may be normal; as a result of previous stimulation the gland may be in the state of colloid goitre (vid. inf.) when a second stimulus affects it: the gland may have already reached the stage of nodular goitre: rests of foetal thyroid tissue may be present in an otherwise normal gland.
(3) **the body cells**: the ability which they possess of responding to the powerful stimulus of thyroid secretion will depend on whether the tissues are those of a young adult, capable of a wide range of metabolic activity or those of an older person whose body cells have already been worn out and buffeted by repeated infections and strenuous living. In the former case a gross degree of hyperthyroidism may exist but yet the body cells can respond and still maintain a little reserve; in the latter type a mild degree of hyperthyroidism may be sufficient to tax the body tissues to their meagre limits, and when we look at the end result we are inclined to say "A very severe grade of intoxication" but it is not so.

The classification and correlation of the six cases may therefore be adopted as follows:

1. **Non-toxic goitres.**

(a) **Colloid goitre** (case 1). This begins as a simple compensatory hyperplasia possibly the result of an insufficiency of available iodine. In such sporadic cases, however, McCarrison is of opinion that the hyperplasia is the result of a vitamin-poor carbohydrate amongst white-flour eating people and some such cause may have been at work in case 1. After a time the gland ceases to be stimulated and so involutes as far as it is able towards the normal. Complete involution, however, is not possible and so a chronic enlargement involving all the vesicles remains: the epithelium
also seems to have suffered in the process and is sub-efficient and thus some degree of hypothyroidism may eventually be present (vide case 1). There is also a tendency to thickening of the normal interlobular septa so that the gland comes to have a faint lobulated structure.

(b) **Nodular or adenomatous goitre.** If to that colloid goitre a further similar stimulus is applied it begins to become hyperplastic once more. The associated further thickening of the interlobular septa lead to definite nodule formation, the enlargement and expansion of the parenchyma accentuating this appearance. The so-called adenomatous thyroid, therefore, is not the result of tumour growth and is more correctly named 'nodular goitre'.

2. **Toxic goitres.**

(a) **Graves' disease** (case 4). In youth the psychic stimuli are most powerful and the thyroid gland most likely to be healthy and capable of responding in every unit to the stimulus: the body cells too are capable of a wide zone of active response and hence the condition of exophthalmic goitre results.

(b) **Toxic adenomatous goitre** (cases 2, & 3). This supervenes on a non-toxic adenomatous goitre or an adenomatous goitre may be toxic from its first development from a colloid goitre. In any case the stimulus is much the same as in Graves' disease though at the age period at which this occurs (30-40) psychic stimuli are not likely to be so severe. The gland
also is somewhat worn out and not so capable of rapid response and from consideration of these two primary factors it is evident that the degree of hyperthyroidism must usually be less than in Graves' disease. The third factor, the body tissues, however, are also worn out and thus are more ready to show signs of exhaustion under the strain of what is actually a mild degree of hyperthyroidism. The heart in particular has often a greatly reduced reserve power and for that reason cardiac symptoms often predominate.

In Case 2 marked goitre had only been present for two years and although the patient had gone through seven pregnancies we must assume that the thyroid gland in her case was more capable of intense reaction to whatever stimuli were present than was the thyroid gland in Mrs. A.B. (case 3). In the latter patient a thyroid swelling had been present for twenty-two years, she had had eight pregnancies and consequently a less severe degree of hyperthyroidism would be expected. This was the precise state of affairs found, for in the former patient (case 2) there was exophthalmos and a higher B.M.R. than in Mrs. A.B. who showed no exophthalmos. There is of course to be considered the stimuli which may have been of different intensity in the two cases.

3. Tumours.

(a) Benign foetal adenoma (case 5). The fault lies primarily in the thyroid gland which contains some rests
of foetal thyroid tissue. The stimulus causing the growth of this undifferentiated tissue is usually the general physiological and psychical upset of puberty, hence clinical evidence of the tumour commonly appears before the age of twenty.

(b) Malignant thyroid tumours are represented in this series by a papilliferous adenocarcinoma. Such tumours practically always arise in a thyroid already the site of goitre and although no history of goitre was obtained in case 6, it seems certain from the extensive calcareous deposits found in the gland, that some pathological condition was present long before malignancy supervened.

The classification of toxic goitre into primary and secondary is therefore artificial and unnecessary: both are similar and only differ in degree. Graves' disease may occur late in life and the so-called secondary toxic adenomatous goitre, if of severe degree, may be indistinguishable in its symptomatology from the exophthalmic type (vide case 2).

PREDISPOSING FACTORS.

The predisposing factors may be

(a) hereditary,
(b) congenital, or
(c) acquired.

Heredity, from a study of the cases, seems to play an
unimportant part, as far as the thyroid itself is concerned, but in two there was a history of goitre in another member of the family. Inherited nervousness of constitution would appear to be a more important predisposing cause than any possible intrinsic goitrous tendency for it is in the sympathetico-tonic type of individual that toxic goitre is most likely to arise (c.f. case 4).

Congenital causes are confined to thyroid tumours. From histological evidence there is no doubt that occasionally small islets of foetal thyroid cells may remain undeveloped, and being in this undifferentiated state, possess greater potentialities of growth, under the influence of normal and abnormal stimuli, than the fully developed and specialised epithelium. Some ascribe the persistence of these 'Wolfler's rests' to lack of iodine in the mother during pregnancy but it is by no means certain that this is so. As in other tissues those primitive epithelial tumours may become malignant and foetal rests may, therefore, predispose to malignancy.

Acquired predisposing causes blend with the exciting causes which have been mentioned under the heading of 'stimuli' on a previous page.
PATHOLOGICAL CONSIDERATIONS.

As the macroscopic and microscopic pathology appended to the various cases is sufficiently descriptive and characteristic of the different types of goitre, I shall refrain from reiteration and only discuss and supplement what has already been said.

General considerations. The naked-eye signs of increased thyroid activity are essentially:

(a) increased vascularity of the gland.
(b) some degree of enlargement of the gland.

The microscopic evidences of activity are:

(a) columnar cells with the nucleus situated well away from the vascular pole of the cell,
(b) presence of papillary intra-acinar growths,
(c) irregular outline of vesicles containing a small amount of colloid,
(d) colloid poorly stained, vacuolated, and staining preferably with haematoxylin,
(e) desquamation of the epithelial cells,
(f) great frequency of the mitochondria.

The microscopic evidences of inactivity are precisely the opposite of this.

This appearance applies particularly to Graves' disease but it is applicable in a slightly lesser degree to all toxic goitres. Where malignancy is present, however, the above does not apply.

Response to iodine.

In considering the histological appearance described
under the various types of goitre, it must be remembered that those cases showing any degree of hyperthyroidism had been treated for one or two weeks before operation by iodine therapy. The iodine administration leads to a varying degree of reduction in the hyperplasia.

In case 1 there seems to be little, if any, change from the typical histopathological picture of simple colloid goitre.

In case 2 the pseudo-acini seem to have been little affected but in other areas the 'colloid' type of vesicles predominate over the hyperplastic - possibly the result of iodine therapy.

In case 3 the dominance of colloid areas over hyperactive areas suggests, when one remembers the toxic condition of the patient on admittance, that here the iodine has had remarkable effect.

In case 4 (Graves' Disease) areas showing a reversion towards the normal are again dominant although that normal is never reached. The epithelial infolding has been smoothed out though a few withered twigs remain, recalling the once abundant epithelial proliferation. Such areas are, however, only focal for other parts still show the characteristic hyperplasia.

In those latter three hyperthyroid cases the excess of
'colloid' over 'active' areas is not in keeping with the original clinical condition of the patients and so the credit of this improvement must be given to the use of iodine as rest alone is known not to give such successful results.

Assuming that, before the pre-operative treatment were begun, the histopathology of these cases was that of a more or less general hyperplasia, one is impressed by three facts:-

(1) The marked variability in the degree of involution.
(2) The involution change is peculiarly focal in character. This may have some bearing on the formation of adenomatous goitre.
(3) The hyperplasia is never completely abolished.

The conclusions to be drawn from this are that the special preoperative treatment employed is justified on pathological grounds, apart from any clinical improvement, but that such use of iodine cannot produce a complete and lasting involution; operation is necessary to complete and stabilise the improvement.

**PATHOLOGICAL TYPES OF GOITRE.**

**Colloid Goitre:** This is a diffuse enlargement, the vesicles being lined by a low cuboidal epithelium and distended with colloid. The general appearance is one of inactivity.
Secondary changes.

(a) Arterio-sclerosis of the vessels within the thyroid gland is often prominent and one wonders whether it may not have something to do with the change of diffuse to nodular goitre.

(b) Fibrous changes short of nodule formation may accompany an arteriosclerotic change.

(c) Haemorrhages are usually slight though numerous (vide fig. 5).

(d) Hyaline or mucoid degeneration may occur.

(e) Cyst formation. Small cysts are usually the result of a confluence of several broken down vesicles; cysts of more than a few millimetres diameter are more likely to be due to a mucoid degeneration in the interstitial tissue.

(f) Calcification occasionally occurs.

(g) Regeneration of new alveoli is often found (vide fig. 6). It is apparently compensatory to the degeneration and inactivity of the old acini.

Adenomatous goitre. The gland is the site of a multiple nodular enlargement; the nodules being encapsulated and separated from one another by fibrous tissue. Its development from a diffuse colloid goitre has already been discussed (vid. sup.).

The same secondary changes as were mentioned under 'colloid goitre' may be found in this nodular goitre; they are particularly common in this type of goitre. Graves' disease (Exophthalmic goitre). The thyroid gland is moderately enlarged, firm and of a meaty appearance when cut. In the specimen described the gland
had rather a translucent look, the result of the pre-
operative use of iodine. The rich arterial supply of
this form of goitre extends also to the surrounding
tissues and the gland is often adherent to its outer-
capsule.

Microscopically the typical gland shows an increase
in the acinar spaces and a great infolding of the pro-
liferated epithelium. The colloid is scanty, thin and
watery and stains very faintly. The change in the colloid
is most marked where it comes into proximity with the
epithelium and this appears to indicate that the colloid,
lying normally in the vesicle as an immersgency ration,
is being rapidly absorbed through the epithelial cells.
Collections of lymphocytes resembling lymph nodes are
usually evident. They may simply be part of the general
lymphoid overgrowth associated with this disease (vid.
case 4) but Boyd considers that they have become much
more numerous since the institution of iodine therapy.
It is when evidence of involution is present that they
make their appearance.

Is Graves' disease a simple hyperthyroidism or a
dysthyroidism or both?

The histological appearance of the glandular
epithelium is conformable with the theory of a hyper-
secretion but the peculiar properties of the colloid -
its fluidity and basophilic reaction — suggest that it is not altogether normal. This histological change, however, may well be explained by a slight alteration in the proportions of the albuminoid substances and other constituents which themselves may be merely the vehicle or excipient for the really active principle. Some of the clinical signs, particularly the exophthalmos, cannot be produced by administration of large doses of thyroxin and this also points to some degree of dysthyroidism being present in Graves' disease.

Pearse and Williamson believe that their 'lymphogenic' secretion, after it leaves the follicles, is in itself normally toxic and has to be detoxicated by the endothelium of the thyro-thymic lymph system, thereby, giving rise to a local lymphocytosis; the change in fact, being similar to that occurring in lymph glands behind a septic focus. They argue, and give good experimental evidence, that in Graves' disease the symptoms suggesting a dysthyroidism arise out of a failure of the lymphatic endothelium of the thyroid and thymus to effect the natural detoxication of the lymphogenic secretion. In almost every case of Graves' disease the thymus is enlarged, but it does not contain an excess of lymphocytes, and this strange association is very suggestive of some such mechanism. According to their studies it is essential for the balanced
action of the thyroid that colloid should circulate through the parenchyma. They conclude, therefore, that the relative absence of the normal colloid reserve would inhibit the proper production of secretion and so they regard the disturbance from a pathological point of view as a dysthyroidism. Foetal Adenoma is usually single and confined to one lobe. The tumour, according to Ewing, arises from an embryonal rest by Centrifugal growth. As it enlarges the stroma around it becomes condensed forming a capsule; on account of its centrifugal growth the older cells occupy the centre and may form vesicles while the peripheral cells tend to remain an undifferentiated mass. The circulation in the adenoma is of the lacunar type, the vessels being merely wide blood-spaces lined by a single layer of endothelium and this explains the haemorrhages which are so often found.

In the section (case 5) examined, the cells were for the most part undifferentiated and arranged in solid lobules. Tumours of this type cannot secrete to any appreciable extent but yet the patient showed definite though slight signs of toxicity, which seemed to coincide with the increase in size of the tumour during the past three years. Possibly some areas of the tumour made up of a more adult and hyperactive structure, were overlooked and may have been the cause of her symptoms. On the other hand, the
peculiar columnar arrangement of the epithelial cells round many of the blood sinuses would seem to indicate that they had taken on the function of secretion, the secretion passing directly through the endothelium into the blood stream (vide fig. 10). Such a secretion according to Williamson would not be detoxicated and would therefore constitute a dysthyroidism and, though slight in amount, might conceivably give rise to the patient's symptoms, which differed in some respects from a true hyper-thyroidism.

**Papillary adenocarcinoma.** Carcinoma of the thyroid commands an interest over other types of malignant tumours, owing to the special features of its metastases.

The carcinomas may be divided into:--

(1) Scirrhous - rare.
(2) Papilliferous adeno-carcinoma.
(3) Malignant adenoma.

The disadvantage of this classification is that the papilliferous adenocarcinoma and malignant adenoma tend to overlap as reference to the pathology of the primary tumour in case 6 will show.

In the papillary adeno-carcinoma mere microscopic examination of the cell structure does not prove malignancy. In none of the cells could I find certain evidence of mitosis, and a papilliferous structure is not confined to this type of tumour alone, similar small papillae being
seen in the sections of nodular goitre (case 2) and Graves' disease (case 4). Apparently stimulation tends to elicit this type of response because of the inherent properties of the thyroid epithelium. It is obvious then that the usual evidences of malignancy do not hold in thyroid neoplasms. What then can we regard as a definite pathological sign of malignancy? The one absolute point is the marked tendency to invade the blood vessels (vide fig. 11). Invasion of the capsule alone is not sufficient to warrant a diagnosis of malignant neoplasia for islets may be found within the fibrous capsule of many a normal gland. When, however, the cells are an obvious extension from the primary tumour and not aberrant portions of thyroid tissue it is valuable evidence of the nature of the primary growth.

As has been mentioned before, this type of carcinoma rarely if ever arises in a normal gland, though Ewing admits it possibility. Previously the gland, although benign, may show extremely diverse types of structure and the alteration from benign to malignant character may occur with barely any architectural or cytological change. Epithelial activity is present long before the pathologist would pronounce a definite opinion that malignant transformation had occurred. Metastases. This feature is of peculiar interest. The malignant primary tumour does not disseminate to the lymph nodes until it has invaded the thyroid capsule; but before
this occurs it is capable of invading the veins and thus setting up distant metastases while the primary growth is yet small. As the rate of growth of papillary adenocarcinoma is slow, the secondary tumours may attain a considerable size before the primary site is suspected.

**Character of metastatic thyroid tissue.** It has lost the papillary structure of the primary growth and is of a more adult type and in many cases seems to be benign (vide case 6). The sections examined showed no tendency to invade the blood vessels and in the section of the metastasis in the rib the capsule was absolutely devoid of invading epithelial cells.

The most remarkable feature of the secondaries is that they function as normal thyroid tissue. In case 6, after total thyroidectomy, the patient was definitely undersupplied with thyroid secretion and required to take thyroid extract by mouth; but as the metastases grew, symptoms of hyperthyroidism began to appear although she had now ceased the oral administration of thyroid tablets. A further interesting feature of this case was that the first metastasis in the occipital bone seemed to enlarge and cause more discomfort whenever she felt cold; apparently the metastasis responded to the physiological stimulus of a fall in temperature in the same way as would a
normal thyroid gland.

Site of metastases. The metastases are commonest in the lungs and the bones. As no evidence of lung metastases could be found in case 6 only the second site will be considered.

Ewing holds that cancer of the thyroid is only second to that of the breast and prostate in the production of skeletal secondaries. The site incidence in order of frequency is

(1) skull bones,
(2) vertebrae,
(3) ribs,
(4) humerus,
(5) femur,
(6) pelvis,
(7) clavicle.

The non-malignant nature of many of these metastases may in some cases be explained by the growth of thyroid rests, as in the origin of intra-thyroid foetal adenoma, but it is a fact that the bones least likely to contain aberrant thyroid tissue are the ones most commonly the site of 'metastases', and even the clavicle, in which metastases may occasionally occur, is developed in a plane altogether anterior to that of the thyroid 'Anlage'.

The metastases generally first appear close to the cranial sutures or near the epiphyses of the long bones and the great vascularity which thyroid tissue demands causes a rarefaction and absorption of the adjacent compact
bone. Why metastases in bone should be so common is not known but it is interesting to note that Kocher, many years ago, obtained his best results by thyroid implantations into the bone marrow.

From the above characteristics, thyroid metastases must therefore be regarded as 'organomata' and so the surgeon is prepared to go to greater lengths in his procedure so long as cellular metastases are not a feature of the neoplasm.
CLINICAL CONSIDERATIONS.

Examination of the patient.

The symptomatology of the varieties of goitre is best obtained from the report on the individual cases.

Physical Examination. General. The general appearance of the patient is first observed, whether calm or nervous, plump or emaciated; exophthalmos if present is usually obvious. The hair may be dry and thin and the skin coarse as in the myxoedematous type of individual; or the patient may be flushed and overheated and with a moist skin where hyperthyroidism is present.

Local Inspection. An investigation of the neck will usually reveal a swelling in the region of the thyroid gland. It may be bilateral or unilateral, diffuse or nodular. The enlarged gland may pulsate and its vertical movement on swallowing gives some indication of its mobility as well as further establishing the site of the swelling. Venous and arterial pulsation may be evident at the root of the neck in hyperthyroid patients and where a retro-sternal goitre is present the subcutaneous veins in that region may be prominent. Some idea of the size and limits of the swelling should be noted, for some goitres, especially the soft colloid type, are more easily seen than felt.
Palpation. The degree of warmth and moistness of the skin is first observed and then, standing behind the patient who should if possible be sitting on a chair, the local swelling is palpated, verifying its association with the thyroid gland. The presence of pulsation in the gland and any systolic thrill is felt for. To investigate the size and extent of the enlargement the patient's head must hang forwards to relax the pre-tracheal and sterno-mastoid muscles. An attempt should be made to delimit the poles of the gland, particularly the lower pole on the left side: if the latter cannot be felt and appears to extend behind the clavicle and sternum, the patient may be asked to swallow when the gland will rise up; if part of the gland is retro-sternal, it may then be possible to feel the lower pole before it dips down again.

The consistence of the swelling is next observed - Is it soft or fluctuating, or is it of firm or of stony hard consistence; does palpation cause the patient any pain? Next attempt to find whether the thyroid swelling seems adherent to its surrounding structure and whether attempts to move it cause pain or coughing.

The other parts of the neck may then be examined for enlargement of lymph glands and the superior mediastinal area may be percussed for evidence of increased dullness due to thymus hypertrophy. Where thyrotoxicosis is
present or suspected an endeavour may be made to elicit
the various eye signs (vid. case 4) but they are not of
much value for they are only present when exophthalmos is
already obvious. Examine the pulse; its rate is a good
index of the metabolic activity of the body but due allowance
must be made for simple nervousness.

Finally a routine examination of the other systems
is made.

**Summary.** The chief points to be determined from the ex-
amination are:-

1. Is the thyroid enlarged or not?
2. What is the character of the enlargement?
3. Is there any hyperthyroidism present?
4. Is there any suspicion of malignancy?

**Special Investigations.**

In spite of a careful clinical examination the examiner
must often remain dubious about certain points; especially
in regard to the presence or absence, or the degree, of
hyperthyroidism. Any excess of thyroid secretion causes
an increase in the basal metabolic rate (B.M.R.), that in-
crease being directly proportional to the excess of thyroid
secretion (Schafer). The B.M.R. is therefore an accurate
index to the degree of activity of the thyroid tissue.

**Estimation of B.M.R.** The usual method of estimating the
B.M.R. in hospital is by the use of the Douglas bag. In
spite of its portable nature, the complete apparatus and
calculations are cumbersome and the first few estimations, though perhaps accurate, are not basal; the patient, particularly the goitrous patient, whose basal metabolic rate it is most desirable to know, is considerably alarmed and excited at the first early morning visits, hence the fallacy; the results returned from the laboratory are invariably much in excess of what one's clinical judgment would lead one to suppose ought to be the correct value. The truth of this statement is evident on reference to the six cases.

Some method which was comparatively accurate and yet easy to carry out and not disturbing to the patient, was obviously required in order to value the benefits of preoperative, operative and subsequent post-operative treatment.

The method adopted was that of measuring each morning at 10 a.m.

(1) the pulse rate (P.R.)
(2) the pulse pressure (P.P.) got by subtracting the diastolic blood pressure (in m.m. mercury) from the systolic blood pressure.

Then by applying these values to the following formula, devised and perfected by J. Marion Read in 1922, the B.M.R. could be obtained.

\[ B.M.R. = 0.75 \times (P.R. + 0.74 \times P.P.) - 72. \]

This formula has been found to give results which are within 10% of the true B.M.R. value and therefore this method was
sufficiently accurate for my purpose, and infinitely more reliable than a single 'Douglas Bag' estimation.

As the patient was surrounded by screens and there had been no bustle in the ward at that hour, the environment was eminently suitable. The patient soon became accustomed to my morning visit and was in no way perturbed by the application of the sphygmomanometer bag to the arm. Even though the conditions were not absolutely basal, they are constant from day to day and so the daily values could be compared.
ANALYSIS OF DAILY B.M.R. CHARTS.

Case 1. (colloid goitre).

As this patient had been suffering from some degree of myxoedema and had been taking thyroid extract, the chart cannot be considered of much value. It shows, however, a post-operative rise in B.M.R. of +12 and a rapid subsequent fall within 4 days of operation to 0. Note the rapid fall in this non-toxic goitre case, in which no very strict post-operative treatment was employed and compare it with the more gradual 'lysis' of the succeeding cases.

Case 2 (toxic adenomatous goitre)

The chart shows a rapid drop in the basal metabolic rate during the first two days in hospital; thereafter a slight gradual fall continued.

Preoperative fall from +45 to +18. The maximum rise following operation was to a level of +45 (a rise of +20) and this occurred within the first 24 hours. After the first day the B.M.R. fell continuously and rapidly throughout the post-operative period until, on discharge, a practically normal level of +6 was registered.

Case 3 (toxic adenomatous goitre).

This chart shows a spectacular fall in B.M.R. from +35 on admittance to +9 on the morning of operation. A marked rise to +40 occurred in the 24 hours succeeding operation but this was followed by a still more dramatic post-operative drop to +2
Case 3  Mrs. A.B.
Toxic Adenomatous Goitre

Case 4  Mr. E.F.
Graves' Disease
on the day of discharge.

Case 4 (Graves' disease).

The first estimation showed the B.M.R. to be +27 (compare the 'Douglas bag' reading, taken a few hours previously, of +79). Under treatment the chart shows a gradual fall to +7.5 at the end of the first week. Thereafter the B.M.R. began to rise, until on the morning of operation, it had reached a value of +53. A post-operative rise to +76 occurred within the first twenty four hours but fortunately this quickly dropped to +30 in the succeeding three days. From then the fall was more gradual but was interrupted on the eleventh day by a temporary rise caused by an anaphylactic serum reaction. 15 days after operation his B.M.R. had touched the normal baseline but the exciting stimulus of his expectation of leaving hospital caused a slight rise again in the last two days.

The rise after the 6th preoperative day was probably due to the iodine having lost its beneficial effect for he had been having Lugol's solution at times before coming into hospital. He should have been operated on on the 6th day when his metabolism had reached its minimum but it was hoped that a further drop would be secured. As a result of the operation's being done when his metabolism had risen again, the twilight sleep and local anaesthesia was not very successful and he had a furious metabolic increase for 18 hours afterwards, during which time he was in a very precarious state.
Case 5. M. NN

Fetal Adenoma

B.M.R.

Pulse Rate

Case 6. M. M.L.

Malignant Goitre

B.M.R.

Pulse Rate
Case 5 (foetal adenoma).

There is little to note in this chart. There was but slight hyperthyroidism present and the case was virtually non-toxic. As in the chart of case 1 (also non-toxic goitre) there is a characteristic slight rise (+10) following operation and a rapid subsequent fall to a B.M.R. level of +3 in the succeeding three days. Further improvement in the metabolic rate was insignificant.

Case 6 (metastases from malignant goitre).

This chart was made at the time of the patient's treatment for the three bone metastases. On admission she had ceased to take thyroid extract by mouth and yet the B.M.R. registered +6 although her thyroid had been completely removed - surely a sufficient proof of the physiological functioning of these metastases. The operation caused a considerable rise in B.M.R. which continued to increase until the end of the second day and was maintained as a 'plateau' for over a week before it gradually fell. This increase in basal metabolic rate after the first 24 hours was probably due to the stimulative effect of the radium emaciations on the tumour cells. Two days after operation the patient was given thyroid extract gr. 5 on alternate days and this probably explains the persistence of the 'plateau' and renders the remainder of the chart of little value.

In each chart I have included the graph of the pulse
rate and it is seen that generally speaking:-

(a) the B.M.R. and pulse rate run a parallel course,
(b) for the higher values, the B.M.R. is not so great as the pulse rate might lead one to expect.

Conclusions.

(1) Single B.M.R. estimations by the Douglas bag method are misleading.
(2) B.M.R. estimations using Read's formula are much simpler to perform and more reliable, especially for comparative purposes.
(3) The pulse rate is a good indicator of the changes in metabolic rate, except when the pulse rate exceeds 100 per minute.
(4) Preoperative treatment with rest and iodine is of great benefit in reducing the B.M.R.
(5) This action of Lugol's iodine solution passes off after the 10th to 14th day of continued use, and the results are therefore better where the patient has not had iodine treatment for some time previous to entering hospital.
(6) The operation in a toxic patient is much more serious, and the method of twilight sleep + local anaesthesia less likely to be successful, when performed when the B.M.R. is high.
(7) The operation if adequate will reduce the B.M.R. to its normal value within 14 days if it is followed by suitable post-operative treatment.

From an enormous stock of data of B.M.R. estimations (both by laboratory methods and by a variety of formulae) obtained from Marion Read, Miss Gale and C.H. Gale have, on mathematical principles, evolved a new formula for bedside basal metabolic rate estimation.

\[
\text{B.M.R.} = \text{P.R.} + \text{P.P.} - 111.
\]
Its mathematical source would seem to give it an advantage in accuracy over Read's formula and I have tested it in all my estimations and found the two formulae to correspond closely in their results.

**ADRENALIN SENSITISATION TEST FOR HYPERTHYROIDISM.**

This test was first used by Goetsch to differentiate hyperthyroidism from early pulmonary tuberculosis with negative physical and X-ray findings.

5 minums of adrenalin chloride solution 1/1000 are injected subcutaneously into the arm. The patient should be at rest and observations at 5 minute intervals are made of:-

1) blood pressure.
2) pulse rate.
3) respiration rate.
4) nervousness.
5) tremor of fingers.
6) size of pupils.
7) pallor or flushing of skin,

over a period of 30 minutes. At the same time the patient's subjective symptoms are asked.

The test is unnecessary and unsafe where the B.M.R. is obviously high and patients with a blood pressure over 160 systolic are not subjected to the test.

I performed the test in case 1 and in case 6 where there was some doubt about the presence or absence of hyperthyroidism and in each case, as a control, I made a similar injection into my own arm.
Case 1 (colloid goitre).

The results, save for a brief rise of 4 per minute in pulse rate, were negative.

Case 6 (thyroid metastases). Shortly after the injection the patient complained that she was "all nervous and hot". Prior to the test the blood pressure was 122/74 and the pulse rate 74.

At end of first 5 minutes - B.P. 134/84 : P.R. 79.
At end of first 10 minutes - B.P. 146/90 : P.R. 82.

In the succeeding intervals the blood pressure and pulse rate slowly fell to their normal limits. There was an increase of 2 per minute in respiration rate but the other signs tabulated were not observed.

The test, therefore, could be regarded as positive.

Conclusion. Goetsch's test is of value in distinguishing borderline cases of hyperthyroidism.

KOTTMANN'S TEST FOR HYPERTHYROIDISM.

This is a photographic test of the patient's blood serum and is dependent on the fact that the serum of a hyperthyroid case has a greater protective colloidal action than normal serum and renders the silver iodide suspension with which it is mixed in finer emulsion and therefore less sensitive to light.

The test is more accurate than Goetsch's test but the technique is too complicated to permit of its use in general surgical ward work.
**X-RAY EXAMINATION.**

Where an intra-thoracic goitre is suspected X-ray examination will reveal a shadow in the superior mediastinum and show a displacement of the trachea to the opposite side. The distinct angle between the aortic shadow and that of an intra-thoracic goitre changes during deglutition and deep inspiration and this distinguishes it from aneurysm.

X-ray examination is also of great value in the investigation of the sites of metastases in thyroid carcinoma (vide case 6).

**DIAGNOSIS** is based on the history, symptomsatology and clinical examination. The presence of hyperthyroidism may be evident or may require special investigations.

The age of the patient may give some presumptive evidence of the type of goitre present. After the age of 40 malignant disease must always be kept in mind: malignancy is so insidious in its onset that operation is warranted on no stronger grounds than suspicion.

**DIFFERENTIAL DIAGNOSIS.**

This covers so wide a field that it is best considered under the following headings:-

A. **Is the enlargement a thyroid or a non-thyroid swelling?**

   In this, diagnosis has to be made from:-

   1. enlarged lymphatic glands.
   2. the various cervical cysts,
(3) enlarged thymus.

B. What is the type of goitre present?
The diagnosis of simple colloid, toxic adenoma, malignant goitre and Graves' disease is sufficiently clearly brought out in my series of cases. A small point, which was investigated in the diagnosis of Graves' disease, is the slightly greater lymphocytosis in that condition as compared with the other types of goitre.

In addition it is necessary to exclude:

(1) simple hyperplasia - it is usually associated with puberty, pregnancy or the menopause and may be physiological or have passed within the bounds of pathology.

(2) inflammatory goitre - (a) Acute suppurative inflammation is rare as also is tuberculosis of the thyroid.

(b) Chronic thyroiditis (Riedel's thyroiditis). It has a typical firm woody feeling and beginning in one part of the gland soon involves the whole gland.

(c) Syphilis - the thyroid may be enlarged and firm and many of the symptoms and signs of hyperthyroidism may be present. A Wassermann test may be of value in such a case.

(3) post-cricoid carcinoma of the cervical oesophagus may invade the thyroid gland and thus simulate malignant
disease of the thyroid. Diagnosis is made by the use of a laryngoscope or oesophagoscope.

C. **Conditions simulating hyperthyroidism** require to be excluded. They are purely medical conditions and need only be mentioned.

(1) Neurasthenia.

(2) Early pulmonary tuberculosis - Goetsch's test is often of value (v. sup.).

(3) Paroxysmal tachycardia.

(4) Neurocirculatory asthenia ("irritable heart").

(5) Simple autonomic imbalance (Easson).

D. **Swellings simulating metastasis in skull bones** (vide case 6).

(1) Sarcoma - periosteal sarcoma is the commonest type of primary tumour of the skull but the pulsatile telangiectatic sarcoma is most likely to be mistaken for a thyroid metastasis.

(2) Aneurysm - the resemblance may be very striking (v. case 6).

(3) Ivory osteoma.

(4) Cerebral meningioma involving the skull by direct extension.

(5) Inflammatory hyperostosis (e.g. syphilitic).

(6) Dermoid cyst.

(7) Lipoma.

(8) Meningocele and the allied conditions.
99

(9) Haematoma.

(10) Subpericranial abscess.

The error in the early diagnosis of case 6 emphasises Trotter's warning that "a diagnosis of primary malignant disease of the skull should never be made until the presence of malignant disease elsewhere has been excluded. The examination should be directed especially to the thyroid, kidney, breast and prostate".
TREATMENT.

Prophylaxis is the ideal in all diseases but until more is known of the aetiology of goitre little can be done in this respect. In endemic regions, however, it has been shown that administration of iodine can prevent the onset of parenchymatous and colloid goitre and coincident with this the incidence of other forms of goitre is also reduced.

Medical treatment, ray therapy or surgical treatment?

Types suitable for medical treatment. It is desirable that certain goitres should, in the first place at any rate, be treated by purely medical means, for a cure may be thus affected. These types are:

1. Parenchymatous goitre.
2. Colloid goitre.

Types suitable for X-ray or radium therapy.

1. Malignant goitre. If possible the primary tumour should be excised by performing a total thyroidectomy but where the condition is very extensive or the patient an unsuitable subject for operation, radium is the alternative. In the case of the bone metastases complete excision is often impracticable on account of the extreme vascularity of the site, as was amply demonstrated in case 6. Apparently malignant thyroid neoplasms show greater radio-sensitiveness than do other malignant tumours, in spite of the relatively slow rate of
growth of the former. The usual disadvantage in using radium for metastases in bone is that radionecrosis of the bone frequently occurs. In thyroid metastases, however, the peculiar vascular nature of the tumour extends into the surrounding bone and appears to render it more immune than normally to the necrosive action of the radium emanations. After a latent period of several days, during which no histological change can be found, the radium causes a coagulative necrosis with disintegration of the protoplasm and fragmentation of the chromatin of the tumour cells. The success of this treatment can be seen on reference to case 6.

(2) Graves' disease. Both X-ray and radium treatment have been tried but with no great success; its chief disadvantage is that if unsuccessful, any subsequent operation which may be necessary is rendered more difficult by adhesion formation. On the continent, however, radium treatment has recently given very good results in many cases. The best results are obtained by the use of a moderate dosage (3000 Mgm. hrs.). No previous iodine treatment should have been given, or, if given it should be continued during the radium treatment.

(3) Riedel's thyroiditis is also included under this form of treatment.

"Surgical goitres".

(1) Benign non-toxic adenomata should all be removed for:-

(a) in the ordinary course of events at least 25% will become toxic, at an age, moreover, when the
cardiovascular system is specially liable to damage;

(b) the growth will increase in size and in time may cause pressure symptoms on the trachea (vide case 3);

(c) haemorrhage may occur at any time within the adenoma and cause serious respiratory embarrassment and even sudden death.

(d) the growth may become malignant.

(2) Malignant goitre. If possible removal of the whole primary tumour by total thyroidectomy should be done. Occasionally a metastasis (e.g. one growing from rib as in case 6) may be excised. Cure rather than diagnosis should be the aim of the surgeon and so the operation must be undertaken early without waiting for definite clinical evidence of malignancy.

(3) Toxic adenomatous (nodular) goitres.

(4) Graves' disease. A preliminary attempt at cure by medical means should almost always be tried first, remembering however, that the results of surgical treatment are best when performed at a comparatively early stage of the disease.

(5) Colloid goitre. This is only operated upon for aesthetic reasons or where the patient complains of pressure symptoms.

Forms of surgical treatment.

(1) Ligation of blood vessels.

(2) Enucleation of local tumour.

(3) Partial thyroidectomy.

(4) Subtotal thyroidectomy.
(5) Total thyroidectomy.

Ligation of vessels. The only form of goitre in which ligation may be beneficial is in Graves' disease where the superior thyroid vessels may be tied. Apparently in this condition the 'stimuli' are partly in the form of nerve impulses transmitted along the sympathetic nerves, the latter running almost entirely along with the superior thyroid arteries. The benefit, therefore, is not due to the ligation of the vessels but to the associated interruption in the continuity of the sympathetic nerves.

Enucleation. This is only possible in encapsulated adenomata which are large and few in number.

Partial Thyroidectomy. It should only be done where removal of one or several adenomata confined to one lobe is desired (c.f. case 5).

Subtotal Thyroidectomy. This is the operation done in most cases of toxic goitre. In order that the operation should be adequate at least ⅛ of the gland should be removed, only a small posterior shell of thyroid tissue being left. This ensures that,

(a) the parathyroids shall remain unharmed;
(b) the recurrent nerves shall not be damaged;
(c) the posterior part and upper pole of the gland is usually the healthiest, and so further enlargement is not likely to occur.
Total thyroidectomy. This operation is confined to malignant goitres where it is essential that no portion of malignant thyroid tissue shall remain (vide case 6).

Conclusions. (1) Surgical excision is the method of choice in malignant thyroid, toxic adenomatous thyroid and benign adenoma of thyroid.

(2) Surgical treatment is indicated in a case of large colloid goitre where the disfigurement is great and there are pressure symptoms; also in Graves' disease where preliminary medical treatment has failed.

(3) Radium is as yet confined to the treatment of metastases or of an inoperable primary malignant growth. Promising results, however, are being obtained elsewhere by the use of radium in cases of Graves' disease.

PREOPERATIVE TREATMENT.

As the basal metabolic rate charts showed, this is a most important item in a toxic patient. The various points are fully given in case 2 but I may summarise and emphasise the important ones here.

(1) Experience has demonstrated that it is desirable to have enlarged tonsils or other septic foci in the mouth and throat removed as a preliminary. It is possible that the thyro-thymic lymph space may still retain some of its connections with the bucco-pharyngeal lymphatics as is apparent in fish.
(2) Absolute rest, both mental and physical; to obtain this, screens are placed around the bed but if they are resented, they should not be forced.

(3) Food - give ample diet, mainly vegetarian, for protein and fat stimulate metabolism: encourage the patient to drink plenty of water.

(4) Administer Lugol's iodine solution (5% iodine in 10% aqueous solution of potassium iodide). Begin with 1 minum t.i.d. and increase the dose by 1 minum t.i.d. each day until a total of 10 m. t.i.d. is being given. If the operation has to be postponed, the dose is reduced a little, for after a fortnight it begins to lose its beneficial effect.

(5) Luminal. If the patient is restless and sleepless 1 gr. luminal is given night and morning. It is remarkable, however, how little 'dope' is required if the patient is reassured and quietened by the ward sister or nurse.

(6) Sodium bromide may sometimes be required for an excited patient.

(7) Digitalis is not often required except when the pulse rate is extremely rapid or shows some arrhythmia.

ANAESTHETIC.

The anaesthesia is obtained by the use of local infiltration and injection around the superficial and deep cervical nerves with ½% kerocain. No adrenalin is added for hyperthyroid patients are peculiarly sensitive to adrenalin. This is com-
bined with scopolamine - morphine narcosis.
(for details see case 1).

The reasons for employing such anaesthesia in place of its alternative, nitrous oxide and oxygen, are:-

(1) the function of the recurrent nerves is under control at any moment of the operation and so the patient gives warning of too close approach of the electric cautery;

(2) there is less risk of sepsis for no anaesthetist is required to be constantly bending over the patient's head;

(3) goitre screens can also be dispensed with and the operator has thus more room in which to work:

(4) the risk of bronchitis and post-operative pneumonia is reduced somewhat;

(5) it does away almost entirely with post-operative vomiting which is particularly distressing to the goitre patient, and this reduces the danger of post-operative haemorrhage etc.;

(6) local anaesthetic is much cheaper than nitrous oxide and oxygen.

Disadvantages of local anaesthesia combined with scopolamine-
morphine narcosis.

(1) The patient may wake up and move during the operation—usually, however, she falls asleep again within a minute but occasionally a whiff of ether may be required.
(2) With scopolamine-morphine narcosis there is a peripheral vaso-dilatation and so the bleeding from the smaller vessels is more difficult to control. The use of the electric cautery in the operation, however, obviates this difficulty.

(3) A scopolamine fit may occur (cf. case 2). It may interrupt the operation for a minute or so but it is not serious.

(4) Scopolamine narcosis is followed by a reactionary phase when the patient is hypersensitive and restless. It can be controlled, however, by the administration of heroin.

Conclusion. Scopolamine-morphine narcosis combined with local anaesthesia has many advantages over the use of general anaesthesia and has but few minor disadvantages.

Position and preparation of patient.

The patient is brought along to the theatre immediately after the second injection of scopolamine and morphine has been given. She is placed on the operating table and falls asleep there. A small sand-pillow is placed high up between the patient's shoulder blades, the hair is tucked under a rubber cap and the head-rest lowered so that the thyroid area is rendered more prominent and accessible. The operation area is then swabbed with tincture of iodine and sterile cloths adjusted, leaving only the thyroid area exposed. All preparations having thus been made the patient is left for quarter
of an hour before the operation is begun. Thus it is ensured that the patient shall be in the desired state of tranquillity and sleep when the operation is due to commence.

OPERATION.

All the details are described under case 1. The main essentials in operating are:

(1) be as gentle as possible, especially in handling the thyroid gland;

(2) work as rapidly as is consistent with accuracy and care, for the post-operative reaction in a toxic patient is always considerable;

(3) catch and ligate all bleeding points.

The use of an electric cauterity greatly facilitates the separation of the gland by occluding all the capillary vessels and so reducing haemorrhage to a minimum; in addition the heat will stimulate the recurrent nerve whenever the operator approaches dangerously close and the patient will at once respond and so give warning. The danger of damaging or dividing the recurrent nerve is thus obviated.

The main trunk of the inferior thyroid artery is not ligated because that vessel supplies the parathyroids on either side and ligation would be likely to cause tetany.

The connective tissue covering the trachea and larynx is left intact for if the sensory nerves there are disturbed, the impulses are registered as coming from the inner surface
of the trachea and so considerable post-operative coughing and production of mucus will result. When the isthmus is being removed a small portion covering the trachea may be left, for thus the normal blood supply of that part of the trachea is guaranteed and the risk of disturbing the mucous membrane avoided.

POSTOPERATIVE TREATMENT.

This again has been fully discussed in case 2 and so I need only stress the main points here.

(1) Rest. As the patient is at first very restless, sleep and quietness is obtained by the repeated use of heroin 1/12 to 1/6 gr.

(2) Nourishment. For the first 48 hours, 8 oz. rectal salines containing 6% glucose are given four hourly. If even sips of water are permitted within the first 24 hours, the pain and irritation from swallowing causes vomiting and the retching is liable to lead to the slipping of a ligature and haemorrhage. Sips of warm water are first given on the second morning and thereafter the diet is gradually increased and the patient encouraged to drink large quantities of bland fluids. It is rarely necessary to give subcutaneous salines after operation.

(3) Lugol's iodine. It is included in the first rectal saline, the dose varying up to 30 minums, depending on the
pulse rate at the time. After the second day Lugol's solution is given by mouth beginning with a small dose (2m. t.i.d.) and mounting up as in the preoperative treatment. In the last few days before leaving hospital, the dosage of Lugol's solution is again slowly reduced and normally no further iodine therapy is found to be necessary after discharge.

On leaving the ward the patient is given a little advice to take life as quietly as possible, to be moderate in all things and regular in habits.

POSTOPERATIVE COMPLICATIONS.

(1) Haemorrhage. It may be reactionary and result from neglect to ligature all the divided vessels; it may be due to the slipping of a ligature. Catgut ligatures soften in fluid and may slip and it is for this reason that fine linen thread is employed. Severe haemorrhage, when it occurs, almost always comes from the pedicle of the superior thyroid artery.

Treatment. If merely oozing haemostatic serum (2 ccs.) may suffice. If considerable, the patient must be returned to the operating theatre immediately, the wound opened up and the bleeding vessel sought for and ligatured.

(2) Marked irritation and excitement. This is treated by the use of heroin and luminal. If this is not successful, a solution of paraldehyde in gum acacia may be given per rectum.
(3) Cough and irritation in trachea. The use of a steam tent, adding a teaspoonful of 2% menthol in alcohol to the boiling water, gives most relief.

(4) Excessive thyroid secretion. Much of this can be prevented by avoiding rough manipulation of the gland during the operation. The treatment lies in the use of Lugol's iodine (v.s.).

(5) Tetany. Mere bruising of the parathyroids may cause this, apart from removal. The symptoms in order of appearance are:

(a) circumoral pallor.
(b) a tight glossy appearance of the skin of the forehead, nose and face.
(c) a drawing sensation about the mouth and nose.
(d) a tingling sensation in fingers and hands.
(e) Trousseau’s sign - i.e. typical spasm of hand on compressing brachial artery for 2-3 minutes.
(f) Chvostek's sign - i.e. sudden momentary spasm of face muscles on tapping over the facial nerve.
(g) Stridor.
(h) Carpo-pedal spasms.

The treatment of tetany is to give parathyroid extract gr. 1/5th t.i.d. and calcium lactate gr. 20 every four hours.

(6) Hypothyroidism. This is evidenced first by loss of interest and lassitude. The treatment is the oral administration of thyroid extract in appropriate doses. In course
of time the remaining gland substance tends to enlarge and the signs of deficiency permanently disappear.

(7) **Heart failure.** Arythmia is more ominous than simple tachycardia. Digitalis is the best available drug.

(8) **Hoarseness.** The importance of this is that it may indicate injury to one of the recurrent laryngeal nerves. Hoarseness was very marked in one of my cases (case 4) but the patient could speak quite well immediately after the operation, so that the loss of voice which was present on the second day was probably the result of oedema in the operation area, causing pressure on the recurrent nerves.

(9) Various other complications such as infection, attachment of scar to trachea at point of drain opening, etc. need only be mentioned.

**PROGNOSIS.**

The prognosis as regards life is excellent once the dangerous early post-operative period has been passed. The chance of recurrence in the colloid and the two toxic adenomatous cases is slight. The case of Graves' disease, however, still retains his nervous constitution and should the remaining gland substance at a later date hypertrophy, it is possible that he may have a recurrence. On the whole the results of such an operation are very satisfactory when performed at an early stage of the disease as in this case.
The average case of Graves' disease does not, even under the most favourable conditions, achieve a normal physiological status in less than a year from the time of operation.

As regards the last patient (case 6) the outlook is different. The metastases seem to be more numerous than was originally supposed but although the patient is now 65, it would be wrong to regard her as an incurable. Treatment of clinically evident malignant disease of the thyroid, however, offers little more hope of permanent cure than does the operative treatment of clinically evident malignant disease elsewhere. From the pathological point of view, which leaves out the time element, we find that the papillomatous type is least malignant and from clinical statistics Herbst gives 33% of five year 'cures' in that same type of neoplasm.
CONCLUSIONS.

(1) That the main factors in determining the type of goitre and the general clinical condition are:-

(a) stimuli,
(b) state of thyroid gland,
(c) state of body tissues.

(2) That the operation on a simple colloid goitre is a relatively safe procedure but is only justifiable where pressure symptoms have arisen or for aesthetic reasons.

(3) That for toxic adenomatous goitre, foetal adenoma, and early Graves' disease, surgical treatment can be adequate and curative.

(4) That for malignant disease, removal of the primary growth by total thyroidectomy and treatment of the bone metastases by radium, is the method of choice.

(5) That B.M.R. estimations are a yard-stick with which to estimate the intensity of the disease at any moment.

(6) That Goetsch's test is of value in the diagnosis of borderline cases of hyperthyroidism.

(7) That the safety of the operation is dependent largely on adequate preoperative treatment and is inversely proportional to the B.M.R. on the day of operation (other things being equal).

(8) That the post-operative treatment, particularly for the first few days, is an important adjunct to the operation itself.
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