CALEB HILLIER PARRY, M.D., 1756—1822
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Frontispiece

JOLL'S DISEASES OF THE THYROID GLAND

BY

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PREFACE TO THE SECOND EDITION

FOR some years before his untimely death in 1945, Mr. Cecil Joll envisaged the production of this second edition. It was proposed that we should revise and rewrite the book jointly. Because of the war this was never possible and I must accept full responsibility for the subject-matter included in the new edition, apart from that in the chapters written by Drs. N. F. Maclagan, J. C. McClintock, S. Rowbotham, and G. Crile, Jnr. I am much indebted to them for their valuable contributions.

The section on Struma Lymphomatosa (Chapter XXI) was written by the late Mr. C. A. Joll and published by him in the *British Journal of Surgery* in 1939. It is still one of the standard papers on the subject and has been included in the text with but little modification. We are grateful to the editors of the *British Journal of Surgery* for permission to reproduce it here.

It will be noted that the mode of presentation of thyroid diseases and general scope of the book have been preserved as in the first edition. Remarkable advances in our knowledge of the pathology and treatment of goitre have occurred in the past twenty years. Perhaps the most spectacular are those resulting from the exploitation of radioactive iodine as an investigative tool; but hardly less important are those accruing from the use of the anti-thyroid drugs. Indeed it is a source of wonder and no small satisfaction how clearly understanding of practically all forms of goitre has widened.

Thanks chiefly to radioactive iodine, growth of thyroid knowledge continues apace at the present day. Any large book such as this can only report the position at one instant of this growth.

Much of the new clinical material included in this second edition was taken directly from my Jacksonian Prize Essay, " The Pathology and Treatment of Thyrotoxicosis ". I am grateful to the Council of the Royal College of Surgeons for permission to do this. I have also drawn freely on case records and experience gained while working as Clinical Research Associate in the London County Council Thyroid Clinic. My grateful thanks are due to all members of the medical and lay staff of the clinic for their help and co-operation, particularly to Dr. J. Piercy and Miss Dean. I am also grateful to Sir Ernest Rock Carling, Consulting Surgeon to the Westminster Hospital, London, for his constant help and guidance with clinical studies of goitrous patients. Much of the clinical research incorporated in this new edition was done with the aid of grants from the Medical

Research Council. I am grateful to many authors and publishers for permission to reproduce tables and illustrations. The source of such borrowed data is acknowledged in each case, the author's name being noted in the caption (the original paper concerned will be found in the list of references at the end of the corresponding chapter). I am also grateful to the library staff of the Royal Society of Medicine for much help with access to reading matter. Finally it is a pleasure to acknowledge the ready and able help given during the closing stages of this edition's preparation by Miss D. M. Drake, Secretary of the Unit of Clinical Investigation at the Royal North Shore Hospital of Sydney.

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135 Macquarie Street,
Sydney, Australia.
November, 1950.

CHAPTER I

HISTO-PHYSIOLOGY OF THE THYROID GLAND

The Thyroid Follicle — The Endogenous Iodine Cycle — Iodide Uptake — Hormone Synthesis — The Thyroglobulin Compartment — The Definitive Secretion of the Follicle — Radio-iodine Uptake and Clearance as Indicators of Thyroid Function — Regulation of Thyroid Secretion — Pituitary Thyrotropic Hormone in Health and Disease —Thyrotropic Hormone in the Blood—Iodine Absorption and Excretion—The Role of the Liver in the Endogenous Iodine Cycle—The *modus operandi* of the Thyroid Hormone—Dosage and Activity of Thyroxine—Thyroid Hormone and Tissue Oxidations.

Iodine, present in the external environment in the pelagic, cellular stage of animal evolution, is also essential for the proper maintenance of tissue activity in man. The function of the thyroid gland is to trap and concentrate iodine, harness it in organic combination, and then to secrete it into the blood in the form required by the tissues. The gland thus governs the endogenous iodine cycle and variations in its activity profoundly influence tissue metabolism.

The Thyroid Follicle

The thyroid is unique in that it has the faculty of storing a provisional secretion outside its cells; hence it can store greater quantities than can other glands. It is also remarkable in that, when it is stimulated, it can probably call on a two-way method of secretion, viz., directly from the basal cytoplasm into the adjacent blood capillaries, and indirectly into the follicle and back by transcellular secretion to the capillary blood. It cannot be over-emphasized that the thyroid follicle is a dynamic unit, subject to a wide range of physiological influences. In ordinary histological sections, we catch this changing pattern at only one instant in its life history.

Thomas (1934) in a valuable monograph, expounds a concept of thyroid histology (Fig. 2) which helps to explain many of the appearances in normal and abnormal glands. The height of the epithelial cells indicates their degree of activity. The flat endothelioid cells secrete colloid only very slowly into the follicle. Tall, cylindrical cells mobilize the stored hormone and excrete it into the blood stream. Such tall cells occur in segments (excretory segments) of the follicle wall and their appearance indicates a phase of considerable activity (Figs. 3 and 4). The original follicle (macrofollicle) tends to collapse as colloid is lost; then microfollicles appear beneath and round the excretory segment.

If as the result of severe physiological or pathological demands, intense resorption of colloid occurs, the macrofollicle may collapse and fragment more or less completely. The whole field is then occupied by microfollicles. If another wave of stimulation sweeps over the complex, the microfollicles become further reduced in size and progressively greater numbers of solid clumps of cells are seen.

Usually, however, after a period of excretory activity the complex enters a phase of intra-follicular secretion. Colloid re-accumulates in the follicles; they fuse successively to re-form the macrofollicle.

The papilliferous formations of the thyrotoxic gland may be regarded as a further development of Thomas excretory segments. His microfollicles, with their cuboidal epithelium, correspond to the microfollicular type of

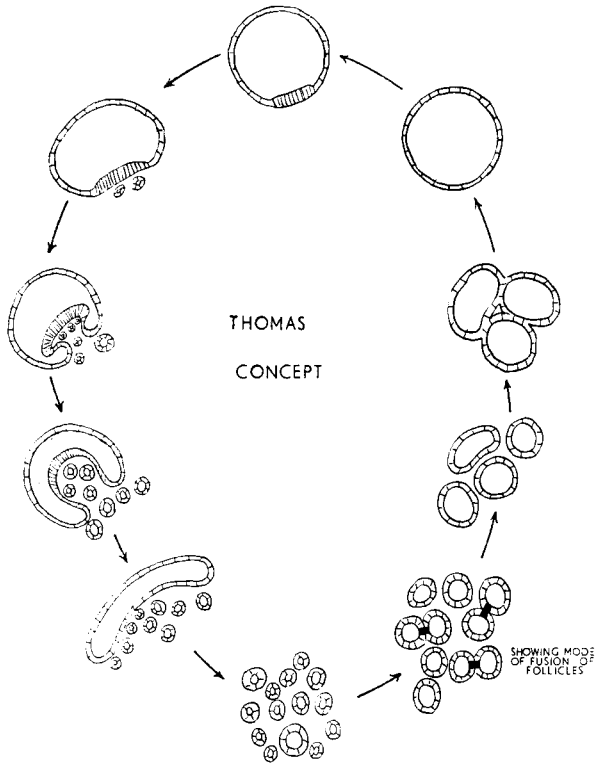

FIG. 2.

hyperplasia also seen in thyrotoxicosis. Finally, great sheets of solid epithelium occasionally occur in intensely hyperplastic goitres (regenerative epithelial hyperplasia of Broders, 1929). On the contrary, during periods of involution after hyperplasia, fusion of many more follicles than existed originally would result in the colloid micro-cysts and other features of colloid goitre.

Lever (1948) enumerates the histological criteria of increased thyroid activity as follows.

(i) An increase in height and number of the follicle cells.
(ii) Resorption of colloid.

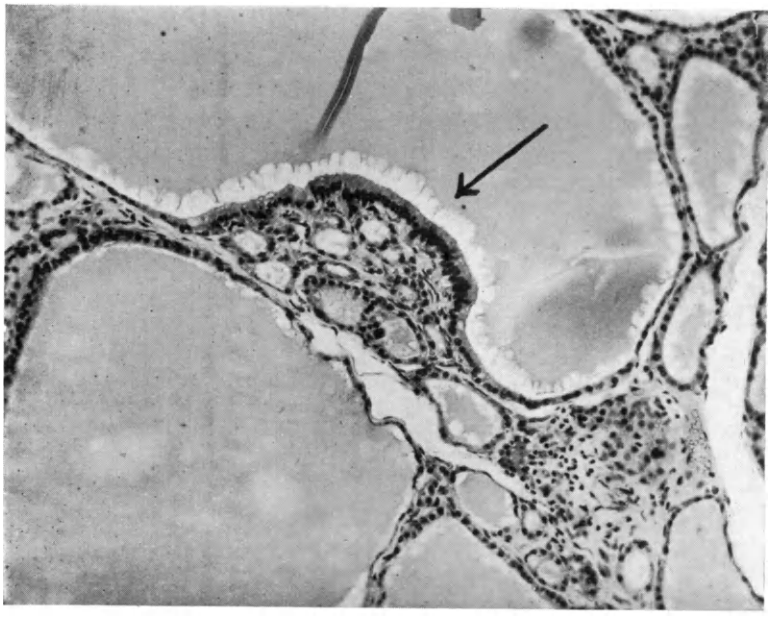

FIG. 3.—Thomas' concept: excretory segment and subjacent microfollicles. (× 150).

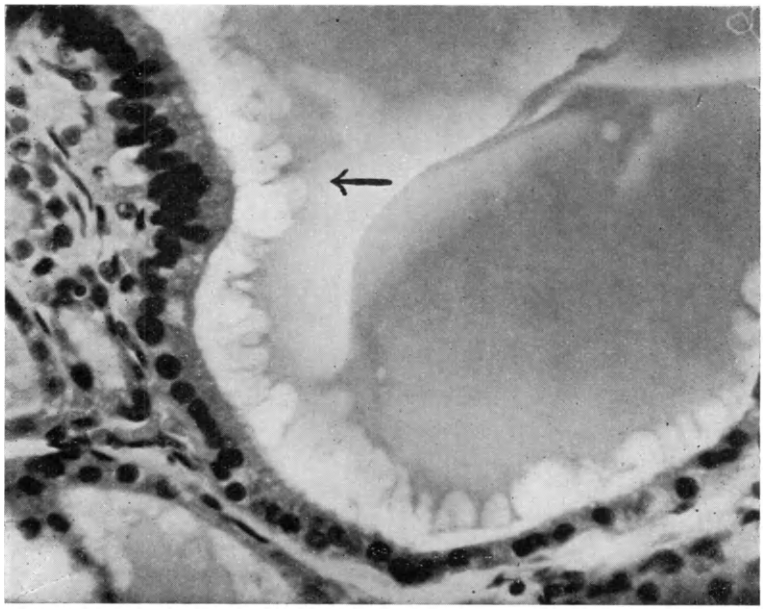

FIG. 4.—Thomas' Type II cells (× 500).

(iii) An increase in the interfollicular space due to enlargement of the blood capillaries.

(iv) The nucleus changes its position from the base towards the apex of the cells.

The average height of the follicular epithelium (mean cell height) has been widely used as a measure of the activity of a particular gland (Rawson and Starr, 1938). The method of fixation must be standardized to avoid errors due to cell shrinkage (Holmgren and Nilsonne, 1948).

Williams (1937–1944), has developed interesting techniques for studying the thyroid follicle *in vivo*. In some cases he has transplanted living follicles into small transparent glass and mica chambers in the rabbit's ear. In others he has observed the reactions and appearance of the follicles in the thyroid

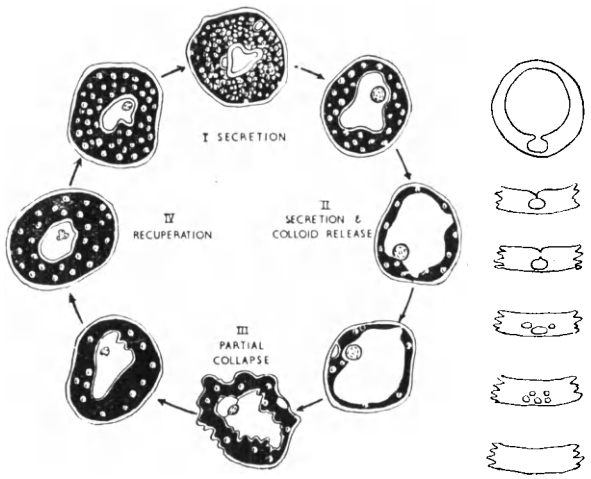

FIG. 5.—Cycle of changes in the living thyroid follicle (after Williams). The insert on the right shows the steps in colloid resorption.

isthmus of the mouse, by transillumination through the trachea and suitable micro-dissection.

He has been able to trace cyclic changes in the living follicles (Fig. 5). Colloid release is followed by partial collapse. The follicle enters a phase of colloid secretion and gradually recovers its shape. The number of cycles which a follicle can complete is apparently indefinite, and the time required is extremely variable, from nineteen hours to twenty-one days or more. Prolonged arrest of the cycle can occur at almost any stage. Most follicles are stationary at any given time, or are undergoing slow oscillation between repletion and partial collapse. The great majority are resting and constitute a potential reserve.

Williams stresses the great activity of the free borders of the cells. Indentations appear in the inner margin of the follicle, colloid flows in. The apical protoplasm finally flows across and cuts off an intramural colloid

droplet. But the droplet never enters the interfollicular space as such. It slowly diminishes in size within the follicle wall, and finally disappears. The time required for the ingestion and assimilation of a colloid droplet is usually about one half-hour.

After stimulation with thyrotropic hormone, the follicle wall may appear loaded with droplets (Williams, 1939). But the intrafollicular vacuoles so common in fixed sections are extremely rare in the living follicle (Williams, 1941).

The classical picture of the normal follicle, one which is round, lined by cuboidal cells, with distinct inner and outer cell boundaries, is only occasionally seen in living follicles; more often the inner cell boundary is faint, extremely irregular or even invisible. The inner cell membrane is seen best when the follicle is inactive.

Williams also observed adjacent follicles fusing. During the exhibition of thyrotropic hormone more follicles had thicker walls and less colloid than

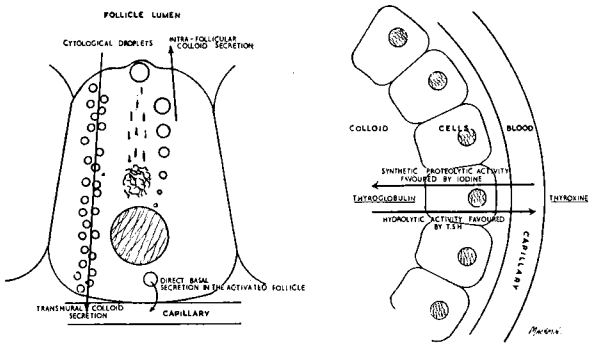

FIG. 6.—De Robertis's Concept

normal and the colloid appeared and disappeared more rapidly, but the essential character of the follicular cycle was unchanged.

The capillaries around the follicles are numerous and of large calibre. The rate of flow in them is rapid and does not fluctuate. No empty vessels are seen. Williams (1944) believes that the ordinary thyroid requirements of the body are met, not by basal secretion, but by the slow utilization of the colloid. This is not necessarily associated with visible changes in cell structure or colloid volume.

The work of de Robertis (1948a) illustrates the approach of the cytological chemist. In earlier studies (1941a) he applied a freezing-drying technique which preserves the different cellular components, particularly the proteins, taking part in secretion. Close study suggests that the normal direction of secretion is towards the follicle (Fig. 6). This is best seen in certain tall, cylindrical cells. The nucleus is basal, the Golgi apparatus and mitochondria are apical. Minute droplets first appear near the nucleus, gradually

increase in size and are largest at the apical pole where they are seen pushing against the apical membrane. Other droplets, large and uniform in size, are seen in rows extending between the apical and basal poles. This is the transmural secretion of colloid into the capillary blood.

In activated glands, however, fluid secretion vacuoles form primarily in the basal cytoplasm of the cell, and may displace the nucleus centrally. De Robertis believes that these vacuoles pass directly into the blood stream (basal secretion). De Robertis confirms Williams's observations on the great activity of the apical cytoplasm, its wealth of droplets during the secretion phase, and how cytoplasmic prolongations reach out to engulf droplets of the intra-follicular colloid.

De Robertis (1941b) found that a proteolytic enzyme capable of digesting a gelatin substrate was present in colloid extracted from single follicles by micro-dissection. This proteolytic activity increased after pre-treatment of the animal with thyrotropic hormone and this increase coincided with the rapid mobilization of stored colloid. There is thus strong evidence of an enzymatic mechanism for the hydrolysis of the colloid protein and its subsequent release into the blood stream. Conversely, Dziemian (1943) found that hypophysectomy decreased the proteolytic activity of fresh whole gland.

In severe thyrotoxicosis, the proteolytic activity in slices of the excised gland is much increased. On the other hand it is reduced to some 26 per cent. below normal after pre-operative iodine therapy (de Robertis and Nowinski, 1946a and 1946b).

The *in vitro* treatment of toxic goitre slices with iodine inhibits proteolytic activity by almost 90 per cent. Incidentally, the proteolytic activity of simple goitre slices was about 30 per cent. below that of normal gland. This may explain the tendency to macrofollicle formation in colloid goitre and the diminished output of hormone per unit weight of gland tissue. Thiourea does not affect proteolytic activity and its point of attack is clearly at an earlier stage of hormone secretion.

The synthesis of thyroid hormone depends on a chain of oxidative reactions, and de Robertis and Grasso (1946) have been able to demonstrate peroxidases in the epithelial cells. In glands stimulated by cold or thyrotropic hormone, this peroxidase activity is also present in the colloid.

Thomas (1944) has remarked on the striking similarity in the thyroid cytology of rats after thiourea and thyrotropic hormone. Yet the functional difference between the two is absolute. With T.S.H.* all phases of hormone synthesis and secretion are accelerated, whereas, since thiourea blocks all hormone synthesis, its hyperplasia is one of " frustration ". It is thought that the decreased production of thyroid hormone results in an increased T.S.H. secretion and that this in turn causes thyroid hyperplasia. Such a mechanism may be responsible for the compensatory hyperplasia of simple goitre, when iodine is deficient.

* The letters T.S.H. (thyroid stimulating hormone) are used in this chapter to signify " thyrotropic hormone ".

Grasso (1946) believes that under thiourea treatment, follicular secretion can occur but that the product is devoid of thyroxine activity. Dempsey and Singer (1946) claim that chains of enzymatic reactions occur within the cells and colloid. They demonstrated phosphatase enzymes in the apices of very active cells. Popoff (1943) similarly claims to have demonstrated intracellular and intra-follicular proteolytic enzymes in crystalline form, and also intra-follicular crystalline thyroxine.

Techniques using radioactive iodine offer a new approach to the problems of thyroid histo-physiology. The exposing effect of radioactivity on a photographic emulsion enables its location in a given slice of thyroid tissue to be determined by autoradiography. The " tracer " doses of radio-iodide

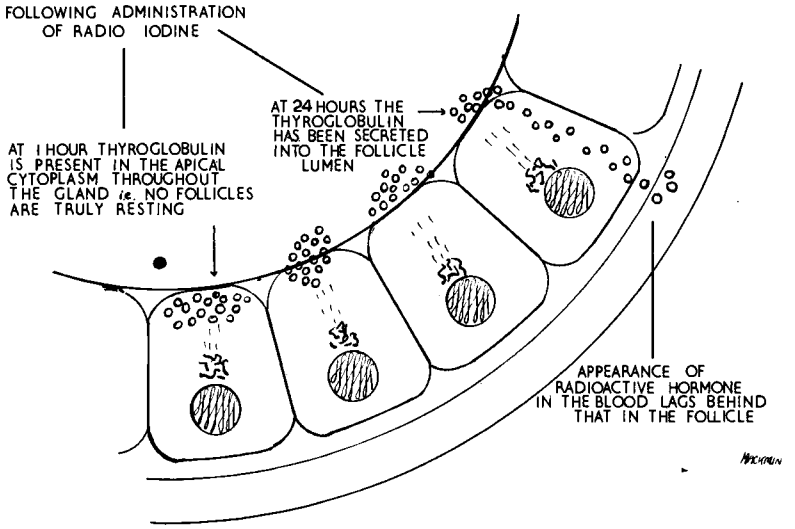

FIG. 7.

used are so minute as not to influence hormone synthesis and secretion. One hour after such a " tracer " dose in the normal rat, the radio-iodine is incorporated in newly formed thyroglobulin throughout the gland, being chiefly present in the epithelial walls of the follicles (Le Blond and Gross, 1948). Since the fixatives dissolve iodides and the smaller organic iodine-containing molecules, such as diiodotyrosine and thyroxine, it is concluded that all the radioactivity present must be in the form of thyroglobulin, whose large protein molecules remain fixed in the section. The rapid generalized appearance of this thyroglobulin discredits the theory that the thyroid follicles function in groups, and only intermittently.

The radioactivity is clearly localized in the apical region of the cells indicating that this is the site of thyroglobulin formation (Fig. 7). In subsequent

autographs the radioactivity is increasingly present in the follicular colloid until at the end of twenty-four hours little can be seen in the cells. Clearly, the cells have now secreted the thyroglobulin into the follicle lumen. There is thus a definite polarity of hormone synthesis and secretion within the cell.

In both normal and hyperactive glands the appearance of radioactive hormone in the blood lags behind that in the thyroid colloid. Le Blond and Gross therefore conclude that the thyroid cell secretes only in the direction of the follicle lumen. Thence thyroid hormone streams back continuously across the cells into the capillary blood.

Using a similar technique, Bourne (1948) has demonstrated that microfollicles elaborate thyroglobulin and secrete it into the colloid more rapidly than do macrofollicles. Since the microfollicles have tall cuboidal epithelium while that of the macrofollicles is generally more flattened, this is not an unexpected finding. Like Le Blond and Gross, Bourne has shown that all parts of the gland are continuously functioning, elaborating and storing thyroglobulin.

The Endogenous Iodine Cycle

Radio-iodide by mouth or injection is handled by the body exactly like non-radioactive iodide. It thus falls in with the ordinary endogenous iodine cycle but because of its radioactivity, we can follow its path and metabolism in detail.

The rate of appearance of ingested iodine in the thyroid gland is exceedingly rapid; within fifteen to thirty minutes, serial counts of its growing concentration can be made with a detector placed on the neck over the thyroid isthmus (Astwood and Stanley, 1947). Conversion of this iodide to thyroid hormone then proceeds apace. Thus Taurog and Chaikoff (1947a) found in rats injected with a small dose of labelled iodine, that as early as fifteen minutes afterwards, 95 per cent. of the radio-iodine in the gland was organically combined, 80 per cent. as diiodotyrosine and fifteen per cent. as thyroxine.

Normally such thyroxine soon begins to appear in the blood (Chaikoff, Taurog and Reinhardt, 1947). Secretion is continuous and it has been estimated that in the dog the whole of the hormone present in the plasma is renewed every four to seven hours (Taurog, Chaikoff and Entenman, 1947). Further, within four hours of thyroidectomy in the rat there is already a notable decrease in the plasma hormone level and in three days it has reached a minimum value.

The metabolism of iodine in the thyroid gland can be divided into three processes for descriptive purposes, iodide uptake, hormone synthesis, and hormone secretion.

Iodide uptake. The epithelial cells of the thyroid follicle show an exceeding avidity for iodide. They suck it in from the adjacent plasma. Thus if a normal dog is given a dose of 50 mg. of potassium iodide, 18·5 per cent. of the iodine can subsequently be recovered from the thyroid gland, though

the latter represents less than 0·15 per cent. of the total body weight (Harington, 1944a). This ability to entrap or concentrate iodide has been demonstrated also in fresh slices of thyroid tissue *in vitro* (Franklin, Chaikoff and Lerner, 1944). And it persists even though the further conversion of the iodide to thyroid hormone is blocked, as by thiouracil. In fact, such blocking of hormone synthesis causes cellular hypertrophy and greatly increases iodide uptake.

Since thiouracil completely arrests hormone synthesis, its preliminary exhibition should guarantee that any radioactivity appearing in the gland depends solely on the iodide. Vanderlaan and Vanderlaan (1947) have in fact demonstrated this radioactivity from the iodide by titration and their

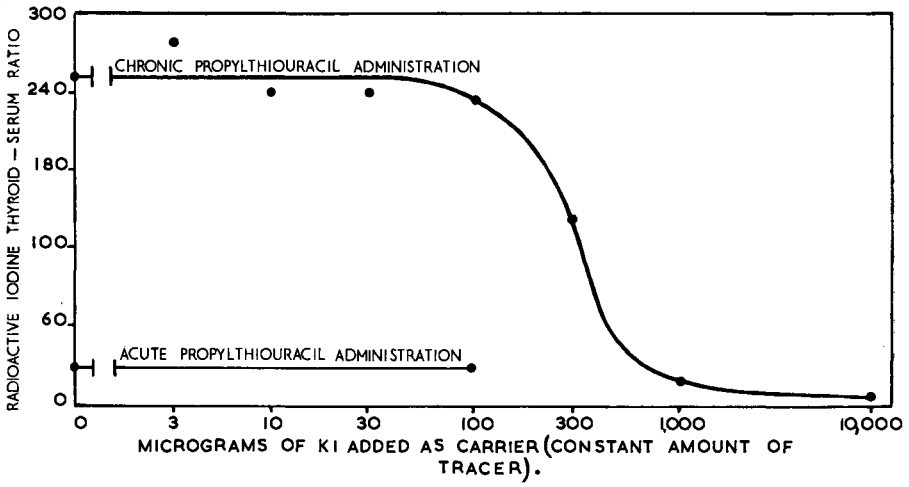

FIG. 8.—Shows that following the chronic administration of propylthiouracil the ratio of the thyroid iodide to serum iodide is 250 to 1 over a wide dosage range. After the acute administration of propylthiouracil the ratio is 25 to 1 over the same range of iodide dosage. (Vanderlaan & Vanderlaan, 1947.)

observations have been fully confirmed by Taurog, Chaikoff and Feller (1947).

Both groups of workers then measured the gradients between the serum and thyroid iodide. Typical results are illustrated in Fig. 8. The gradient in two groups of rats is shown. In the one, a single dose of propylthiouracil was given one hour before the radio-iodide (acute propylthiouracil administration) merely to block hormone synthesis and ensure that the whole of the thyroid radioactivity was due to iodide. Such a preliminary dose causes no anatomical change in the gland, and Taurog *et al.* found that such glands have the same initial rate of fixation of injected iodide as do the glands of untreated rats, so that their gradients may be regarded as sensibly normal.

Their concentration of iodide is twenty-five times greater than that in the plasma. In the second group propylthiouracil was fed for two weeks previously and the glands were much hypertrophied. The trapping power of the cells is seen to be greatly increased, the thyroid iodide concentration being 250 times that of the serum. The gradient is thus ten times the normal. Since the glands were three times the normal weight they could probably accumulate about thirty times more iodide than the normal gland.

Fig. 8 also shows that this great trapping power exists over a wide range of iodide dosage but at levels greater than 100 mg. of potassium iodide, as carrier, it decreased sharply. It is not unnatural that the gradient should decrease when the serum iodide level becomes very high.

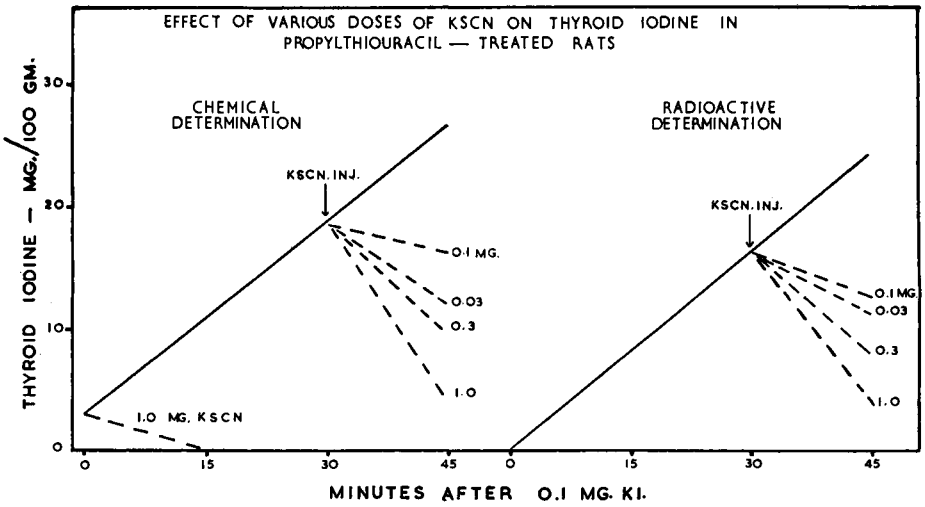

FIG. 9.—Shows the effect of increasing doses of thiocyanate in causing the discharge of iodide. (Vanderlaan & Vanderlaan, 1947.)

In normal human subjects, blockade of hormone synthesis by an antithyroid drug combined with the injection of T.S.H. markedly increases the gradient, the thyroid iodide concentration rising to some 500 times the serum iodide (Stanley and Astwood, 1949).

Thiocyanates prevent the trapping of iodine. Franklin, Chaikoff and Lerner (1944) demonstrated that thiocyanate inhibits the iodide concentrating capacity of slices of sheep's thyroid *in vitro*. In fact potassium thiocyanate both paralyses the iodide uptake mechanism and destroys the gradient between the cells and serum. A single dose will cause the discharge of iodide already trapped by the cells (Fig. 9). It is thought that the thiocyanate ion competes with the iodide for the enzyme concerned in the first of the chemical reactions leading to thyroxine synthesis (Wood and Williams, 1949).

It can be seen that even a small dose of potassium thiocyanate significantly lowers the thyroid iodide within fifteen minutes, and 100 mg. practically empties the iodide compartment. Taurog *et al.* (1947) accept that this iodide is not stably bound to the cellular protein although the possibility of a very labile protein linkage is not ruled out. It is not surprising that Barker, Lindberg and Wald (1941) found in the course of treating hypertensives with thiocyanate that some patients (11 of 246) developed goitre. These were, then, true iodine-deficiency goitres.

A knowledge of the physiology of this iodide " compartment " is important because tests for thyrotoxicosis, and tests of the adequacy of therapeutic control, are being based on it (Stanley and Astwood, 1948; Stanley, 1948). Thus, after a tracer dose, the curve of iodide uptake in thyrotoxic subjects is much sharper and higher than in normals and the rate of discharge after thiocyanate is extremely rapid. The adequacy of antithyroid medication is measured by observing the loss of radioactivity following a full dose of thiocyanate. Any radioactivity persisting after the thiocyanate is due to the combination of an aliquot part of the test dose of radio-iodide in organic form and to that extent, blockade of hormone synthesis is incomplete.

Hormone synthesis. In the biosynthesis of thyroxine two oxidative processes are involved. In the first, iodide is oxidized to elemental iodine

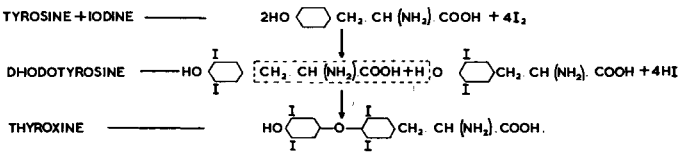

FIG. 10.

which then iodinates tyrosine, to form diiodotyrosine. In the second, there is coupling of two molecules of diiodotyrosine to form the final product 3 : 5 : 3′ 5′–tetraiodothyronine (thyroxine), of which the laevorotatory isomer is the naturally occurring form, d-thyroxine being relatively inactive (Pitt Rivers and Lerman, 1948).

Using radioactive iodine, Taurog and Chaikoff (1947a) have obtained convincing evidence that di-iodotyrosine is in fact the normal biological precursor of thyroxine in the gland. Soon after injecting radioiodide, radioiodine is being incorporated into organic compounds in the gland. Fifteen minutes after injection, five times as much radioiodine is present in diiodotyrosine as in thyroxine but the relative amount in thyroxine increases with time.

Our knowledge of the biochemistry of the thyroid gland owes much to the pioneer work of Harington and his group (Harington, 1933). Harington (1944a) has also reviewed later knowledge and speculated on the molecular groupings that may be involved in the oxidations mentioned above. It is a problem in the chemistry of proteins. No detailed review of the subject need

be given here. Two points of interest to the clinician may, however, be mentioned.

The one is that any alteration of the thyroxine molecule only serves to reduce its biological potency; it may be concluded that hyperthyroidism derives from secretion of normal hormone in excessive amounts. Thus the removal of two iodine atoms gives a product, diiodothyronine, which is only one fortieth to one twentieth as active as thyroxine (Gaddum, 1930). Thyronine itself, which results from the complete removal of iodine from the thyroxine molecule, is quite inactive (Harington, 1935). The same is true of

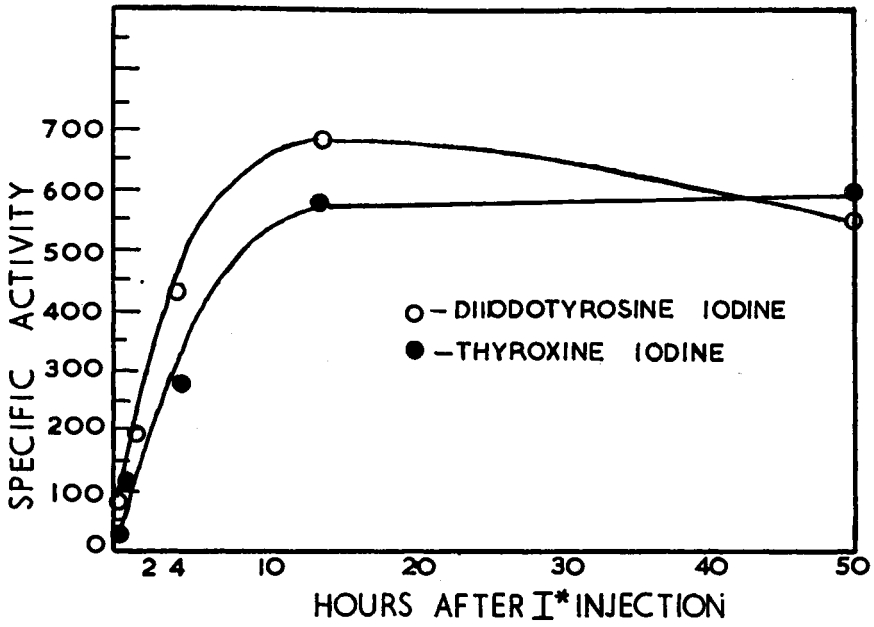

FIG. 11.—Specific activity-time relations for diiodotyrosine iodine and thyroxine iodine. (Taurog & Chaikoff, 1947.)

diiodotyrosine. Thus the full complement of four iodine atoms, as well as the phenyl-ether linkage, is necessary for normal physiological activity. The aminoproprionic acid side-chain also appears to be necessary since decarboxylated thyroxine is inert. Two other substances, closely related to thyroxine structurally, do possess feeble activity. They are tetrabromthyronine, tetrachlorthyronine and the keto-analogue of thyroxine.

The other is that in recent years considerable progress has been made in the direct iodination of proteins. Ludwig and von Mutzenbecher (1939) first recovered thyroxine from a simple mixture of iodine and casein, submitted to slow alkaline hydrolysis. This development is of practical importance because it " offers the possibility of the cheap and easy preparation in

large quantities of products having the specific physiological property of thyroid gland" (Harington, 1944*a*). Thus Harington now claims a net yield of 3·4 per cent. by weight of thyroxine from the alkaline hydrolysis of diiodotyrosine, and Reineke and Turner (1946), a net yield of 2·8 per cent. thyroxine. The prolonged *in vitro* exposure of serum proteins to high concentrations of iodide likewise results in their iodination, the products having the same precipitation reactions as the protein-bound iodine of the plasma (Swenson and Curtis, 1948).

The thyroglobulin compartment. Following its synthesis, thyroxine normally passes into the follicle to be stored in protein combination as thyroglobulin. If sections of frozen gland, 40μ in thickness, are floated on to Ringer's solution, the colloid drops out of the follicles and goes into solution. Centrifugation then separates the cellular mass, which can be dried, weighed, and analysed for iodine. Estimation of the total iodine in a comparable piece of gland makes it possible to state the proportion of the total iodine in the cells (Tatum, 1920).

Using this method it is found that 60–85 per cent. of thyroid iodine is present in the colloid (Tatum, 1920, Van Dyke, 1921, and Grab, 1932). Incidentally this percentage remains much the same in thyrotoxicosis though the iodine content of the gland is greatly reduced.

Normally, nearly one-third of the thyroid iodine is present in thyroxine. Thus Taurog and Chaikoff (1946) found in rats that the percentage of the total thyroid iodine present as thyroxine remained remarkably constant at 31·0 $\pm$ 0·51 despite large differences in the total iodine. Similarly Parkes (1946) tested the biological activity of fresh thyroid gland from the ox, sheep, pig, horse and dog, and found it to be closely related to the iodine content. The proportion of total iodine present as thyroxine (acid-insoluble fraction) was roughly the same in all.

Finally, Wolff and Chaikoff (1947) measured the proportion of the total thyroid iodine present as thyroxine in a wide range of animals and found that, despite individual iodine concentrations fluctuating from 17 to 300 mg. per cent., the fraction present as thyroxine remained relatively constant between 25 and 32 per cent. with an average of 30·2 $\pm$ 0·7 per cent. They observe that it is difficult to imagine how this ratio could be so constant unless the mechanism involved in the synthesis of thyroxine were quite similar throughout the vertebrates.

In abnormal conditions, however, the constitution of the colloid quickly changes. Thus after hypophysectomy the proportion of radio-iodine in the thyroxine fraction remains low though iodide to diiodotyrosine conversion occurs readily enough (Morton *et al.*, 1942). Presumably the thyrotropic hormone facilitates the final oxidative coupling of diiodotyrosine.

After injecting thyrotropic hormone into the normal rat, the proportion of radioiodine present as thyroxine also falls sharply (average of 17·5 $\pm$ 0·6 per cent.). This depends not on defective synthesis but on abnormally rapid release (Wolff and Chaikoff, 1947). These findings in the hyperactive rat agree with the lowered proportion of thyroxine in the thyrotoxic glands

from human subjects (Gutman *et al.*, 1932). Rawson *et al.* (1945), observed the effect of Lugol's iodine on thyrotoxic patients under the control of thiouracil. The latter of course blocks thyroxine synthesis but, curiously enough, iodine still produces a well-marked involution in the gland with the accumulation of clear colloid material in the follicle. Is this follicular material quite devoid of thyroxine?

At all events it seems clear that under the influence of proteolytic enzymes present in, and secreted by the thyroid cells, a variety of synthetic and breakdown reactions can go on in the thyroglobulin compartment. Diiodotyrosine and thyroxine are only loosely combined with protein and are present in varying concentrations. It is possible that the thyroxine content can vary from almost nil up to the normal 30 per cent. of the total organic iodine.

The definitive secretion of the follicle. The thyroglobulin molecule is very large; its weight has been estimated at almost 700,000 (Heidelberger and Pedersen, 1935). Minute portions of colloid may be engulfed by the apical cytoplasm of the epithelial cells but both within the follicle and the cells the thyroglobulin molecule is believed to be broken down into much simpler and smaller molecules which pass as the definitive secretion into the capillary blood. The organic iodine fraction of the blood has a molecular weight of less than 69,000 (Riggs *et al.*, 1942).

Lerman (1940) showed that thyroglobulin cannot ordinarily be found in the blood of normal, myxoedematous or thyrotoxic subjects, nor in the urine of thyrotoxics. Moreover, blood from the thyroid veins of thyrotoxic patients undergoing thyroidectomy was negative early in the operation though towards the end of the operation seven out of eight samples showed appreciable amounts of thyroglobulin. The amount of thyroglobulin in the blood towards the end of, or immediately after, the operation could not be correlated with the severity of the post-operative reaction but Lerman does not exclude the possibility that it plays a part in crisis.

Riggs *et al.* (1942) regarded the circulating thyroid hormone as either an iodine-containing molecule of approximately the same size as serum albumin or one of smaller size which is restrained from diffusion by serum albumin. Riggs (1947) gives the following values for the protein-bound iodine:

Euthyroidism	3·5 to 7·0 gamma per cent.
Thyrotoxicosis	more than 8 gamma per cent.
Hypothyroidism	less than 3 gamma per cent.

After radio-iodine is injected into normal rats, it quickly makesits appearance in the protein-bound iodine fraction of plasma ; indeed, 90 er cent. of the plasma radio-iodine is protein-bound at the end of twenty-our hours. Thyrotropic hormone hastens the appearance of radio-iodine in the protein-bound iodine. But in the completely thyroidectomized rat, only minimal amounts of the radio-iodine are protein-bound after twenty-four hours. Thus, with respect to both its concentration and rate of formation, the

protein-bound iodine of the plasma responds exactly as would be expected of the circulating thyroid hormone.

After reconsidering the earlier data, Harington (1944b) came to the conclusion that thyroxine itself is probably the circulating hormone and this has now been brilliantly established by Taurog and Chaikoff (1947b, 1948).

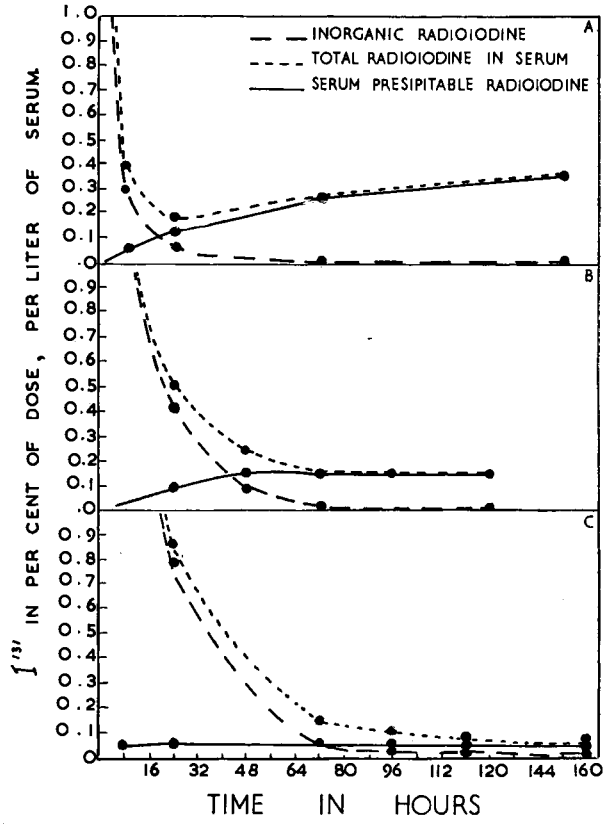

FIG. 12.—Separation of the concentration of total radio-iodine in serum into a serum precipitable fraction and an inorganic fraction. The latter was obtained by subtracting precipitable radio-iodine from total radio-iodine. (A) A case of hyperthyroidism. (B) A person who had normal thyroid function. (C) A case of myxoedema. (Wm. McConahey, F. R. Keating and M. H. Power (1949), *J. Clin. Invest.*, 28, 191.)

The hormone is loosely attached to the plasma proteins, especially to the smaller globulin molecules (Salter and Johnston, 1948).

Radio-iodine uptake and clearance as indicators of thyroid function. As early as 1940 Hamilton and Soley, using a counter placed on the skin over the thyroid isthmus, found clear differences between the uptake curves of normal, thyrotoxic and hypothyroid subjects. In normal subjects the count

increases rapidly during the first few hours and then more gradually to reach a maximum in two to three days, the plateau being then maintained sometimes for weeks.

In untreated thyrotoxics, the count rises sharply from the first few minutes after ingestion of the tracer dose. The maximum value attained is much higher than in normals and it is reached after an average of only ten hours (Myant *et al.*, 1949). The plateau is of short duration, the curve beginning to fall usually within twenty-four hours. Conversion of the iodide into radiothyroxine proceeds apace; in fact radiothyroxine has been detected in the plasma three hours after the tracer dose of iodide (Myant *et al.*, 1949). In other words, in untreated thyrotoxics the gland hungrily seizes a high proportion of the ingested iodide and quickly turns it over into plasma radiothyroxine. Inversely, in completely thyroidectomized or myxoedematous

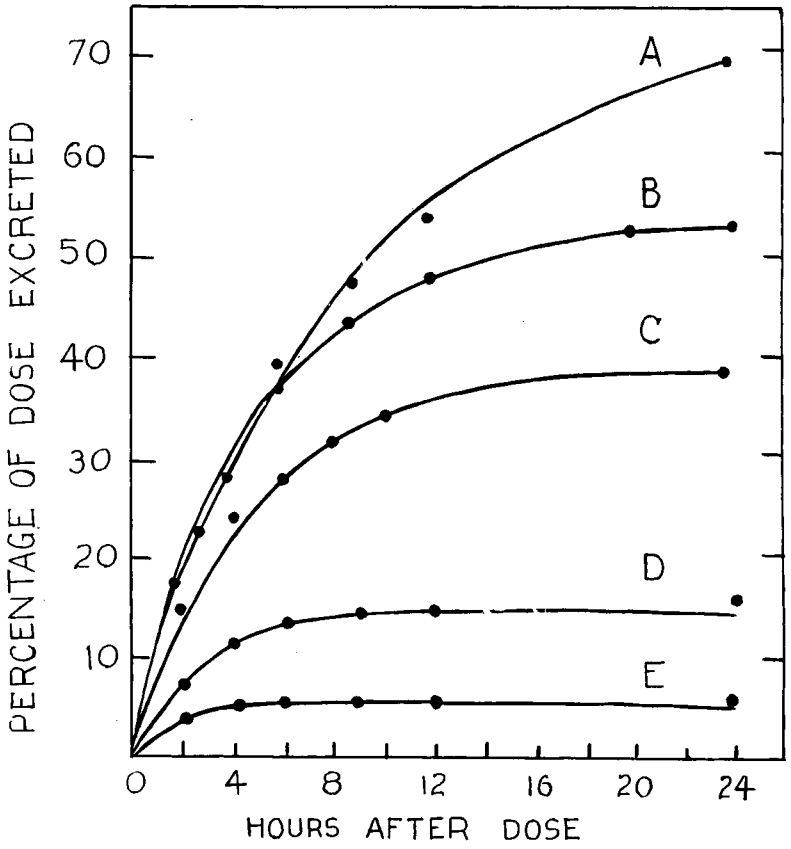

FIG. 13.—Urinary excretion of radio-iodine in different states; A, myxoedema; B, normal health; C, slight thyrotoxicosis; D, moderate thyrotoxicosis; E, severe thyrotoxicosis. (From Mason & Oliver.)

subjects, counts over the neck show only " background " activity. These variations in the avidity of the thyroid for the tracer iodide are reflected in the proportion of the dose excreted by the kidneys (Fig. 13). Typical figures are those of Skanse (1948).

Type of Subject	Number	Range of radio-iodine excretion in 48 hrs. (percentage of tracer dose)
Normal	15	52·7 to 84·1
Myxoedematous	6	72·4 to 91·7
Hyperthyroid	25	6·2 to 32·3

A detailed, quantitative study of the urinary excretion of radio-iodine has been made by Keating *et al.* (1947). But the most sensitive and direct measure of the iodine-collecting activity of the thyroid appears to be the " iodine clearance rate ", as recently defined and studied by Myant *et al.* (1949). This rate is calculated on similar lines to the conventional renal clearance for other substances and is a function of the plasma thyroid flow and efficiency with which iodide is removed from this plasma. The plasma thyroid flow is not accurately known but the clearance rate can be simply calculated when the rate at which radio-iodine is entering the gland and the simultaneous plasma concentration of radio-iodine are known. Myant *et al.* found that in normal subjects 16 ml. of plasma were cleared of iodide per minute as compared with an average of 486 ml. in eleven untreated thyrotoxics. In all cases the thyroid clearance greatly exceeded the highest rate observed in normal subjects (Fig. 14). It is possible that this iodine clearance rate will be of more value in diagnosing minor degrees of thyrotoxicosis than is the basal metabolic rate.

Regulation of thyroid secretion. Hormone synthesis may be regarded as a chain reaction including in turn iodide, iodine, diiodotyrosine and thyroxine. A single enzyme or groups of enzymes, or oxidation systems, may be involved in these steps.

The inhibitory effect of thiocyanate on iodide uptake has been described. Other agents exert their action at points further along the chain. Thus Miller, Roblin and Astwood (1945) found that thiouracil combines with several equivalents of elemental iodine at a *p*H of 6·8; the reaction rate was such that the iodination of tyrosine and casein present was prevented. The authors conclude that the sulphydryl compounds act *in vivo* by reducing iodine as soon as it is formed, thus blocking the iodination of the hormone precursors.

According to Lerner and Chaikoff (1945), a cytochrome-oxidase system is concerned in the synthesis of diiodotyrosine and thyroxine. The thio-drugs do not interfere with the activity of this oxidase; this confirms that they block synthesis at the iodine stage.

Taurog *et al.* (1945) studied the effect of forty compounds, structurally related to the sulphonamides and aminobenzoic acid, on the *in vitro* conversion

of radioactive iodide to thyroxine. They found that a free aromatic amino- or hydroxyl- group favoured inhibitory activity. There appeared to be a definite correlation between the oxidizability of the agent and its inhibitory activities. Some, at least, of these inhibitors may act by competing with the hormone precursors for the oxidases.

In an interesting paper, Mackenzie (1947) has shown that the inhibitory actions of thiouracil and sulphaguanidine on hormone synthesis are funda-

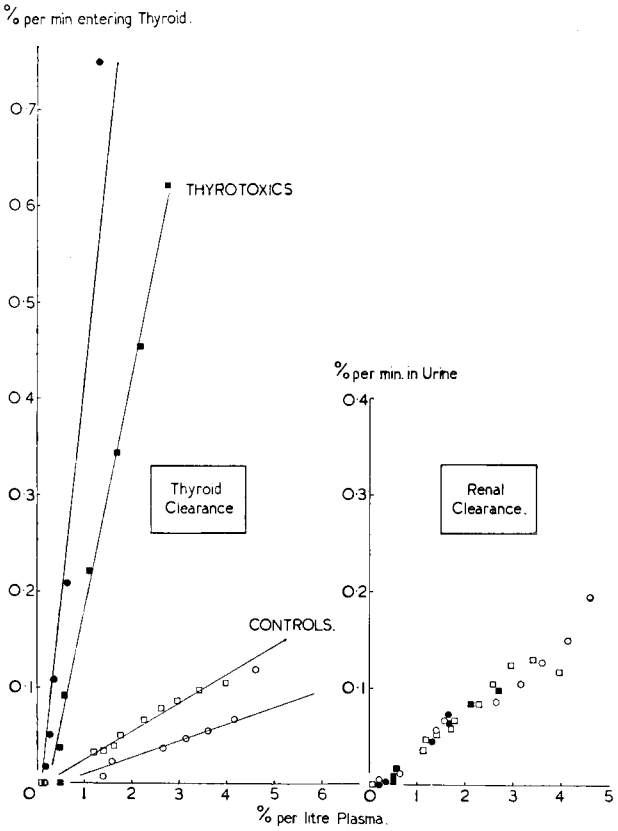

FIG. 14.—Thyroid and renal clearances in two thyrotoxic (solid squares and discs) and two control (open squares and discs) subjects, showing greatly increased thyroid clearance in thyrotoxicosis. (From Myant *et al.*, 1949.)

mentally different. Iodide scarcely affects the thyroid hyperplasia associated with thiouracil feeding (Ferguson and Sellers, 1949) but distinctly increases that following sulphaguanidine.

Observations of exceptional interest have recently been made on the relationship between iodine intake and the rate of hormone synthesis and secretion. Thus, Taurog and Chaikoff (1946) supplemented the basic diet of groups of rats with different amounts of iodide to provide an average daily intake ranging from 1 to 2 gamma to 400 gamma. It was found that at levels

between 1 or 2 gamma and 78 gamma, the total and thyroxine iodine in the thyroid both increased steadily as did the curve for protein-bound iodine in the plasma. Above 78 gamma iodine per day there was no further increase;

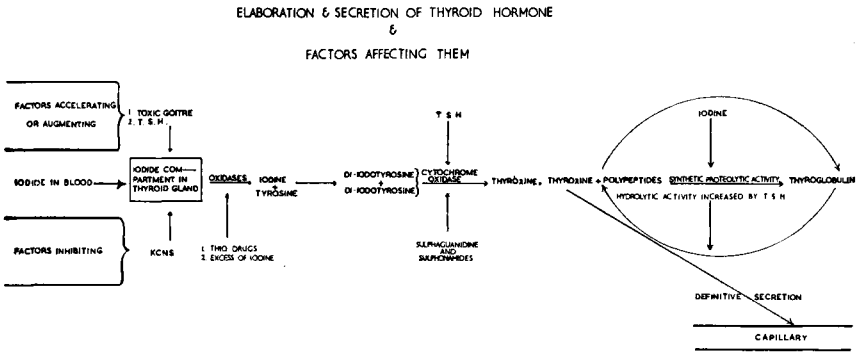

FIG. 15.

the storage capacity of the thyroid for total iodine and thyroxine iodine had evidently been reached. At all levels the protein-bound iodine of the blood ran parallel to the curve for thyroxine iodine in the thyroid.

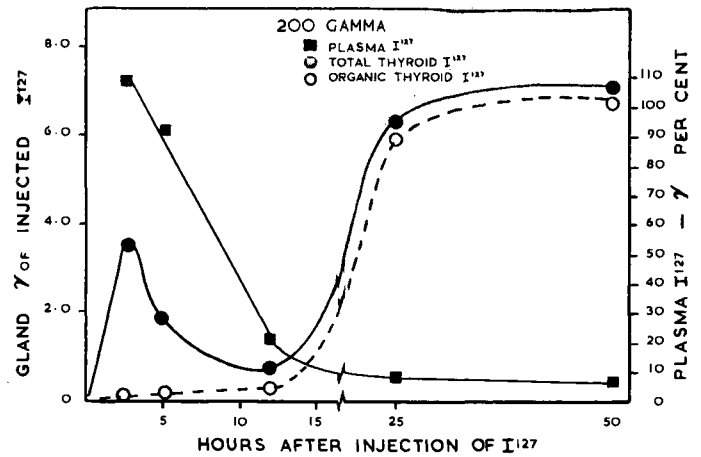

FIG. 16.—Changes in plasma and thyroid iodine with time, following the injection of 200 γ of iodide in rats. (Wolff & Chaikoff, 1948.)

Finally, there is now exciting evidence that the level of the plasma inorganic iodide acts as a homeostatic regulator of thyroid function. In experiments on rats, Wolff and Chaikoff (1948a) have shown that so long as the plasma iodine remains above 20–35 gamma per cent., organic binding of injected iodide in the thyroid is blocked. Organic binding only begins to

occur again when the level of plasma iodine falls below the critical range of 20–35 gamma per cent. Thus very high levels of plasma iodine *inhibit the formation of hormone in the gland* and this may help to explain the beneficial effect of large doses of Lugol's iodine in patients suffering from thyrotoxicosis. This inhibition of hormone synthesis persists as long as the high plasma iodide level is maintained (Wolff and Chaikoff, 1948b). But up to the inhibitory level, the rate of hormone synthesis increases with the blood iodide concentration (Raben, 1949).

This lead has been brilliantly followed up by Stanley (1949) using a method for the direct estimation of thyroid hormone formation in man. It is the concentration of iodide ion in the thyroid cells rather than the serum iodide level which is the ultimate regulator of hormone formation. Since the gradient of iodide between the serum and the cells is steeper in the hyperplastic gland of thyrotoxicosis complete inhibition of hormone formation could be achieved at clearly lower levels of the serum iodide in thyrotoxic than in normal subjects. But even in normals a serum iodide level of 6–12 micrograms per cent. was inhibitory and it is clear that where the object is to increase hormone formation (as in the iodine prophylaxis of endemic goitre) only very small doses of iodide should be used.

To achieve maximal inhibition in thyrotoxicosis only 100 mg. of the iodide daily need be administered. In previously untreated glands, this dose results in complete cessation of hormone synthesis. Why then does such therapy fail to control thyrotoxicosis permanently? Stanley concludes that fundamental changes in the above reactions must occur after prolonged periods of iodization.

Pituitary thyrotropic hormone in health and disease. There is now very strong evidence that the exophthalmos of Graves' disease has an extra-thyroid origin (Chapter XV). And since exophthalmos and hyperthyroidism so commonly co-exist, it is tempting to ascribe a common extra-thyroid origin to both.

Experimental data suggest that the anterior pituitary is at least a link in the disease chain. Thus, simple aqueous extracts of the anterior lobe of the pituitary, when injected into the guinea-pig, not only activate the thyroid gland and cause secondarily all the manifestations of hyperthyroidism, but also result in exophthalmos. Within twenty-four to thirty-six hours of its injection, there are enlargement and hyperplasia of the thyroid (Loeb and Bassett, 1929, Aron, 1929), an increase in the metabolic rate (Verzar and Wahl, 1931), tachycardia (Schittenhelm and Eisler, 1932a and b), exophthalmos (Loeb and Friedman, 1932), reduction of the iodine content of the thyroid gland (Schockaert and Foster, 1932), an increase in the organic iodine fraction of the blood (Closs, Loeb, and MacKay, 1932; Grab, 1932), depletion of liver glycogen (Eitel, Lohr and Loeser, 1933) and creatinuria (Pugsley, Anderson and Collip, 1934).

Eight hours after the injection of a single large dose of T.S.H. in normal human subjects, there is a marked acceleration of radio-iodine uptake by the thyroid, becoming maximal after twenty-four to forty-eight hours and

returning to the pre-injection level in four to five days (Stanley and Astwood, 1949).

Except for exophthalmos, none of these signs develops if the animal has been previously thyroidectomized. That the hormone acts directly on the thyroid epithelium is shown by the fact that the characteristic changes occur

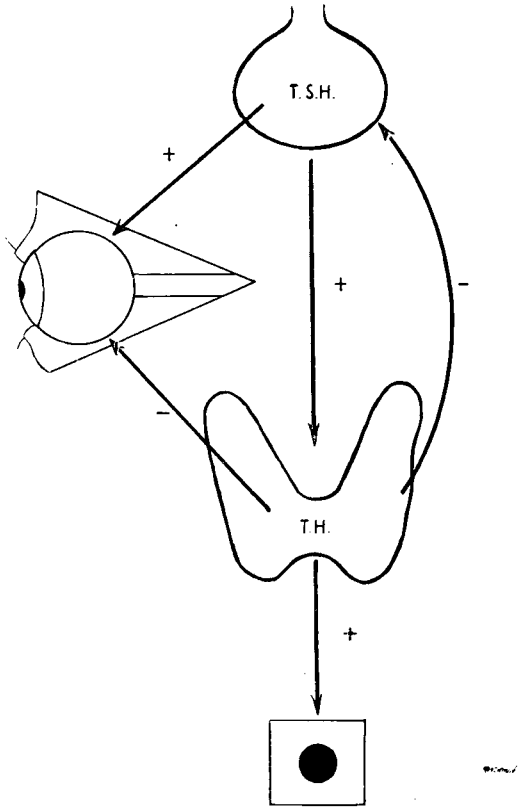

FIG. 17A.

T.H. (Thyroid hormone). 1. Promotes and maintains all phases of cellular activity. 2. Inhibits elaboration of T.S.H. (thyroid stimulating hormone) in the anterior pituitary. 3. Causes wasting of orbital tissues and exophthalmos.

T.S.H. (Thyroid stimulating hormone). 1. Promotes and maintains all phases of thyroid hormone synthesis and secretion. 2. Causes oedematous swelling of the orbital tissues in experimental animals. ? similar effect in man.

when slices of the gland are perfused *in vitro* (Eitel, Krebs and Loeser, 1933). Moreover, the presence of thyrotropic hormone in the human anterior pituitary has been repeatedly shown (Kunkel and Loeb, 1935; Müller, Eitel and Loeser, 1935; and Cope, 1938). That its effects in man are identical with those in the experimental animal has also been demonstrated (Starr, 1935;

Thompson *et al.*, 1936; Scowen, 1937; Sharpey-Schafer and Schrire, 1939). Moreover, thyrotoxicosis is greatly aggravated by the injection of T.S.H. (Thompson *et al.*, 1935; Starr, 1935; Stallard, 1937).

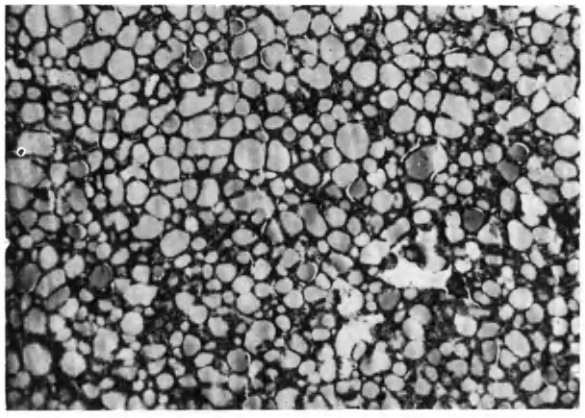

FIG. 17B.—Normal thyroid gland of five-day chick.

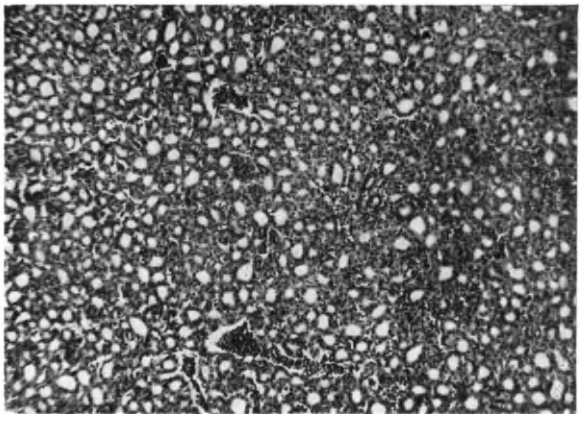

FIG. 17C.—Thyroid gland from chick injected with thyrotropic hormone daily for four days. Note epithelial hypertrophy and hyperplasia, loss of colloid and increased vascularity.

The role of T.S.H., in regulating iodine metabolism by the thyroid gland, has been fully confirmed and extended by studies with radio-iodine. Morton, Perlman and Chaikoff (1941) found in guinea-pigs that treatment with T.S.H. facilitated the conversion of injected radio-iodine into thyroxine by the thyroid gland. The appearance of radioactive thyroxine in the blood was much accelerated and its amount increased in the T.S.H.-treated pigs. Conversely,

in hypophysectomized animals comparatively little of the injected radio-iodine is ever incorporated as thyroxine in the gland or found in the blood plasma (Morton *et al.*, 1942).

An excess of thyroid hormone in the body fluids also suppresses iodine uptake nearly completely (Stanley and Astwood, 1949). Such excess may be produced by thyroxine injections or by thyroid feeding. There is firm experimental evidence that such exogenous administration completely inhibits the production of thyrotropic hormone in the anterior pituitary. Thus, McQuillan *et al.* (1948) have injected shorthorn cows with some 800 mg. of thyroxine over a ten-week period and found not only atrophy and a reduced thyroxine content of the thyroid but also that thyrotropic hormone could not be detected in the anterior pituitaries of the treated animals, though it was abundantly present in those of the controls.

It is thus clear that in addition to stimulating tissue metabolism, thyroid hormone has an important chemical action in the cells of the anterior pituitary regulating their production of thyrotropic hormone. This regulating mechanism is brought into play when thyroid hormone synthesis is blocked by one of the antithyroid drugs. The consequent fall in the hormone content of the tissue fluid excites those cells to an increased production of thyrotropic factor, with resulting thyroid hyperplasia.

Harington (1948) has recently raised the exciting possibility of controlling thyrotropic hormone production by administering compounds with a chemical constitution closely similar to that of thyroxine but lacking its peripheral metabolic effect. If a peripherally inert compound could be found having the same effect in the pituitary cells as thyroxine itself, its therapeutic possibilities might be enormous. Lerman and Harington (1948) began preliminary trials of two such compounds, namely tetrabromthyronine and tetrachlorthyronine, which of course differ from thyroxine itself in having bromine and chlorine atoms respectively in place of iodine.

Careful assays in patients with spontaneous myxoedema showed that tetrabrom- and tetrachlorthyronine have, respectively, only one-seventeenth and one two-hundred-and-fiftieth, the calorigenic activity of thyroxine (Lerman and Harington, 1949). Preliminary trial of tetrabromthyronine in a patient with thyrotoxicosis suggested that its thyroid-depressing action more than outweighed its calorigenic effect. In a parallel experimental study, Richards *et al.* (1949) have confirmed that, like thyroxine, both tetrabrom- and tetrachlorthyronine will inhibit goitrogenesis in thiouracil-fed rats by preventing the release of pituitary T.S.H.

The reactions between T.S.H. and its end-organ, the thyroid epithelium, have also been studied in recent years. Trikojus (1939) was one of the first to suggest that the negative results of blood assays for T.S.H. in thyrotoxicosis might be due to the fact that the hormone is fixed or in some way altered by the thyroid gland that it is stimulating. It was subsequently found (Rawson, Graham, and Riddell, 1943) that the thyroid-stimulating effect of an anterior pituitary extract is, in fact, significantly diminished following its exposure to normal thyroid tissue. Non-toxic goitrous tissue exerted no

effect on the activity of T.S.H., but tissue slices from thyrotoxic goitres inactivated about twice as much T.S.H. as equal weights of normal human thyroid tissue. All this rather strengthened the original proposition of Trikojus.

The addition of free iodine to pituitary extract also results in abolition of 90–100 per cent. of its thyrotropic activity (Albert *et al.*, 1946). The free iodine may oxidize some enzyme system in the T.S.H., thus inactivating it. Other oxidizing agents are known to act similarly (Albert *et al.*, 1942–46).

On the other hand, thiouracil or any other of a large series of reducing agents of varying goitrogenic activity, increases the natural potency of anterior pituitary extract. Moreover, when iodinated T.S.H. is treated with these reducing agents, including thiouracil, it largely recovers its original activity (Albert *et al.*, 1947a and b).

Nothing is known of the chemical constitution of T.S.H. except that it is a sulphur-containing protein. It is possible that it contains an oxidation-reduction enzyme system which is inhibited by oxidizing agents including elemental iodine, but potentiated by reducing agents including thiouracil.

Thiouracil administration in rats is followed by thyroid hyperplasia, as indicated by increased mitotic activity, within twenty-four hours (Paschkis *et al.*, 1945). Similarly thiouracil therapy in human thyrotoxicosis is quickly followed by intensification of the thyroid hyperplasia and rapid fall in thyroid iodine content. These changes occur even before the metabolic rate reaches normal and may result from potentiation of existing T.S.H. by the thiouracil; the latter may also reactivate any iodinated T.S.H. present in the gland (Albert *et al.*, 1946).

de Robertis (1941b) found that T.S.H. increases proteolytic activity in the cells and colloid of the thyroid gland. An increased proteolytic activity was also found in glands from thyrotoxic subjects (de Robertis and Nowinski, 1946a and b). But exposure to iodine greatly reduced this high proteolytic activity in the thyroid of T.S.H.-treated rats and thyrotoxic subjects.

It thus seems clear that T.S.H. accelerates and augments the whole chain of reactions leading to secretion of the thyroid hormone into the blood. It facilitates iodine uptake, catalyses the conversion of diiodotyrosine into thyroxine (Morton *et al.*, 1942; Stanley and Astwood, 1949), and increases the oxidase and proteolytic activity in the cells and colloid. Iodine on the other hand varies in its effect according to its concentration; small doses of iodine appear not to inhibit hormone synthesis and secretion and, if the previous iodine concentration were very low, may actually promote them, but large doses of iodine inhibit T.S.H. at its end-organ, the thyroid epithelium, and may compete for the oxidase systems with the hormone precursors, their normal substrates. Hormone synthesis is arrested. In the thyroglobulin compartment also, iodine excess favours colloid synthesis by reducing proteolytic activity and hormone secretion (Junqueira, 1947). It is possible, also, that high concentrations of iodide in the blood depress anterior pituitary secretion and thus counter T.S.H. at its source (McClendon *et al.*, 1948).

Thyrotropic hormone in the blood. One objection to the pituitary theory

of Graves' disease is that the thyrotropic hormone content of the blood has not been shown to be increased (Fellinger, 1936; Hertz and Oastler, 1936; Cope, 1938). But normally the hormone is circulating in such low concentration that, even if the latter were distinctly raised, its detection would probably still be difficult. Chemical methods of detecting it are not available and the far less accurate technique of biological assay must be used. The chief factors involved in such assays are the material to be injected from the patient, the test object to be used, and the criterion of T.S.H. activity to be accepted. Collard, Mills, Rundle and Sharpey-Schafer (1940) carried out assays in which relatively large quantities of blood were freed of iodine by extraction and then injected into the day-old chick, the criterion of activation being an increase in the height of the follicular epithelium. The method appeared to combine the advantages of previous techniques of blood assay for thyrotropic hormone. In other observations in progress at the time, normal human subjects were being injected with thyrotropic hormone, with consequent thyroid enlargement, tachycardia, raised basal metabolic rate and creatinuria (Sharpey-Schafer and Schrire, 1939). In two of these subjects blood samples were taken immediately before the injection of T.S.H. and at one, four, and twelve hours afterwards, yet all the assays from these samples were negative, thus demonstrating that T.S.H. could not be detected in the blood even when it was actually known to be causing a thyrotoxic state. A similar experiment by Robinson (1941) gave the same result.

In spite of its admitted deficiency, however, the technique of Collard *et al.* (1940) did occasionally give positive results especially in patients with recurrent thyrotoxicosis, myxoedema, or severe ophthalmic manifestations.

More recently, de Robertis (1948b), using refined cytological criteria of activation, has succeeded in demonstrating T.S.H. in the blood of normal subjects. Too few patients have been studied for the results to be conclusive, but his data suggest that in classical Graves' disease the T.S.H. titre of the blood is lowered nearly to the vanishing point whereas in patients of the ophthalmic type it is greatly raised. However, the evidence from such blood assays must still be regarded as uncertain and consequently the role of T.S.H. in the pathogenesis of Graves' disease must remain an open question.

At first glance, experimental data point almost irresistibly to the anterior pituitary, if not as the point of origin of Graves' disease, at least as an intermediary link in a disorder, perhaps originating in the hypothalamus or higher nervous centres. Closer study however, has shown that there are important differences between the pathology of pituitary exophthalmos in guinea-pigs and the exophthalmos of classical Graves' disease. Thus, the latter depends on fatty enlargement of the orbital tissues (Rundle and Pochin, 1944). Pituitary exophthalmos, on the other hand, is due to swelling of the orbital tissues from oedema (Pochin, 1944). Further, in Graves' disease, exophthalmos develops gradually over months or years, whereas pituitary exophthalmos comes on acutely within twenty-four hours of the first injection, and begins to subside at the end of ten days, despite continued injections.

The only instances of goitre and hyperthyroidism in which T.S.H. is almost certainly involved are those associated with acromegaly. Hyperpituitarism is too often accompanied by toxic goitre for the association to be coincidental (Cushing and Davidoff, 1927; Davis, 1934). By contrast, in classical Graves' disease there is no evidence of any anatomical or even histological abnormality in the anterior pituitary lobe (Hawking, 1936). Yet from experimental observations (Griesbach and Purves, 1945; Gasche, 1946), it might be expected that such cytological changes would occur if the pituitary theory of causation were valid.

Iodine absorption and excretion. Iodine is absorbed as the iodide with remarkable ease from the alimentary and respiratory tracts, and from the skin. The plasma concentration of iodide is directly proportional to the quantity ingested and the plasma level drops to normal within seventy-two hours of stopping its administration (Nelson *et al.*, 1947).

For over a century iodine has been painted on the skin of the neck for goitre; surprisingly rapid absorption with rise in the blood iodine follows such treatment (Köhler and Jürgens, 1933). Similarly, after a bath in water containing iodine there is a prompt rise in the blood and urinary iodine (von Fellenberg, 1930). The administration of inorganic iodine has no metabolic or other effect, in normal subjects.

As far as oral administration is concerned Cohn, as long ago as 1932, showed that iodine is absorbed and presented to the thyroid gland as the iodide, whether it is given in the elemental form, or combined as the iodate, or iodide.

The active principle of the thyroid is of course readily absorbed in its full potency when whole gland extracts are given by mouth. Similarly up to 90 per cent. of an oral dose of diiodotyrosine passes directly into the blood; large quantities are even excreted unchanged in the urine. Thyroxine also retains its activity when given by mouth.

Excretion of iodine is chiefly in the urine and sweat. Sweat concentration is 35 per cent. of the plasma concentration (Nelson *et al.*, 1947). Similarly, the general iodine intake is reflected fairly accurately in the urinary iodine output. Diiodotyrosine, but not thyroxine, will also pass through the urinary filter (Elmer, 1938).

The role of the liver in the endogenous iodine cycle. The dietary iodine passes freely into the portal blood but the liver does not allow it to pass readily over into the systemic circulation. It is arrested and re-excreted into the duodenum. Normally little iodine is lost in the faeces. There is a constant circulation of exogenous iodine from the intestine to the portal blood and liver, thence back in the bile and the intestine. Small amounts of this circulating iodine spill over into the blood stream whenever the serum iodine tends to fall (Elmer, 1938).

The liver also plays a predominant role in the excretion of thyroid hormone, decomposing part of it in the process. Gross and Le Blond (1947) injected large quantities of radiothyroxine into rats and found that a high proportion of the radioactivity quickly accumulated in the liver and intestines.

Ligature of the common bile duct increased the radioactivity of the liver and blood and sharply lowered that of the faeces.

Gross and Le Blond found that up to 90 per cent. of the radiothyroxine is lost with the faeces after twenty-four hours. It is clear therefore that liver damage in thyrotoxicosis may be of peculiar importance by interfering with the normal decomposition and excretion of the hormone. It is relevant that Kellaway, Hoff and Le Blond (1945) have shown that partial hepatectomy aggravates the toxic effect of thyroxine in the experimental animal.

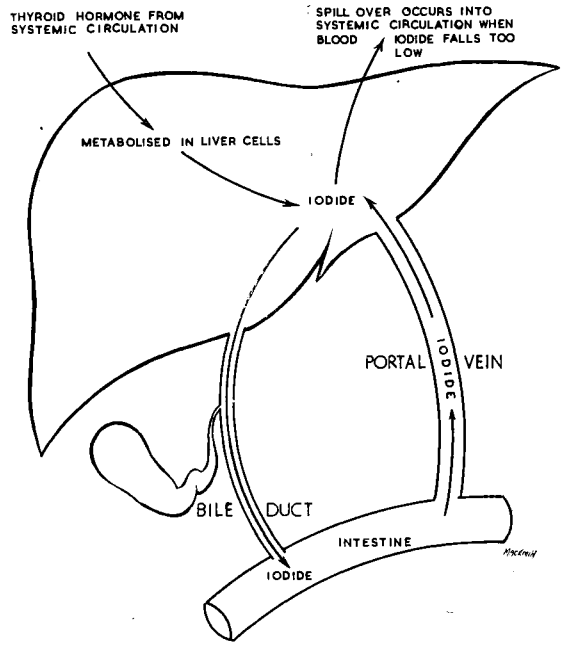

FIG. 18.

The modus operandi of the thyroid hormone. The clearest demonstration of the action of thyroid hormone is provided by injecting thyroxine into a patient with myxoedema. Ten mg. of thyroxine intravenously raises the metabolism about 32 per cent. in from three to ten days and the effect persists for seventy to eighty days (Thompson *et al.*, 1935). No change is observed for twenty-four to forty-eight hours after the injection but by the end of the first week the reaction may be very marked, with pyrexia up to 104° F., aching and tenderness of the muscles, falling of the hair, and peeling of the skin. There is considerable sweating and increased nitrogenous elimination. At the end of the response the body weight is much reduced.

Relapse occurs slowly. Only when the metabolic rate has persisted for many weeks or months at a level of 40 per cent. does the full-blown picture of myxoedema re-develop.

Many remarkable features are revealed in this simple experiment, namely the delay in the action of thyroxine, the extraordinary duration of the effect in spite of its rapid disappearance from the blood stream, and the lack of correspondence between the calorigenic and clinical responses.

The delayed effect is believed by Mansfield (1946) to be due to an indirect path of action; he claims that thyroxine is concentrated in the basal ganglia and passes from them along the peripheral nerves to its site of action in the tissues, in a manner comparable to the toxin of tetanus. But the weight of evidence indicates that thyroid hormone circulates in the body fluids and everywhere exerts its action directly on the cells. Its rate of fixation in the cells is, however, much slower than that of other hormones, *e.g.* adrenaline, and it is possible that injected thyroxine has to be conjugated with a polypeptide before it can produce its characteristic effect.

McIntyre (1931) showed conclusively that total denervation of the dog's heart does not in any way prevent the characteristic tachycardia developing when the animal is subsequently thyroxinized. In fact, the heart rate was practically identical with that in thyroxinized but non-denervated dogs. Her work has since been abundantly confirmed.

The rate of " washout " of the hormone is also very slow. Thus the heart and auricles of rabbits thyroxinized *in vivo*, if isolated and suspended in Ringer's solution, will continue to beat at a much faster rate (25–50 per cent.) than those of normal controls throughout the duration of prolonged experiments (Lewis and McEachern, 1931).

The prolonged interval elapsing between hormone fixation and cell response and the slow rate of " washout " are perhaps evidence that thyroxine has to penetrate the cell and produce great physicochemical changes within its substance. The calorigenic response signifies that the chemical reactions initiated by fixation are in full swing. The further delay before clinical changes are manifest is probably related to the time required for structural alterations to occur in the tissues including the mobilization of the " deposit protein " of myxoedema and elimination of its associated fluid. The mucinous ground substance which supports the tissue cells is much increased in myxoedema. It is the latter, the deposit protein, which is first attacked and mobilized by thyroxine therapy (Byrom, 1934).

The increased heat production following thyroid therapy is but part of the hormone-cell effect. This is convincingly demonstrated by dinitro-o-cresol, which greatly stimulates metabolism. In a case reported by Dodds and Robertson (1933) the dosage of this drug was adjusted so that the basal metabolic rate remained at a level of + 20 to + 30 per cent. Yet the characteristic clinical features of myxoedema persisted unchanged. Subsequently, however, when thyroid extract was given, all the manifestations of myxoedema disappeared with the metabolic rate between 0 and + 10. Barker (1946) has produced evidence that the thyroid hormone may potentiate the

dinitrophenols, but of themselves the latter cannot produce all the effects of thyroid hormone.

Dosage and activity of thyroxine. Thompson *et al.* (1929) calculated that a given dose of thyroxine exerts about seven times as great a calorigenic effect on the patient with myxoedema as on the normal subject. As the heat production approaches normal, increasing doses of thyroxine are required to produce the same effect. Indeed, Riggs, Man and Winkler (1945) found that euthyroid subjects were able to tolerate considerable quantities of thyroid extract without much alteration in either blood iodine or basal metabolic rate, though larger amounts did raise both. Their results agree with the experimental findings of Krogh and Lindberg (1945). The tolerance of euthyroid subjects for thyroid extract probably depends on concomitant inhibition of their own thyroid secretion, the administered extract depressing secretion of T.S.H.

Winkler *et al.* (1945) found that the protein-bound iodine in patients with myxoedema rose by 2·0 γ per cent. for every 1 grain increase in the daily dose of thyroid extract. In terms of iodine content the daily production of hormone by the gland must be roughly equivalent to 3 grains of desiccated thyroid (U.S.P.). The basal metabolic rate responds much more slowly than does the serum iodine.

Thyroid hormone and tissue oxidations. McEachern (1935) believes that the thyroid hormone is concerned with the aerobic side of cellular respiration and that it facilitates the action of catalase. He also found that hyperthyroidism is associated with an increased combustion of all the foodstuffs normally concerned in the metabolism of a given tissue; there is no selective " toxic " destruction of protein, carbohydrate, or fat. Williams and Whittenberger (1947) have fully confirmed McEachern's conclusions.

The ultimate target of thyroid secretion is the peripheral tissues but as Salter and Johnston (1948) remark so much attention has been focused on the neck that we are comparatively ignorant of the fate of the hormone in the tissue cells, how it is incorporated, and what it does. Their precipitation studies confirm that the circulating thyroxine is protein bound. The smaller protein molecules of the plasma are relatively richer in iodine; and as they escape from the plasma into the tissue spaces and lymph, the proportion of iodine increases. In order to effect its peripheral binding, thyroxine may thus be consigned to specific carriers, the smaller protein molecules. Similarly, when the various muscle proteins are fractionated it is found that the iodine bound to them is not uniformly distributed; but the hormone is combined with at least one intra-cellular constituent.

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CHAPTER II

STRUCTURE AND DEVELOPMENT OF THE THYROID GLAND

Comparative anatomy — Embryology — Anatomy — Micro-anatomy

Comparative Anatomy

Nothing comparable to the thyroid gland is found among invertebrates. Its first appearance is in the lowest vertebrates concomitantly with the thalamus and hypothalamus, the pituitary, thymus and adrenals (Fig. 19). At this level too, with notable exceptions, animals become definitely dioecious.

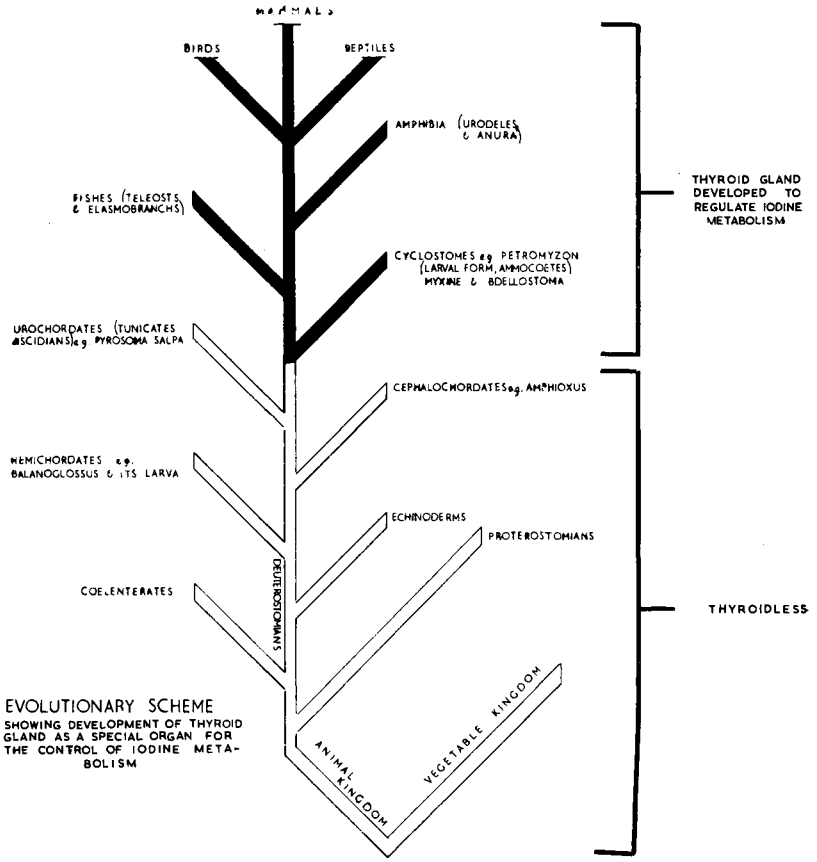


FIG. 19.

In the Tunicata, Amphioxus and Ammocoetes (larval lampreys) there is a ventral pharyngeal groove, the endostyle organ, of which no trace appears in the higher vertebrates, though indications of it occur in the development of the cartilaginous fishes. A. Müller in 1856 described the larval lamprey, Ammocoetes, and followed the changes in it during its metamorphosis into the adult. In 1873 W. Müller drew attention to the resemblances between the product of the endostyle organ of Ammocoetes in the adult lamprey and the thyroid gland of the higher vertebrates. Marine (1913a and b) and more recently Leach (1939) have further elaborated and confirmed Müller's work. They have demonstrated that in Ammocoetes the endostyle organ is the equivalent of two simple endostyles of Amphioxus placed side by side. It is placed in a deep gutter in the ventral pharyngeal region and the cells lining it show greater differentiation than those of the endostyle of Amphioxus. In the former, five types of epithelial cells can be differentiated, some ciliated, others apparently of a secretory type. The latter alone become converted into the cells of the adult thyroid follicles.

The pore by which the gutter communicates with the pharynx narrows and later disappears, and the glandular epithelium of the endostyle proliferates to form a series of closed follicles containing a colloid-like material, thus reproducing in its simplest form the thyroid gland of the higher vertebrates.

In the *cartilaginous fishes* the thyroid, which varies greatly in shape even among individuals of the same species, lies near the anterior end of the ventral aorta. The follicles of which it is composed are massed together, and the cells lining them are of the high cuboidal or columnar type.

In *bony fishes* the thyroid gland consists of widely scattered follicles along the ventral aorta, from the level of the first to the third gill arches. The epithelial cells lining the follicles are cuboidal in shape. Goitrous enlargements of the thyroid occur in some bony fishes. Marine and Lenhart (1910) have described the structure and pathogenesis of these in great detail. No trace of parathyroid glandules has been discovered in the fishes.

Among *newts, salamanders, toads, and frogs*, the thyroid first becomes a paired organ, and parathyroid glandules appear.

In *reptiles*, the unpaired thyroid is situated above the pericardium. The parathyroid glandules are anatomically distinct from the thyroid.

In many *birds* the thyroid does not lie in intimate contact with the trachea, but the two ovoid bodies of which it is composed are closely applied to the internal jugular vein and the carotid artery. The parathyroid glandules are either embedded in the substance of the thyroid gland or are closely apposed to it.

In *mammals* the thyroid gland is either a compact, bilobed organ moulded over the anterior and lateral aspects of the trachea, the lateral lobes being connected by an isthmus, or, if the latter be absent as in certain dogs and the cat, the thyroid consists of a pair of symmetrical organs. In the higher mammals, including the gorilla, its form and structure closely resemble those in man (Grafflin, 1940).

The possible locations of an ectopic thyroid gland in man correspond to its positions in lower forms. When in contact with the pericardium it occupies the same relative position as in the snake. Ectopic nodules around the hyoid and thyroid cartilages correspond to the scattered thyroid tissue around the second and third arches found in certain fishes.

Embryology

The thyroid is one of the first organs to be differentiated in the human embryo. Norris (1916, 1918) has given the fullest description of its embryology, and much of what follows is taken from his paper. As early as the

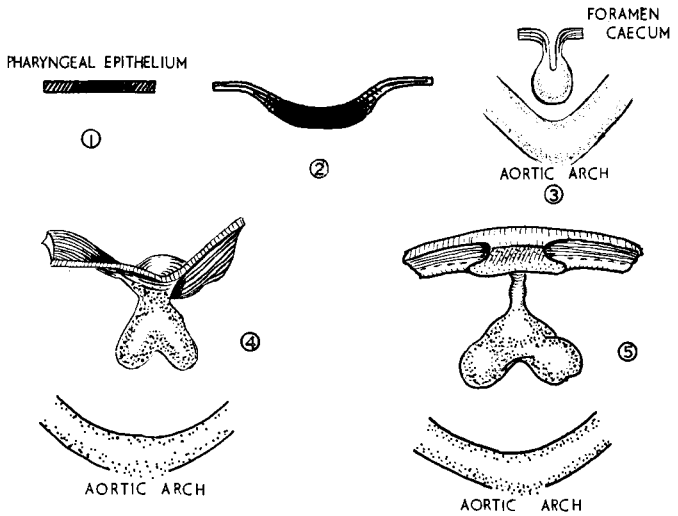


FIG. 20.

third week of foetal life (1·5-mm. embryo) it arises as an epiblast-lined diverticulum from the floor of the pharynx in the region between the first and second pharyngeal grooves. It soon becomes drawn out into a hollow, stalked structure, the end of which becomes globose. The stalk later loses its lumen and becomes solid. The bud then grows laterally on each side, and traces of its bilobed character can be detected in 5-mm. embryos (Fig. 20). The stalk begins to fragment as early as the 6-mm. stage, but vestiges of it can still be found in 15-mm. embryos and sometimes even later. An occasional variation is that the epithelial thickening marking the site of the thyroid anlage at first projects into the pharynx as a distinct tuberculum (Sgalitzer, 1941).

The connexion of the stalk with the pharyngeal floor is lost in 7-mm. embryos, and, as Norris has shown, the stalk may divide either near the pharynx or remote from it. In the former case there is a tendency for a pyramidal lobe to form, or for a thyroglossal duct to persist; in the latter, for lingual thyroid rests and suprahyoid cysts to develop. The pharyngeal end of the original thyroid anlage is indicated by the position of the foramen caecum, but, owing to the changes in the pharyngeal floor determined by the

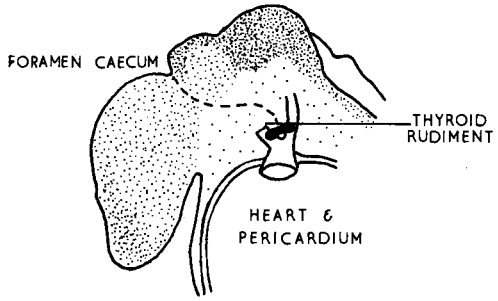
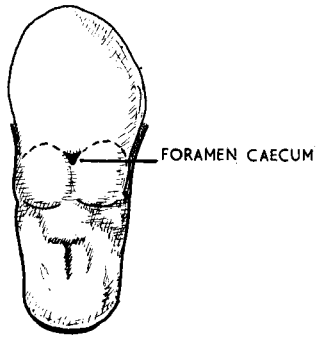


DIAGRAM OF DIFFERENTIATION OF LINGUAL & PRE-VISCERAL PORTIONS OF THYROGLOSSAL DUCT DURING DESCENT OF HEART (FROM FRAZER)



CLOSURE OF FORAMEN CAECUM

FIG. 21.

development of the tongue, the actual site of the original thyroid diverticulum is buried underneath the foramen caecum (Fig. 21).

In addition to this median thyroid anlage, it was formerly usual to describe a lateral anlage derived from the fourth and fifth branchial pouches. This was an erroneous observation, and Grosser recommended that the term " lateral anlage " be dropped. Confusion arose because in the descent of the thyroid, the postero-medial surface of each lateral lobe comes into

intimate contact with the ventral end of the caudal pouch complex consisting of the superior parathyroid from IV and the ultimo-branchial body from V (Fig. 22). The inclusion of the ultimo-branchial body in the lateral lobe is thus purely fortuitous. It later undergoes progressive reticulation and degeneration (Kingsbury, 1935). Gilmour (1938) concludes that the non-parathyroid component of complexes IV and V represents rudimentary thymus. A little may occasionally persist and then thymic tissue is found intimately associated with parathyroid IV. The practical importance of this conclusion is that radical removal of a lingual thyroid must result in hypothyroidism; only

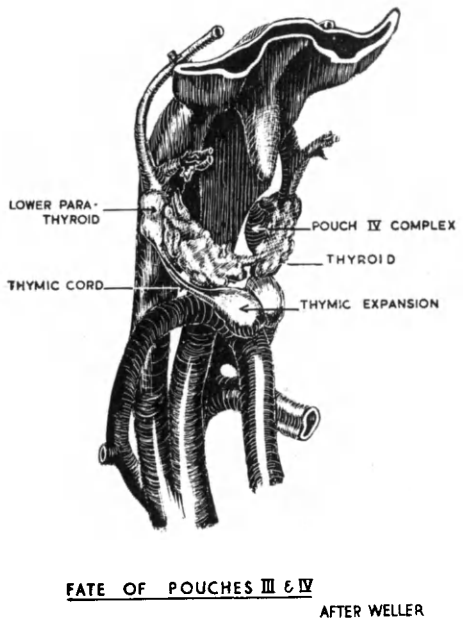


FIG. 22.—On the right side, parathyroid III is being dragged down by its attenuated connexion with the corresponding lobe of the thymus. On the left, parathyroid IV is shown deep to the medial aspect of the lateral lobe.

minimal amounts of such a thyroid should, therefore, be resected (Hartley, 1922).

The formation of thyroid follicles is quite independent of the original lumen of the thyroid anlage, and occurs after its separation from the pharynx and after it has assumed its definitive shape, with lateral lobes and isthmus, and definitive location, on the junction of the developing larynx and trachea (Fig. 23).

At this stage the gland is composed of a number of fenestrated epithelial plates two cells in thickness and arranged longitudinally. From these the first follicles develop at about the 24-mm. embryo stage. The surface of

the plates becomes roughened by irregular scattered hillocks. At these hillocks the cells are growing actively and sections show a circlet of darkly staining nuclei within which is a clear cytoplasmic zone. Centrally a small spherical lumen appears, outlined by a definite cell margin. These primary follicles then bud off secondary follicles in embryos of about 56 mm., though

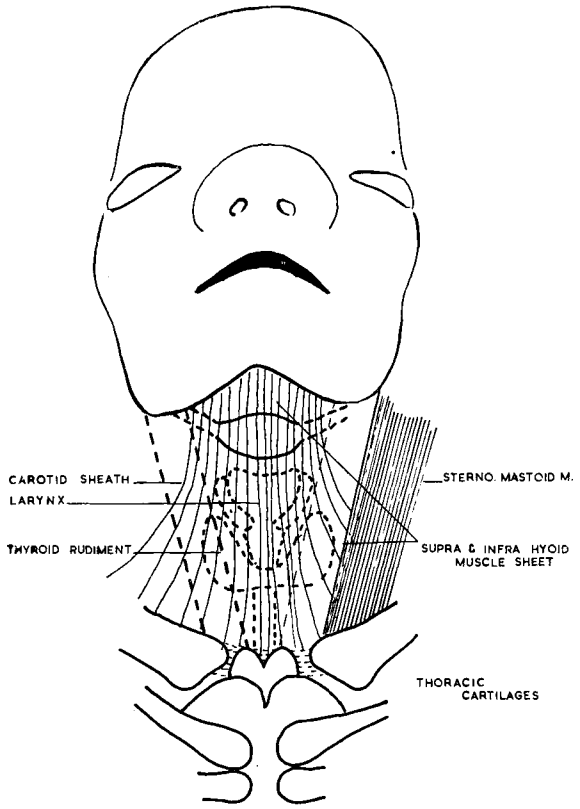


FIG. 23.—Embryo of approximately 19 mm. showing migration of muscle sheets superficial to gland and fixation to thoracic inlet.

primary follicles continue to be differentiated for some time after the secondary follicles first make their appearance; but it is doubtful if primary follicles are ever formed after birth or in the adult thyroid. Norris described three general methods by which new follicles arise in the foetal thyroid:

(1) By development of solid epithelial buds from the follicular wall;

(2) From hollow buds whose cavities are continuous with that of the mother follicle;

(3) By simple division of the parent follicle.

By the time the embryo has grown to 65 mm. the original epithelial plates and bands have been completely broken up into isolated solid or hollow masses, so that any follicle formed after this stage is of the secondary type. From now onwards a rapid increase in the number of follicles occurs until the 158-mm. stage is reached, but there is no great enlargement of the gland, as the later-formed follicles are smaller than the earlier ones. Little new follicle formation occurs subsequently, and any increase in the size of the gland is due to enlargement of the individual follicles.

Although Wolfler and many others have denied that colloid formation takes place until just before or soon after birth, Elkes (1903) was able to demonstrate it in the thyroid gland of a foetus of four months. More recently Chapman *et al.* (1948) have given tracer doses of radio-iodine to pregnant women, twelve to forty-eight hours before therapeutic abortion. No radioactivity was ever detected in foetuses aged seven to twelve weeks, but from fourteen to thirty-two weeks the radio-iodine uptake increased progressively. Parallel histological studies showed that colloid appeared simultaneously with the development of functional activity, as indicated by iodine collection. Hogben and Crew (1923), Rumph and Smith (1926) and others, have also demonstrated that extracts of foetal thyroid exert the characteristic biological effects once the follicles have differentiated and colloid has appeared.

Ablation experiments on amphibian larvae show that the integrity of the pituitary rudiment is essential for the normal development of the thyroid gland (Smith, 1920; Allen, 1929). If the developing anterior pituitary lobe is removed, thyroid size is reduced to about one-sixth of the normal. Both thyroid and pituitary are necessary for metamorphosis and proper bodily development.

Gross Anatomy

The thyroid gland or body is the largest endocrine gland. It consists of two lateral lobes and an isthmus uniting them across the front of the trachea.

Size. This varies so much with the race, age, sex, and physiological state of the individual, that it is impossible to do more than quote approximate figures.

Measurements of the thyroid gland (Great Britain):

Vertical diameter	6–8 cm.
Antero-posterior diameter	2–3 ,,
Transverse diameter	5–8 ,,
Vertical diameter (isthmus)	1–2 ,,
Antero-posterior diameter (isthmus)	0·5 ,,

Weight. In the adult male this varies from 20 to 60 gm., with an average of 25 gm. In women the gland is rather heavier. The average weight of the thyroid among the inhabitants of inland districts is greater than in those

living near the coast (Fig. 24). Marine (1922) estimates that the thyroid should not exceed 0·35 gm. per kilogram of body weight.

Situation. The gland lies beneath the deep cervical fascia and the infrahyoid muscles at approximately the junction of the upper two-thirds and lower third of the neck. It is situated in front of the larynx and trachea, to both of which it is moulded.

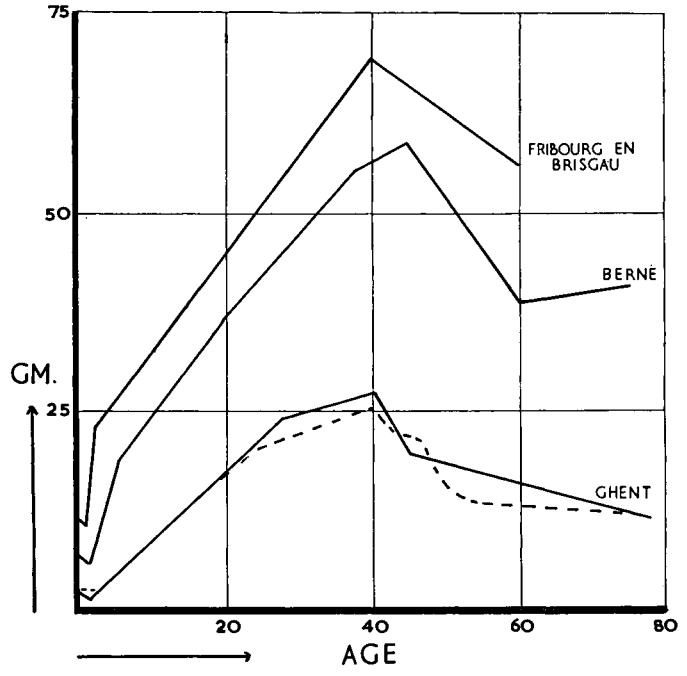


FIG. 24.—Variation in weight of thyroid gland with age. (Ghent is in maritime Belgium, Fribourg and Berne are, of course, alpine.)

Methods of Fixation. These are four in number:

(1) Connexions between the true capsule and the false or surgical capsule.
(2) Certain thickenings of the false capsule, the thyroid ligaments.
(3) The fascial sheaths of the entering vessels.
(4) Connexions between the trachea and larynx and the gland.

(1) The fibrous strands which run between the false or surgical capsule and the true capsule, which invests it so closely, provide the main support to the gland, though individually they are delicate and inconspicuous. In

goitrous glands these fibrous strands may be both coarse and vascular, especially after iodine therapy in thyrotoxicosis (Rienhoff, 1926).

The False or Surgical Capsule of the Thyroid Gland. This important structure is derived from the pretracheal fascia, one layer of which passes

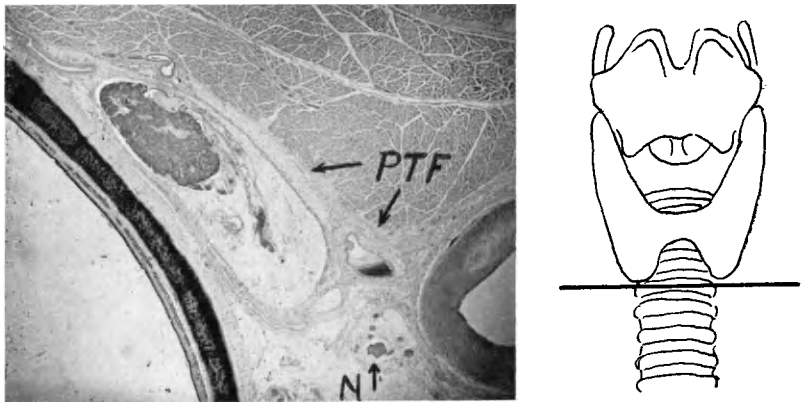


FIG. 25—Section below the lower pole of the lateral lobes. The pre-tracheal fascia (P.T.F.) has split to form the "thyroid space"; the veins and a parathyroid glandule are enclosed within this. The recurrent laryngeal nerve is indicated. (× 7.)

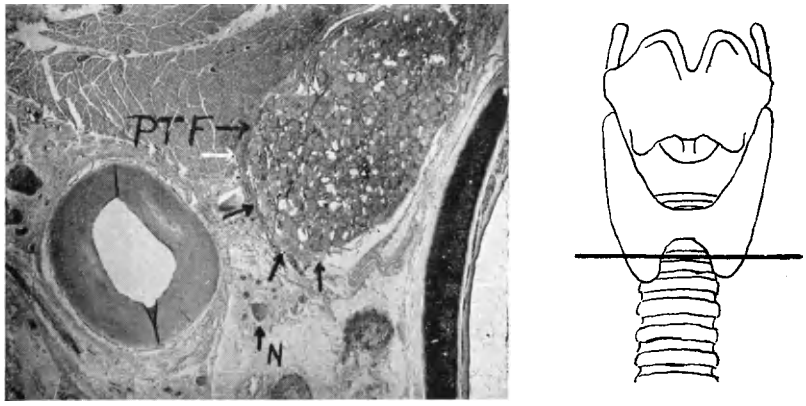


FIG. 26—Transverse section below the isthmus. The pre-tracheal fascia (P.T.F.) is shown surrounding the lateral lobe and the recurrent laryngeal nerve (N.) is indicated. (× 7.)

in front of the gland and the other behind it. The typical arrangement is most clearly seen in cross-sections of the neck (Figs. 25–28). The pretracheal fascia splits to enclose the lateral lobe. Thorek (1949) emphasizes that it is widely adherent to the lateral surface of each lobe through the middle thyroid

vein and its branches. Hence division of these vessels in operations for goitre facilitates access to the posterior part of the perithyroid " space ". On the inner side the two layers fuse again and run over the front of the trachea.

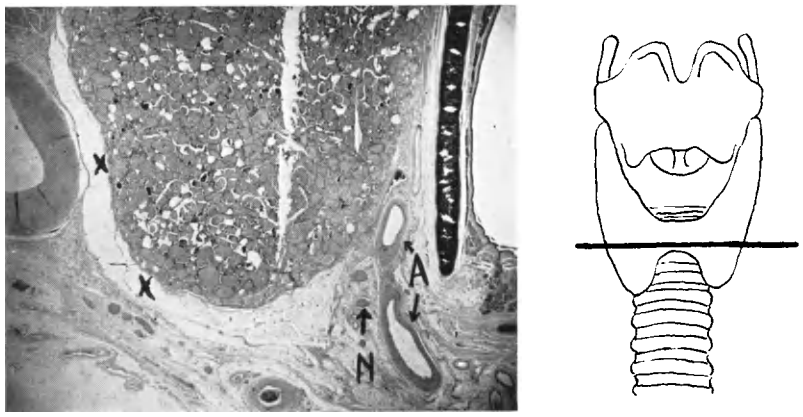


FIG. 27.—A transverse section of the neck at the level of the isthmus of the thyroid. X indicates the space in which the surgeon must work in dislocating the lateral lobe. The branches of the recurrent laryngeal nerves are indicated (N). Note the danger to which they will be exposed by clamping the inferior thyroid artery (A) near the gland. (× 7.)

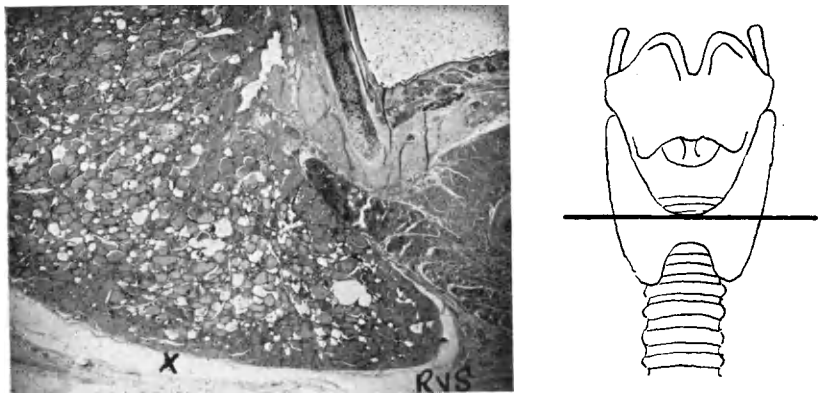


FIG. 28.—The same at a higher level, showing the extension backwards of the posterior border of the lateral lobe into the " retro-visceral space " (R.V.S.) (× 7.)

On the outer side they re-unite and become continuous with the carotid sheath. The recurrent nerve lies behind this ensheathing fascia. The false capsule is not of uniform thickness, nor is it quite a complete envelope for the gland. It is strong and thick above and laterally, but below it is thin and

imperfect, so that it offers little resistance to extension of the gland downwards.

The *true capsule* is, in the normal gland, thin and translucent, though it is slightly thickened where it sends septa between the parenchymatous masses. It is impossible to detach the true capsule without injury to the underlying gland tissue.

(2) The *Ligaments of the Thyroid Gland.* These are three in number and are nothing but thickenings of the false capsule in certain situations.

(*a*) The *anterior or median ligament*, which arises from the deep surface and upper border of the isthmus and adjacent parts of the lateral lobes, is attached above to (i) the anterior surface of the cricoid cartilage between the cricothyroid muscles; (ii) the aponeurosis covering the cricothyroid muscles; (iii) the inferior border of the thyroid cartilage. The ligament is well defined and strong in the centre, but weak laterally.

(*b*) The *lateral ligaments*, one on each side, pass from the sides of the cricoid cartilage and the upper three tracheal rings to the postero-internal surfaces of the lateral lobes.

The lateral ligaments so constituted lie in a plane nearer the posterior than the anterior surface of the trachea. They are the chief factors in maintaining the gland in position, indeed Berry (1887) gave the name " suspensory ligament " to that part arising from the side of the cricoid cartilage. The mode of insertion of this lateral ligament into the thyroid lobe is interesting. It blends with the true capsule and sends radiating septa into the substance of the lateral lobe. Through, and immediately behind, this ligament run branches of the ascending and inferior terminals of the inferior thyroid artery. They pass into the gland substance along the septa and also penetrate the trachea to anastomose with the intratracheal system. The recurrent nerve and its branches also run through the posterior part of the ligament presenting an intimate relationship to the branches of the inferior thyroid artery and to the parathyroid glandules (Figs. 29, 30).

It should be emphasized that the lateral ligament is inserted into the intermediate part of the postero-internal surface of the gland; the medial aspect of the upper and lower pole receives none of its fibres. Thus if the lateral part of the superior ligament and the superior thyroid vessels are divided, the whole of the upper pole is easily separated as far down as the cricoid. After ligation of the inferior veins, the lower pole can be similarly drawn away from the side of the trachea.

(*c*) A *suspensory ligament*, running from the tip of the pyramidal process, or, should this be absent, from the upper border of the isthmus to the hyoid bone, has been described. It is merely a vestigial structure, a remnant of the thyroglossal duct, and has little suspensory function.

(3) *Fascial Tissue Around the Vessels.* The superior thyroid artery and vein have a considerable amount of strong fibrous tissue about them as they reach the upper pole of the gland, and this passes on with the vessels into the thyroid, acting as an accessory ligament. Similarly, the inferior thyroid artery carries with it into the gland supporting connective tissue which has

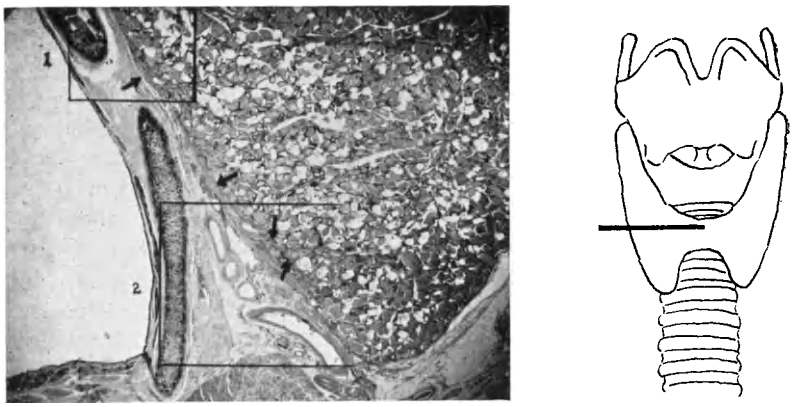


FIG. 29.—Section at the level of the isthmus. The branches of the inferior thyroid artery and the recurrent laryngeal nerve are shown traversing the connective tissue between the postero-medial surface of the gland and the lateral aspect of the trachea and oesophagus. The pre-tracheal fascia which here forms the lateral ligament of the thyroid is shown fusing with the tunica adventitia of the trachea. (× 7.)

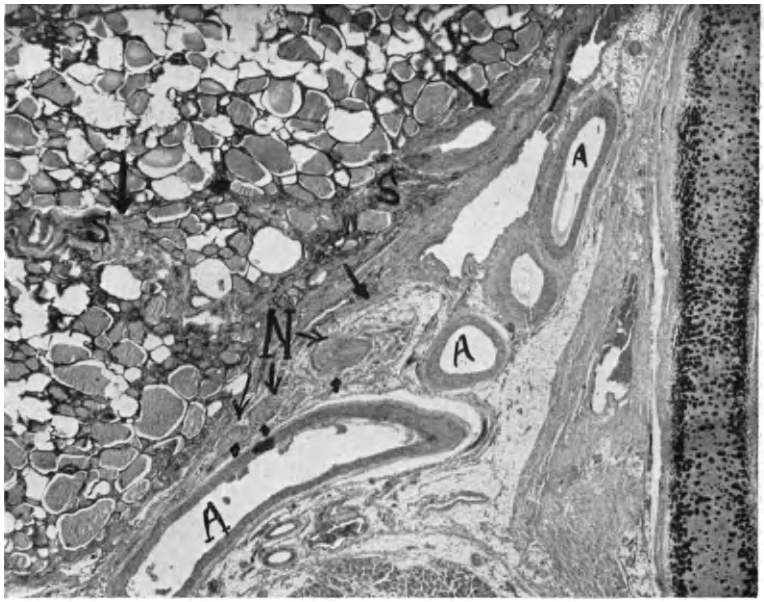


FIG. 30.—High power view of area (2) in the first section. Note the intimate relationship between the branches of the recurrent nerve (N) and the inferior thyroid artery (A). Note that branches of the latter pass into the gland along fibrous tissue septa (S). (× 12.)

considerable strength. Very little support to the gland is given by the fascial sheaths of the middle thyroid veins, but around the inferior venous plexus the fascial tissue is stronger than at the superior pole and has a correspondingly greater supporting value.

General structure and relations. From the front the gland has roughly an H-shape, each lateral lobe representing a vertical, and the isthmus the transverse element of the letter, but the lateral lobes in fact converge below, and the isthmus lies considerably nearer the lower than the upper poles of the gland. In transverse section the gland is seen to have a strongly convex anterior surface and a deep concavity posteriorly where it rests on the larynx and trachea. Frequently the general shape of the gland approaches that of a thick and rather clumsy-looking horseshoe, as the lower border of the isthmus may merge with that of the lateral lobes, no definite demarcation between them being visible.

The gland is described as having two *lateral lobes*, an *isthmus* and a *pyramidal lobe*.

The lateral lobes lie on the right and left of the trachea and larynx. Each resembles a three-sided pyramid, with its blunt apex, the superior pole above, and its rounded base pointing downwards and somewhat inwards. The lower extremity or pole reaches to within 2 cm. of the suprasternal notch, where it is at the level of the sixth tracheal ring. The lower pole here comes into close relation with the inferior thyroid plexus of veins.

The *apex*, or *superior pole*, is directed upwards and backwards; it is blunt and rounded, and reaches the posterior border of the thyroid cartilage at the level of the junction of its lower and middle thirds. Surrounding the superior pole is the superior plexus of veins, and the superior thyroid artery enters it on its antero-internal surface a little below its extremity.

Each lateral lobe has an *external*, an *internal*, and a *posterior* surface. These surfaces, however, are not sharply demarcated except in certain parts.

The *external* surface is convex and covered by the following muscles: the sternothyroid, the sternohyoid, the anterior belly of the omohyoid, and the sternomastoid, with their associated fasciae. More superficially are the deep cervical fascia, the platysma, subcutaneous fat, and skin.

The *internal* surface is moulded on the sides of the larynx and trachea. It lies in contact with the oesophagus, especially on the left side, and with the lower part of the pharyngeal wall.

The *posterior* surface lies in contact with, and is grooved by, the carotid sheath and its contents.

The *borders* of the lateral lobe are anterior, postero-external, and postero-internal. The *anterior border* is distinct and passes from above downwards, forwards, and inwards, blending with the upper margin of the isthmus, and is continuous with that of the opposite lateral lobe to form the superior notch. It comes into contact with the wing of the thyroid cartilage, the cricothyroid muscle, and the cricoid cartilage. The cricothyroid branch of the superior thyroid artery and, with it, the external branch of the superior laryngeal nerve lie in close relation with the anterior border of the lateral

lobe. The *postero-external* border, generally ill-defined, lies on the internal jugular vein. The *postero-internal* border is rounded, and lies between the common carotid artery on the outer side and the larynx and trachea on the inner side. It is this border which is associated with the oesophageal and laryngeal walls, particularly on the left side. The relationships between this border, the inferior thyroid artery, and the recurrent laryngeal nerves are important, and will be described in detail later.

The *isthmus* is very variable in both size and shape. In extreme cases its height may be nearly as great as the vertical limits of the lateral lobes, or it may be reduced to a narrow band or be absent. Gruber (1876) stated that it is missing in 5 per cent. of cases, Marshall (1895) in 10 per cent.; but operative experience with goitrous glands would suggest that both these figures are too high. Absence of the isthmus may be associated with:

(1) Two separate lateral lobes, such as are commonly found in many birds and other vertebrates; or

(2) A single lateral lobe, the other being atrophic or absent.

The isthmus is continuous on each side with the lateral lobes, and in proportion as the latter tend to envelop the trachea the transverse diameter of the isthmus is reduced, so that in extreme cases it may be represented merely by a groove where the lateral lobes come into contact. As a rule, the isthmus covers the second, third, and fourth rings of the trachea, but it often extends higher and comes into contact with the lower border of the cricoid cartilage, or it may be displaced downwards and leave a wide gap below that structure. The lower border of the isthmus is usually concave, and reaches to within 2 to 3 cm. of the suprasternal notch, but not uncommonly the concavity is absent or is replaced by a slight downward convexity continuous with that of the lateral lobes.

Pyramidal lobe. Connected with the upper border of the isthmus is a narrow, elongated process, its base below and its apex above. It runs up towards the hyoid bone, and is called the *pyramid of Lalouette*. It is flattened or strap-like antero-posteriorly. It ends above at the level of the larynx, the thyrohyoid membrane, or the hyoid itself. Its apex may be attached to the lower border of the hyoid bone, or to its posterior surface, but never to its anterior surface. The pyramid is very variable in size and development. It arises from the middle of the upper border of the isthmus, or, more commonly, to one side of the middle line, especially the left; or it may spring from the junction of the isthmus and the lateral lobe, or from the latter itself. It may be short or may reach the hyoid bone above, and it may be triangular, cylindrical, or ovoid in shape. Occasionally it is duplicated, one part lying on each side of the middle line, and in rare cases it has an inverted **Y** shape. Zoja (1878) found it in 75·5 per cent. of cases and more recently Beilby and McClintock (1935) identified it in 92·8 per cent. of dissected thyroids and at 85 per cent. of operations for goitre. In some few cases the pyramid has been found entirely cut off below from the main body of the thyroid, in others broken up into a beaded structure.

The pyramid has exactly the same histological structure as the rest of the gland. Covering its surface is a layer of fibrous tissue, which has to be remembered, as it is not easily stripped off in attempting to isolate the pyramid during operations. Muscle fibres may be found adherent to the pyramid and have been given the name *levator glandulae thyroideae of Soemmerring* but the expression is a misnomer, as they have nothing to do with the thyroid gland, and are merely aberrant fibres derived from the infrahyoid muscles covering the pyramid.

Blood Supply

The gland is very well supplied with blood, and it has been stated that bulk for bulk it receives five times as much blood as the kidney. Tschuewsky (1903) estimated that the whole of the blood of the dog passes through the gland sixteen times a day.

Thyroid arteries. There are four main arteries:

(1) The superior thyroid artery (paired);
(2) The inferior thyroid artery (paired),

and occasionally a fifth, the thyroidea ima. Besides these there are numerous unnamed arteries, small in size under normal conditions, but capable of great enlargement in goitrous conditions of the gland. They come chiefly from the pharyngeal, oesophageal, and tracheal arteries.

(1) *The Superior Thyroid Artery.* This usually arises from the external carotid trunk as its first branch, though in exceptional cases it may take origin from the trunk of the common carotid, or from its bifurcation in common with the lingual or the facial artery (Quain, 1844; Henschen, 1927). Rogers (1929) in commenting on the downward curving course of the superior thyroid arteries emphasizes that it shows they play an early part in the vascularization of the caudally-migrating thyroid anlage.

The artery reaches the gland just below and internal to the apex of the upper pole, which its branches embrace. They are (*a*) the antero-internal, which continues in the general direction of the main vessel, following the anterior border of the lateral lobe and anastomosing with the corresponding artery of the opposite side at the upper border of the isthmus; (*b*) the antero-external, which courses over the outer surface of the lateral lobe; and (*c*) the posterior, which descends along the postero-internal surface of the lateral lobe, lying between it and the trachea. It has a constant branch which communicates with the superior branch of the inferior thyroid artery. Rogers (1926) has emphasized that the posterior branch may arise from the main trunk at some little distance above the upper pole and may therefore not be included in a low ligature.

The cricothyroid artery, which lies on the cricothyroid membrane and supplies the pyramidal lobe, may originate from the superior thyroid trunk or from the superior laryngeal artery. It gives off muscular branches to the cricothyroid, sternohyoid, sternothyroid and the thyrohyoid muscles respectively. Those to the sternothyroid and sternohyoid are fairly constant

and may need to be controlled during the separation of the muscles from the gland during operations on the latter. That to the sternohyoid is particularly definite and, turning down in the substance of the muscle, it may require special treatment when the muscle is divided at operation (Rogers, 1921). Variations in the size of the superior thyroid artery occur, but it is very rarely absent altogether (Adachi, 1928). In exceptional cases it may pass directly to the isthmus.

(2) *The Inferior Thyroid Artery.* This arises from the thyroid axis, a branch of the subclavian artery, though it has exceptionally been found to come from the common carotid, the subclavian trunk, the innominate, the transverse cervical, the suprascapular, the vertebral, the internal mammary, or the aorta itself. Henschen states that both inferior arteries may arise together from the subclavian or the common carotid.

The artery passes upwards, deep to the carotid sheath and behind, or less often in front of, the trunk or the middle cervical ganglion of the sympathetic, gives off the ascending cervical branch, and then after a short course bends downwards rather abruptly, leaving the common carotid artery. It continues in a downward and inward direction on the longus colli until it meets the false or surgical capsule of the thyroid at or near the junction of the upper two-thirds and lower third of its posterior border. It pierces the false capsule at this point, and almost at once breaks up into its main branches, four to six in number. It should be emphasized that the inferior artery approaches its corresponding lobe from the lateral, not from the inferior aspect.

Two important and almost constant branches are (*a*) the *ascending*, which passes upwards to anastomose with the superior thyroid artery (posterior branch), and (*b*) the *descending*, which runs along the inferior border of the gland to meet its fellow of the opposite side. The main trunk sometimes bifurcates fully an inch and one-half away from the gland at the point where it emerges from behind the carotid sheath (Crile and Shiveley, 1941). In addition to its thyroid and parathyroid branches, the inferior thyroid artery gives off small branches to the oesophagus, trachea, and neighbouring muscles, and a fine twig which accompanies the recurrent laryngeal nerve.

Von Eiselsberg (1901) believes that in goitrous conditions the inferior artery is larger than the superior, which accords with my own clinical experience. Mastin (1923) measured the lumina of the main thyroid arteries and found that the inferior exceeded the superior by a third, a difference which, in the case of large goitres, is very greatly exceeded. The inferior thyroid artery may be absent on one or on both sides, or it may be duplicated throughout its course. Adachi reports its absence five times on the left and twelve times on the right in 286 dissections (143 bodies).

The thyroidea ima artery of Neubauer (first described by Nicolai in 1725). Usually single, this artery may be paired and is the least constant of the thyroid arteries. Wangensteen (1929) found two examples in seventeen dissections, both of them on the right side. Gruber (1872), who studied

twenty-three subjects in which the artery existed, found that it was right-sided in twenty-two, and left-sided in only one; in two of the subjects in which this artery was present the inferior thyroid was missing. The thyroidea ima may arise from the innominate artery, the aortic arch, the internal mammary, right or left common carotid, right subclavian, right thyroid axis, or right transverse cervical artery. It passes upwards to the lower border of the isthmus, where it breaks up into several branches, which are distributed over its surface, and which communicate with the branches of the inferior thyroid and with the internal branch of the superior thyroid. We have seen the thyroidea ima equal in size to the main trunk of the superior thyroid artery.

Blood supply of the parathyroid glandules. The superior parathyroid (parathyroid IV) receives its main blood supply from the anastomotic branch uniting the superior and inferior thyroid arteries. The small branch from this communication may be only a few millimetres in length, though it is usually longer. Occasionally the main artery to the superior parathyroid comes from the inferior thyroid artery or from one of its principal branches.

The inferior parathyroid (parathyroid III) is supplied by a small artery from the lower branch of the inferior thyroid artery or, exceptionally, from the main stem.

Anastomotic system of the thyroid arteries. Beneath the true capsule of the gland there is a rich arterial anastomosis, and the arteries of the two sides communicate freely at the upper and lower borders of the isthmus, as Sobotta (1915) emphasizes. Some doubt has been expressed as to the existence of free arterial anastomoses in the deeper parts of the gland; Major (1909) could find no evidence of any such anastomoses, but does not go so far as to deny their existence. However, Mastin (1923) and Kurkowsky (1930) have since convincingly demonstrated by injection methods that they not only exist but are rich and free. Kurkowsky also showed that even after ligation of the four main arteries in the experimental animal, opaque medium injected into the aorta passes freely into the intra-glandular circulation.

Thyroid veins. These commence as a perifollicular plexus, and follow the smaller arteries as far as the periphery of the gland, where a conspicuous venous plexus is developed which covers the whole gland, lying just beneath the true capsule. The main venous trunks arise from this plexus, and although very variable—far more so than the arteries—they can be divided into three main groups:

(1) Superior;
(2) Lateral, or middle; and
(3) Inferior.

The thyroid veins are usually stated to be devoid of valves but Modell (1933) has shown this to be untrue.

(1) The *superior* thyroid veins arise in the upper part of the gland and leave it at or near the superior pole, close to, but not necessarily in contact with, the artery. They run upwards and outwards, cross the carotid artery, and join the internal jugular, the common facio-lingual trunk, or the lingual vein.

These veins communicate by a superior transverse communicating vein, which passes along the upper border of the isthmus. The anterior jugular vein and this superior communicating vein, as Kocher (1883) first pointed out, are connected.

(2) The *lateral*, or *middle*, thyroid veins are especially variable. They arise from the outer surface of the lateral lobes and pass to the anterior surface of the internal jugular vein. They may be entirely absent, but it is more usual to find one or two on each side, though there may be as many as three or four. They may be short and pass out from the postero-lateral surface of the gland, but when they leave its anterior surface they are comparatively long and lie in intimate contact with the deep surface of the false or surgical capsule. If the middle thyroid veins are of the latter type they tend to tether the gland in place, and special care is needed to avoid damage to them during surgical operations.

(3) The *inferior* thyroid veins are rarely single, but usually form a large plexus of vessels running downwards and slightly outwards towards the sides of the trachea, communicating with the venous plexus surrounding that structure. They emerge above from the inferior borders of the isthmus and lateral lobes, and empty below into the innominate veins.

The more lateral veins of the inferior group may empty into the internal jugular vein, and in rare cases a vein on the right side passes into the superior vena cava. The fascia which surrounds the inferior thyroid plexus is often so dense and tough that isolation of an individual trunk in surgical operations is not always easy. When a thyroidea ima artery is present there is always an accompanying vein.

Lymphatics. Rienhoff (1931) describes an intra-glandular plexus consisting of bursellae and lymph capillaries. The former vary in size from small endothelial sacs forming knob-like enlargements at the junction of two or more lymphatic vessels to broad sheet-like structures which may partly embrace a group of follicles. Like lymphatic spaces elsewhere, these bursellae are blind or caecal-ended. They do not communicate directly with the follicle lumen. The lymphatic plexus lies outside the perifollicular blood capillary network. It is probably of altogether secondary importance in ferrying away the secretory products. Free anastomosis occurs between adjacent lymphatic capillaries and between those of the two lobes via isthmic channels.

The smaller intraglandular lymphatics unite to form a coarser network, which lies in the trabeculae between the masses of follicles in association with the walls of the arteries; here it may be called an interstitial plexus. They pass towards the surface of the gland and form under the capsule a close-meshed anastomosis which envelops the whole gland—the *perithyroid lymphatic plexus*. This again is placed externally to the superficial vascular plexus. Bartels (1901) states that while the lymphatic communication between this plexus on the two sides of the body is very free in animals, it is not conspicuously so in man.

The main lymphatic vessels leave the gland in (1) an *ascending*, and (2) a

descending group. Both these are further divided into *median* and *lateral* sub-groups.

(1) *Ascending Lymphatics*. (a) The *median*, two or three in number, arise from the upper border of the isthmus and the inner border of the lateral lobe, and drain into one or two glands situated on the front of the larynx in relationship with the cricothyroid muscle.

(*b*) The *lateral* group, six or eight in number, correspond to the superior thyroid artery. They arise from the upper pole and empty into—

(i) the gland lying between the jugular vein and the common carotid artery at the level of the upper border of the thyroid cartilage; and

(ii) the deep cervical glands lying along the internal jugular vein.

(2) *Descending Lymphatics*. (*a*) The *median* arise from the lower border of the isthmus and run downwards towards the thoracic inlet, ending in a number of glands lying in front of the trachea and above the thymus gland. These *pretracheal* glands are in series with the retrosternal glands, particularly with one group, described by Bartels, placed behind the right sterno-clavicular joint in the angle between the two innominate veins. From this group several efferent vessels pass from right to left along the left innominate vein to empty into the thoracic duct near its termination.

(*b*) The *lateral* group arise from the base and posterior surface of the lateral lobe and run downwards and outwards, some in front of and others behind the carotid sheath, and empty into the lower deep cervical glands. One of these lateral vessels, according to Mahorner *et al.* (1927), after crossing the carotid sheath runs downwards and empties directly into the subclavian vein near its junction with the internal jugular, without the intervention of a lymphatic gland.

These authors as well as Rienhoff (1931) and Chouke *et al.* (1932) were unable to trace any direct, and very little indirect, lymphatic connexion between the thyroid and thymus. In the cat a comparatively great number of the thyroid lymphatics may drain directly into the veins without first traversing lymph nodes (Ramsay and Bennett, 1943). Undoubtedly this may also occasionally happen in man.

Thyroid nerves. (i) Sympathetic. Postganglionic non-medullated nerve fibres emerge from all three ganglia of the cervical sympathetic trunk, and pass into the substance of the thyroid gland in plexuses surrounding the superior and inferior thyroid arteries, chiefly the latter (Bölönyi, 1948).

(ii) Parasympathetic. The superior and recurrent laryngeal branches of the vagus supply branches to the gland. That from the former is a minute twig given off after the external laryngeal branch to the cricothyroid muscle, or from the latter branch itself (Dilworth, 1921). The recurrent laryngeal nerve gives one or more twigs at the level of the second and third tracheal rings, which are distributed to the stroma of the lower third of the gland (Bölönyi, 1948).

There is no firm evidence that these autonomic nerve fibrils end on the follicle wall, or that they possess any true secreto-motor function. They are solely concerned with the constriction and dilatation of the thyroid

vascular bed. Nonidez (1931a–37) has studied the problem closely in the dog. He has demonstrated ganglion cells in the inter-follicular stroma and round these, end the myelinated fibres of the vagus. Post-ganglionic fibres then pass on to the intra-glandular vessels in great profusion to join with those from the sympathetic system in the supply of their plain musculature. In addition there are medullated afferent nerves, whose terminals lie in the capillary endothelium and are sensitive to chemical changes in the blood and are thus able to effect local circulatory adjustments. Nonidez's general conclusions have been confirmed by Rossi and Lanti (1935).

Electrical stimulation of the sympathetic nerves running to the gland does not change its rate of secretion (Hicks, 1926; Hektoen *et al.*, 1927). Nor does prolonged stimulation of the parasympathetic supply alter the histological appearance of the corresponding lobe (Ross and Moorhouse, 1937). Such stimulation does, however, effect changes in the calibre of the thyroid blood vessels.

Surgical anatomy of the laryngeal nerves. (i) *Recurrent laryngeal nerve.* This is directly involved in certain diseases of the thyroid gland. If large, and especially if nodular, the goitre may also displace the nerve, and thus predispose to its injury during thyroidectomy. A precise knowledge of its anatomy and relationship to the thyroid gland, the inferior thyroid artery, and the inferior parathyroid is essential.

There is a slight difference in the topography of the nerve on the two sides of the neck. Jaboulay and Villard (1893) described the nerve on the right as lying in a rather more anterior plane than that on the left. Its relationship to the inferior thyroid artery and its branches has been studied in great detail by Reed (1943) in over 500 dissections, his observations confirming

TABLE I

THIS SHOWS RELATIONSHIP OF RECURRENT LARYNGEAL NERVE TO THE INFERIOR ARTERY AND ITS BRANCHES (MODIFIED FROM REED, 1943).

TYPES	Right Side		Left Side		Both Sides
	Absolute number	Per Cent.	Absolute number	Per Cent.	Per Cent.
Nerve anterior to the artery or its branches	65	25·7	29	11·5	18·6
Nerve posterior to the artery or its branches	68	26·9	130	51·4	39·1
Nerve anterior to one half and posterior to one half of the branches of the artery ..	56	22·1	55	21·7	21·9
Relations of the nerve to the artery alike on the two sides	—	—	—	—	Per Cent. 17·0

the earlier work of Fowler and Hanson (1929) and Berlin (1935). Reed found twenty-eight different types of anatomical relationship between the nerve and artery, or its branches. The frequency of the principal relationships is shown in Table I. It will be seen that the nerve usually lies posterior to the artery or its branches, or runs through them. Its precise position on the two sides is rarely the same (Fig. 31). Berlin (1935) emphasizes that on the right the nerve is rather farther away (up to 1 cm. or more) from the trachea,

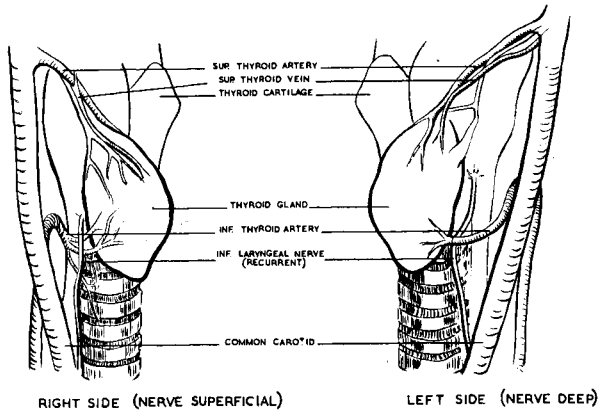


FIG. 31.—Differing relationship of the inferior artery and recurrent nerve on the two sides. (Reed, 1943).

than on the left. He describes three main distributions of the nerve at the mid-thyroid level.

(1) In 65 per cent. of cases it lies posteriorly in the tracheo-oesophageal groove.

(2) In 25 per cent. it traverses the lateral ligament or " adherent zone ", being then concealed beneath a stratum of fascia, when the lobe is turned medially.

(3) In 10 per cent. it is partially embedded in the gland.

It is at the mid-thyroid level that damage to the nerve is most likely to occur during thyroidectomy. It is also in hazard if the upper end of the thyroid stump be pulled forwards with the haemostats and a sizable mass of tissue be included in a ligature (Luchetti, 1944). At the level of the lower pole of the gland it is 1–2 cm. from the side of the trachea on the right, but much closer on the left.

Contrary to the usual impression, the nerve is of considerable thickness, and can be felt through the posterior layer of the false capsule as a cord passing obliquely upwards and inwards to its position behind the artery, or it can be palpated against the side of the trachea. Lahey (1944) begins by clearing the inferior thyroid artery. The nerve can usually be seen running posteriorly during this procedure. If not, the artery can be divided

and the inner end lifted upwards and the nerve sought further. Bachhuber's technique (1943) is similar. The recurrent nerve finally dips under the lower edge of the inferior constrictor muscle of the pharynx, just posterior to the cartilaginous prominence of the inferior cricothyroid articulation. Berlin (1935) mentions this as a valuable landmark.

If the nerve cannot be found in its normal position, it should be sought at the level of the upper pole of the thyroid gland for when the right subclavian artery arises as the last branch of the aortic arch and runs to the right behind the trachea and oesophagus, the nerve on the right side is not *recurrent* but passes directly from the carotid sheath to the larynx, at a level between the superior pole and middle thyroid veins. Work (1941) gives a valuable discussion of the embryological basis of this abnormality.

The recurrent nerve frequently divides extralaryngeally, Weeks and Hinton (1942) observing this in 78 per cent. of their dissections. The division usually occurs behind the lower or middle thirds of the lateral lobe and the inclusion of but one of the subdivisions in the surgeon's ligature may account for the substantial measure of functional recovery that may occur in some patients with a recurrent nerve injury.

(ii) *Superior laryngeal nerve.* This ends on the pharyngeal wall deep to the carotid sheath by dividing into internal and external laryngeal branches, which run downwards and forwards to the larynx. In goitrous enlargements, the upper pole of the gland may enter into close relationship with the termination of the parent trunk, and the external branch normally lies deep to the anterior border of the upper pole. Vandenberg (1944) claims that when lateral traction is made on the upper pole the external laryngeal nerve can be identified as a fine thread, 1 mm. in diameter, on its inner aspect. It should be gently dissected medially. It is generally agreed that the upper pole should be carefully dislodged from its capsule before ligation of the superior vessels in all cases.

Micro-anatomy of the Thyroid Gland

Micro-dissection and reconstruction techniques have been used to elucidate the minute anatomy of the thyroid parenchyma and its supporting connective tissue stroma. The true capsule of the gland is formed by a thin and almost transparent layer of connective tissue. When this is teased up it is seen to be continuous with numerous strands of connective tissue forming septa which pass into the substance of the gland and break up the parenchyma into " bands, bars, plates, stalks, and bulbs " (Rienhoff, 1929). The presence of a true lobular system has been disproved by Wilson (1927), Rienhoff and others. The parenchymatous masses are themselves penetrated by finer strands of connective tissue which isolate the individual follicles. The thyroid follicle is the *structural* unit of the gland (Flint, 1903). The stroma becomes more conspicuous as the age of the subject increases. The follicles also increase gradually in size and their epithelium becomes more flattened (Lansing and Wolfe, 1944). Histologically, the

interfollicular stroma consists of bundles of rather loose connective tissue containing only a few elastic fibres. In it run vessels and nerves which break up into finer and finer radicles as they pass to their ultimate distribution among the secretory elements of the gland.

Small portions of thymic tissue, identifiable by the Hassall's corpuscles they contain, may be found embedded in the connective tissue of the thyroid, usually, but not invariably, near the surface. Parathyroid tissue is not uncommonly found within the thyroid gland in man; when it occurs it is sharply cut off from the surrounding thyroid tissue by a definite capsule of connective tissue.

The essential secretory elements of the gland are the *follicles*, or vesicles, which are closed cavities not communicating with each other (Streiff, 1897). They vary considerably in size: the smallest are about 20μ and the largest nearly 1 mm. in diameter, though this range of variation is seldom found in any one gland. Most of the follicles in a normal gland are less than 120μ in diameter (87 per cent. according to Stein, 1938). Their average diameter is slightly greater in thyrotoxic than normal glands and is about doubled in colloid goitre (Wilson, 1927; Jackson, 1931).

The follicle may show facets, especially when enlarged as in thyrotoxicosis and colloid goitre, due to pressure by neighbouring follicles. Reconstructed follicles may also be hour-glass shaped and irregular, their surfaces showing many excrescences, diverticula and bud-like processes (Cresswell Baber, 1881; Streiff, 1897; Gale Wilson, 1927; Moritz, 1931; and Stein, 1938).

Stein (1937) by careful measurement found that 63·8 per cent. of normal follicles had a volume of less than 0·0001 cu. mm. So irregular was their shape that little correlation existed between the length and volume of individual follicles.

Isenschmid (1910) ascribed the increase in the size of the gland in young children to division or budding of the follicles. Rienhoff held, on the contrary, that an increase in the size of the smaller resting follicles explains the growth in size of the gland. However, the weight of evidence suggests that intramural proliferation does result in the budding off of new follicles (Moritz, 1931, and Severinghaus, 1933). In fact, new follicles arise, as in the foetus, by the cavitation of solid mural outgrowths, the constricting off of small out-pouchings, and by the simple division of a main follicle. Contrariwise, in the involuting gland, fusion of follicles occurs (Allara, 1938).

The interfollicular stroma. Modell (1932) claims that at the origins of the smaller intraglandular arteries there are muscular cushions whose contraction may close down the circulation in the territories they supply. The exceedingly rich nerve supply of the thyroid vessels has already been noted. It is suggested that local chemical factors govern the ebb and flow of blood to groups of follicles.

The interfollicular capillaries show themselves capable of great hypertrophy in thiourea-fed rats (Thomas, 1945). A supplementary system of intrinsic capillaries is developed on the surface of the follicle running in betwee

the bases of adjacent epithelial cells and among projecting parafollicular cells.

Many histologists have described small collections of cells, the so-called interfollicular epithelium, in the connective tissue of the gland between the follicles. Rienhoff, Stein and others have, however, now shown that these are in fact merely the normal follicular cells cut tangentially.

Small collections of lymphocytes are frequently found in the interfollicular connective tissue; lymph nodes with germinal centres may even occur but they are exceptional. If present in any number, the gland is probably pathological (cf. Chapter XXI).

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CHAPTER III

CLASSIFICATION OF THYROID DISEASES

It is hoped that the following classification will help the clinician to diagnose and treat goitrous patients coming under his care. The term " goitre " is used to indicate any palpable or visible thyroid gland.

1. **Simple goitre.** Simple goitres are classifiable on an aetiological or a clinico-pathological basis.

(*a*) Aetiological
- endemic
- sporadic or " residual "

(*b*) Clinico-pathological
- Diffuse
  - Parenchymatous (Wegelin 1926).
    - (i) Solid embryonal structure.
    - (ii) Trabecular and tubular structure.
  - Colloid
    - (iii) Small follicles. (struma microfollicularis).
    - (iv) Large and small follicles. (struma macrofollicularis et microfollicularis).
- Nodular
  - Single
    - (v) predominantly large follicles. (struma macrofollicularis).
  - Multiple
    - (vi) with papillary large follicles.

Clinically also, simple goitres are classifiable as adolescent or established, symmetrical or asymmetrical.

2. **The hypothyroid states.**

(1) Congenital cretinism (congenital thyro-aplasia).
(2) Cretinism with congenital goitre.
(3) Infancy or childhood cretinism.

(4) Myxoedema
- spontaneous thyroid atrophy.
- myxoedema, post-operative, post-irradiation, post-thiouracil.
- pituitary myxoedema.
- localized pretibial myxoedema.

3. **Graves' disease.**

(1) Full-blown or " classical " Graves' disease, exophthalmic goitre, toxic diffuse goitre, primary toxic goitre.
(2) Toxic multi-nodular goitre (multiple nodules exist).
(3) Toxic adenoma (hyperfunctioning single nodule).
(4) Thyrotoxicosis factitia.
(5) Ophthalmic forms of Graves' disease.

A further differentiation of thyrotoxicosis results from the fact that for known and unknown reasons, one system or organ is selectively affected by some damaging complication or shows functional derangement out of all proportion to the intensity of the thyroid intoxication. Thus, if it is the heart, we have the thyrocardiac, if it is the skeletal muscles, the patient with thyrotoxic myopathy, and so on.

4. **Developmental anomalies of the thyroid gland.**

(1) Aplasia and hypoplasia.
(2) Abnormal descent (i) lingual thyroid.
(ii) arrest near hyoid bone.
(iii) mediastinal ectopia.
(3) Accessory thyroid nodules.
(4) Thyroglossal cysts and fistulae (suprahyoid and infrahyoid).
(5) Struma ovarii.

5. **Acute inflammations.**

Thyroiditis } non-suppurative.
Strumitis } suppurative.

6. **Granulomatous diseases of the thyroid.**

Tuberculosis
- acute miliary.
- focal or caseous.

Syphilis
- localized gumma.
- diffuse fibrosis.

7. **Other lesions—probably inflammatory.**

Struma lymphomatosa.
Riedel's struma.
Subacute (pseudo-tuberculous) thyroiditis.

8. **Neoplasms of the thyroid.**

Benign.

Malignant
- Papillary carcinoma.
- Adeno-carcinoma (malignant adenoma).
- Sundry highly malignant forms.

9 **Amyloid Goitre.**

10. **Hydatid disease of thyroid.**

CHAPTER IV

SIMPLE GOITRE

Definition — Classification — Mechanism of Simple Goitre Formation — Iodine deficiency — Geographical Distribution — Relationship of Adolescent to Established Goitre — Sporadic, or Residual Goitre — Diet — Aetiological Role of Infections — Geology, Mineralogy, and Soil in relation to Goitre — Heredity — Social Status and Occupation.

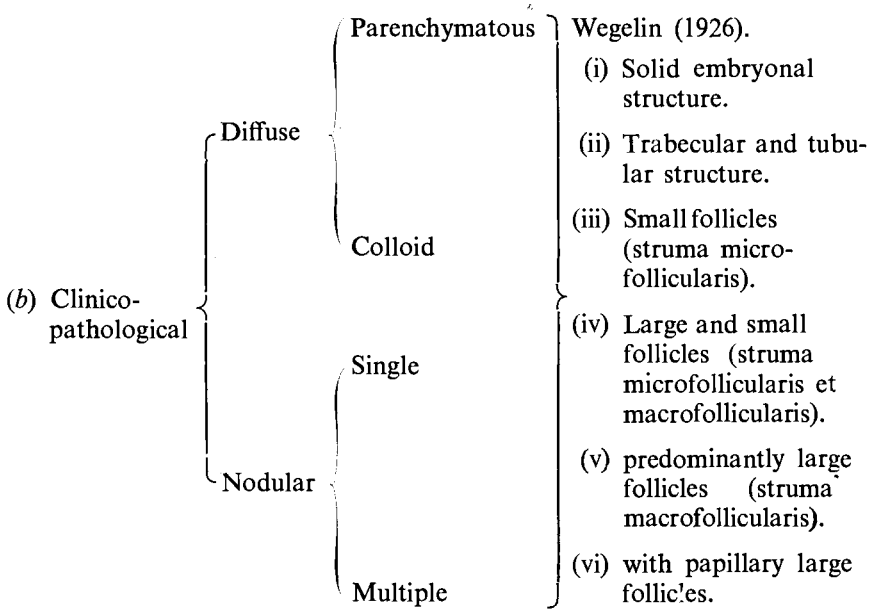
Definition. In the mountains of western Bulgaria arises a river which flows southwards across eastern Greece to the Aegean. It is called the Struma and it has given its name to the cervical swelling for so long prevalent along its banks and tributaries. The term, " struma ", is here used synonymously with " goitre " to indicate any visible or palpable enlargement of the thyroid gland. The word, " goitre ", is probably a corruption of the Latin, *gutter*, meaning *throat*. It is known that with the approach of puberty the gland enlarges, especially in girls, but provided the iodine intake is adequate this enlargement is not detectable by clinical methods.

Any goitre which is neither inflammatory nor malignant and not associated with toxic features may be considered as simple; but it must be admitted that there are objections to such a definition. On the other hand, it is sometimes impossible to distinguish between a goitre with toxic symptoms and one free from such; on the other, certain adenomata may be virtually indistinguishable histologically from their malignant counterparts. The term " simple goitre " is therefore justifiably retained only for clinical convenience.

Classification. This may be on an aetiological or a clinico-pathological basis:

(*a*) Aetiological
- endemic.
- sporadic or " residual ".

There is now much evidence, summarized by Kelly (1946) and Murray *et al.* (1948), that the incidence of established goitre in adults is proportional to that of puberty goitre, and that this in turn depends on the iodine intake. As Ryle (1947) remarks, " the percentage incidence of visible glands in an adolescent population is a useful index of its iodine consumption ". Granted a liberal iodine consumption, both puberty and adult goitres are infrequent. This low residual incidence (sporadic goitre) is probably determined by genetic, sexual, dietary and other factors.



Clinically also simple goitres are classifiable as adolescent or established, symmetrical or asymmetrical.

In thyroid pathology the term "adenoma" is not used in its strict sense to denote an innocent new growth of glandular tissue, for it is often impossible to distinguish benign neoplasia from an area of focal hyperplasia.

The term is used loosely to describe any encapsulated nodule of thyroid tissue which presents a different histological pattern from that of the gland generally. Clearly, however, the probability of a given nodule being a true adenoma is great when it occurs in an otherwise healthy gland.

Wegelin's valuable classification is based on the degree of differentiation of the goitrous tissue. Generalized or nodular enlargements present histological patterns very similar to the progressive stages of development seen in the embryonic gland. Dobyns and Lennon (1948) have recently shown by radio-autographs that functional capacity and histological differentiation run roughly parallel.

Mechanism of simple goitre formation. It is probable that whenever the concentration of thyroid hormone in the body fluids falls so low as to prejudice normal growth and metabolism, thyroid stimulating hormone is secreted in increased quantities by the anterior pituitary. Thyroid hypertrophy and hyperplasia then follow. Thus any factor which interferes with the elaboration and secretion of thyroid hormone may result in goitre. The stages of hormone synthesis within the gland are shown diagrammatically in Fig. 10. Obviously, however, the first requirement is iodine itself, and it is this which is deficient in simple goitre. The labours of a century are summed up in the

conclusion of the Goitre Sub-Committee of the Medical Research Council of Great Britain (1944):

> " The immediate cause of simple goitre is failure of the thyroid gland to obtain a supply of iodine sufficient to maintain its normal structure and function. This failure is usually brought about by an absolute environmental deficiency of iodine; it may also be caused by factors which interfere with the availability of dietary iodine or which impose an abnormal demand on the thyroid gland."

Other authorities (Marine, 1923; Kimball, 1947) are in complete agreement.

Though the factor immediately responsible for simple goitre is a deficiency of thyroid hormone, such patients do not present hypothyroidism presumably because, by its hyperplasia, the gland effects an adequate compensation. Its hyperplastic follicles probably extract iodide more fully from the plasma.

Thus, the aetiological factors in simple goitre are:

(i) Exogenous	Iodine deficiency.
	Dietary.
	Infections.
	Geological.
	Mineralogical.
(ii) Endogenous	Heredity.
	Sex.
	Age.

The exogenous factors all act by interfering with the ingestion, absorption or retention of iodine within the organism. Dietetic and endogenous factors probably account for many simple goitres occurring sporadically.

Iodine deficiency. History. A valuable summary of this subject is given by Orr and Leitch in a Special Report to the Medical Research Council on " Iodine in Nutrition," from which source we have borrowed freely in the following pages.

A few years after the discovery of iodine by Courtois in 1811, Coindet (1820) suggested that the beneficial effects (which were known to the ancient Greeks) of preparations of sponges and seaweed in goitrous conditions might be due to the iodine which Davy, in 1815, had shown these natural substances to contain. For some years the matter was actively debated, and on the whole Coindet's views were substantiated. Confirmation was also provided by Angelini (1824) and Cantu (1825), who found iodine in the water of springs noted for their powers to cure goitre, and by Boussingault (1831), who described the good effects on goitre in the Andes following the use of Guaca sea salt, which is rich in iodine. He also stated that where this salt was in general use goitre was absent.

Prévost (1849) first formulated the theory that goitre is a deficiency disease, but related it to the use of water poor in iodine and bromine. Chatin

TABLE II

Incidence of Enlargement of the Thyroid Gland in Children, aged 11 to 15 years, from Four Areas with Drinking Waters Varying Greatly in Iodine Content (Murray *et al.*, 1948)

Area.	Iodine-content of Water (μg. per (litre).	Total Hardness of Water (as mg. $CaCO_3$ *per* 100 *ml.*).	Number of Children Examined:			State of Thyroid Gland:			Total Number of Visible Thyroid Glands Observed. (*b*, *c* and *d*)	Mean Percentage Incidence of Visible Thyroid Glands: (*b*, *c* and *d*)			Ratio of Percentage Incidence of Thyroid Glands Visible in Girls to that in *Boys* (*F*/*M*).
			Total.	Boys.	Girls.	Visible at Rest. (*b*)	"Rossetti" Neck. (*c*)	Pathological. (*d*)		Total.	Boys.	Girls.	
Okehampton, Devon	1·1 (very low)	0·48 (soft)	298	153		27	1	2	30	26·2	20		1·7
					145	38	7	3	48			33	
North Oxfordshire	mean 2·0 (low)	mean 30·16 (hard)	451	188		21	2	6	29	18·0	15		1·3
					263	40	6	6	52			20	
Windsor, Berks	10·1 (high)	31·65 (hard)	461	225		7	—	—	7	6·7	3		3·3
					236	21	—	3	24			10	
Maldon, Essex	50·2* (very high)	5·02 (soft)	527	220		2	—	—	2	2·5	1		4·0
					307	11	—	—	11			4	

* Wantz Road Well.

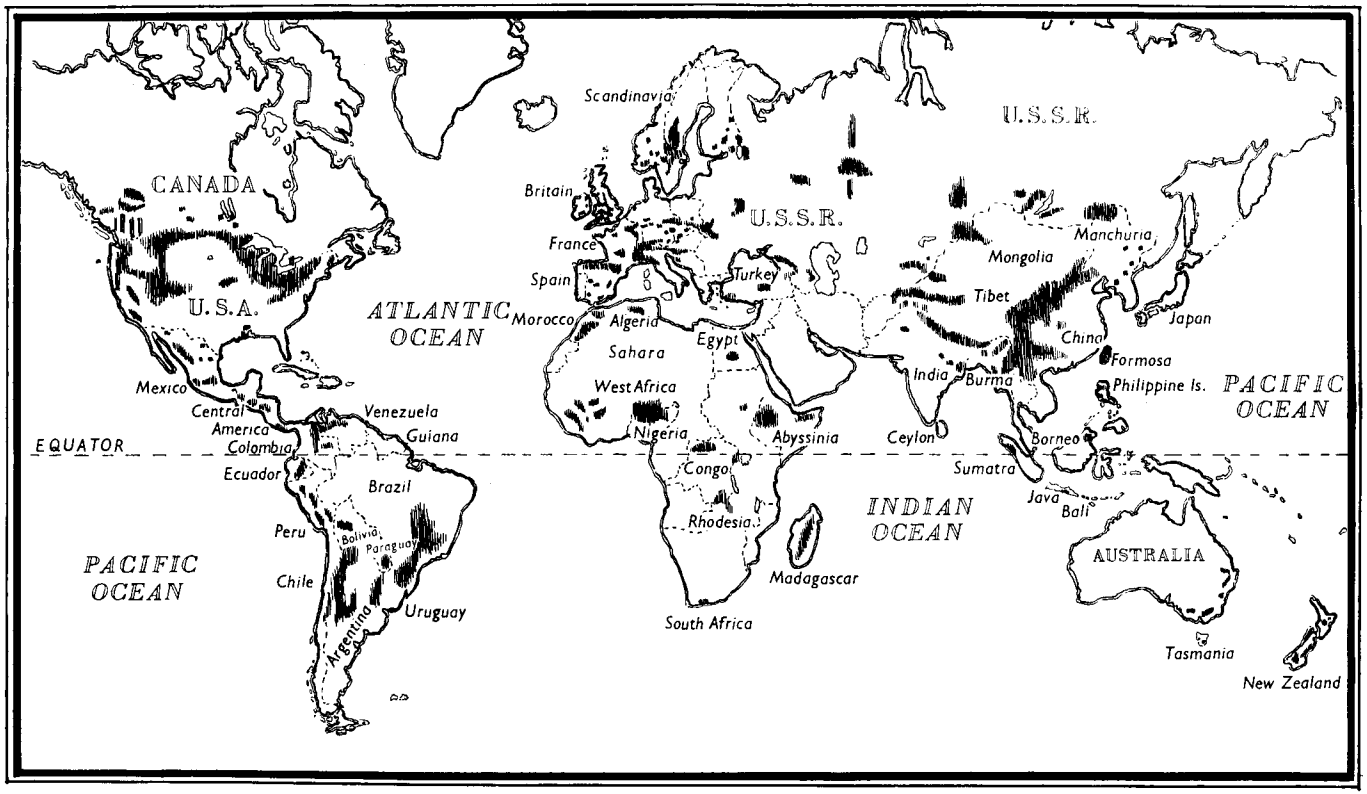
(1850) correlated the distribution of goitre with the amount of iodine in the foodstuffs in the various districts. Köstl (1855), in Austria, advised the use of iodine for all goitrous persons within certain age limits, and also for farm animals. The first experiment on a large scale was that of Boussingault and Grange in 1860, who gave iodized salt and potassium iodide daily in tablet form to school children. Unfortunately the dosage was large, and toxic symptoms were produced in so many cases that the method was dropped for thirty years, except by a few physicians who still believed in the value of iodine, and in certain districts where it was used by the country folk. The whole matter was revived by Baumann's discovery of iodine in the thyroid gland in 1895. In fact, during the past fifty years, endemic goitre has become recognized as one of the most important of the deficiency diseases. The exact daily requirement of iodine in the human is not known with certainty, but only minute amounts are necessary, namely from 100–150 micrograms. In endemic areas, the iodine consumption is even less than this minimal requirement.

Recently, a sub-committee of the Medical Research Council has reported (1948) on the incidence of thyroid enlargement in the United Kingdom in relation to the mineral content of the drinking water. Their findings conform closely with those of other surveys in the U.K. and elsewhere, by Hercus *et al.* (1925, 1927), von Fellenberg (1923, 1933) McClendon (1939), O'Shea (1946), Clements (1948) and Parra (1948). All point irresistibly to the conclusion that simple goitre is an iodine-deficiency disease.

Murray *et al.* (1948) like previous workers in the U.K. and elsewhere, found a disconcertingly high incidence of goitre when it was looked for systematically. They estimate that not far short of 500,000 adolescent goitres exist in the U.K. and that the number of established goitres is probably many times greater. In some localities nearly 50 per cent. of the adolescent females were goitrous. Their Table (Table II) shows the results of surveys from four illustrative areas.

The number of children examined in each of the four areas was 300–500, and there were no important social or nutritional differences between them, with the exception that the Maldon group probably consumed more sea fish. It will be seen that a high incidence of thyroid enlargement existed in the two areas with water supplies deficient in iodine. In these areas, too, there was a low ratio for the female/male incidence. By contrast, in Windsor and Maldon, with waters relatively rich in iodine, there was only a low " residual " rate of incidence, and a high female/male ratio.

Geographical distribution. We are indebted to Kelly (1946) for making a world survey of simple goitre reports (Fig. 32). McClendon (1939) gives valuable goitre maps for the U.S.A. (Fig. 33). The goitre belt extends throughout the whole length of the Appalachian range, through the states bordering on the great lakes, westward to North Dakota and into the far western states of Montana, Idaho, Utah, Oregon and Washington, where the incidence is particularly high. Little systematic attention had been paid to goitre by the U.S. public health authorities until the first world war, when, in 1917, it was



KELLY. 1946.

THE GOITRE AREAS OF THE WORLD

FIG. 32.

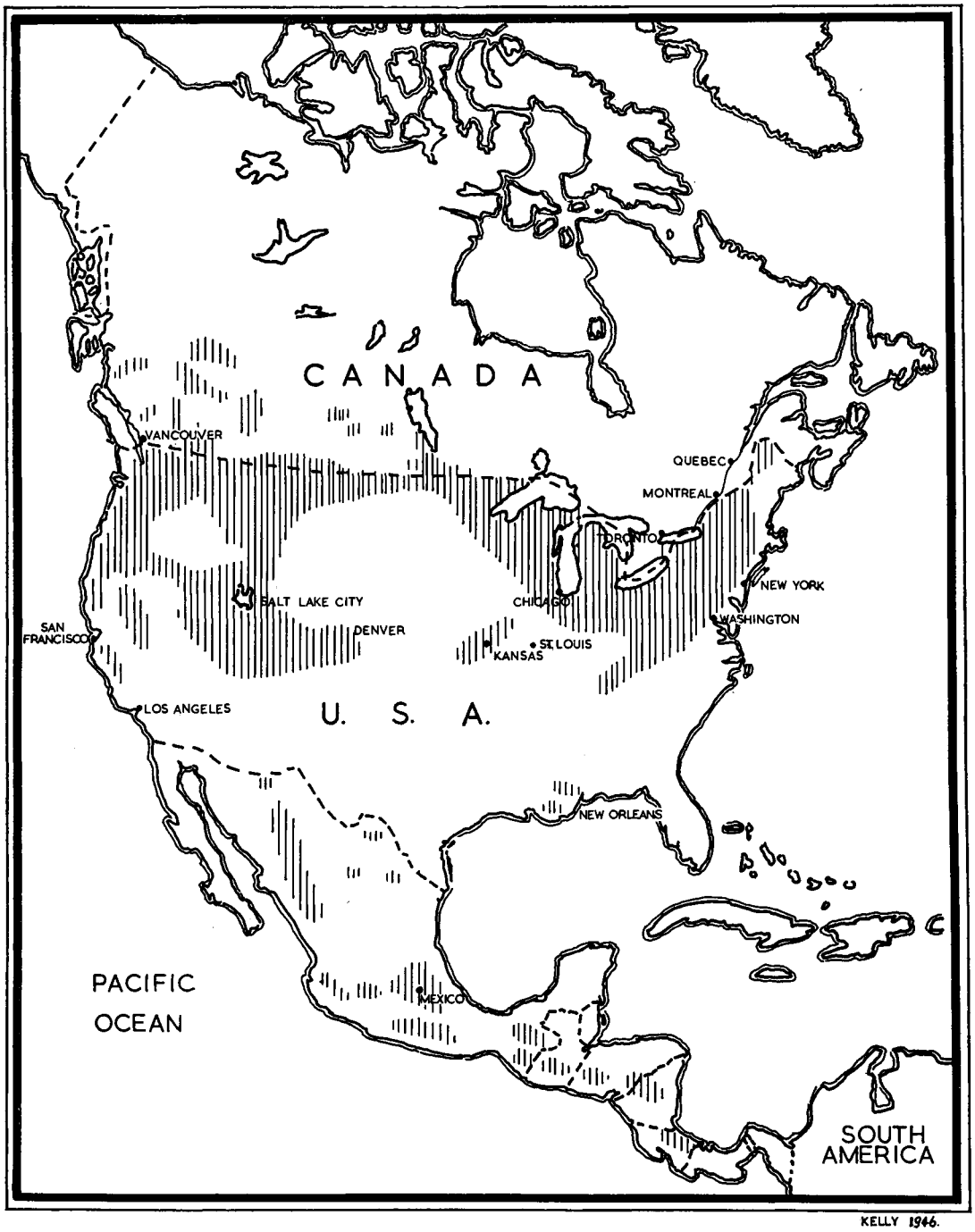


FIG. 33.—North America: areas of endemic goitre are hatched.

found that among 2,510,701 men examined for military service, 11,971 had simple goitre, and of these 31 per cent. were rejected because their necks were so large that the collar of the military tunic could not be buttoned around them. In Canada, also, there are endemic areas in British Columbia, Alberta, and the provinces of the great lakes.

In Central and South America fewer surveys have been made but it is clear that there are many regions of high endemicity. In a recent survey of goitre in Colombia, Parra (1948) found that 56·5 per cent. of 140,000 children were goitrous. The incidence rose to 81 per cent. in the interior of the country as compared with 10 per cent. in the coastal regions.

The areas of highest incidence in Europe are shown in Fig. 34. O'Shea (1946) reported an incidence of up to 80 per cent. in some of the schools in the Tipperary ranges of western Ireland (Table III).

TABLE III

(FROM O'SHEA, 1946)

Place	County	Goitre per cent.	Established Goitre	Iodine Content				
				Soil μg./kg.	Water μg./litre	Milk μg./100g	Soda-bread μg./100g	Potato μg./100g
Cloran	Tipperary	65	common	3,721	1·9	1·0	1·6	0·5
Kilsheelan ..	,,	70	,,	3,809	0·9	0·9	0·9	0·6
Tipperary town	,,	65	,,	3,071	0·5	1·5	4·7	0·6
Maryborough ..	Leix	40	rare	3,010	1·7	3·5	12·6	11·7
Claremorris ..	Mayo	10	,,	5,050	0·4	3·6	10·7	7·0
Spiddal	Galway	0	none	14,390	20·1	55·6	18·3	5·6

In Norway, Devold and Closs (1941) carried out an interesting survey in the district of Forsland. They found that the incidence of goitre increased with the distance from the sea. In women, for example, the percentage affected rose from 29·9 near the sea to 62·8 in the village farthest up the valley. Significantly, the consumption of fish decreased as the distance from the sea increased.

In Iceland, with a maritime population consuming enormous quantities of fish, the thyroid contains one of the highest known concentrations of iodine. Endemic goitre is non-existent. Similarly, in Japan, where the inhabitants actually eat seaweed, there is a remarkable freedom from simple goitre. It has been calculated that 10 gm. (dry) of such seaweed, a not unusual amount to be served at a single meal, would contain an average of about five milligrams of iodine or sufficient to satisfy normal requirements for fifty days.

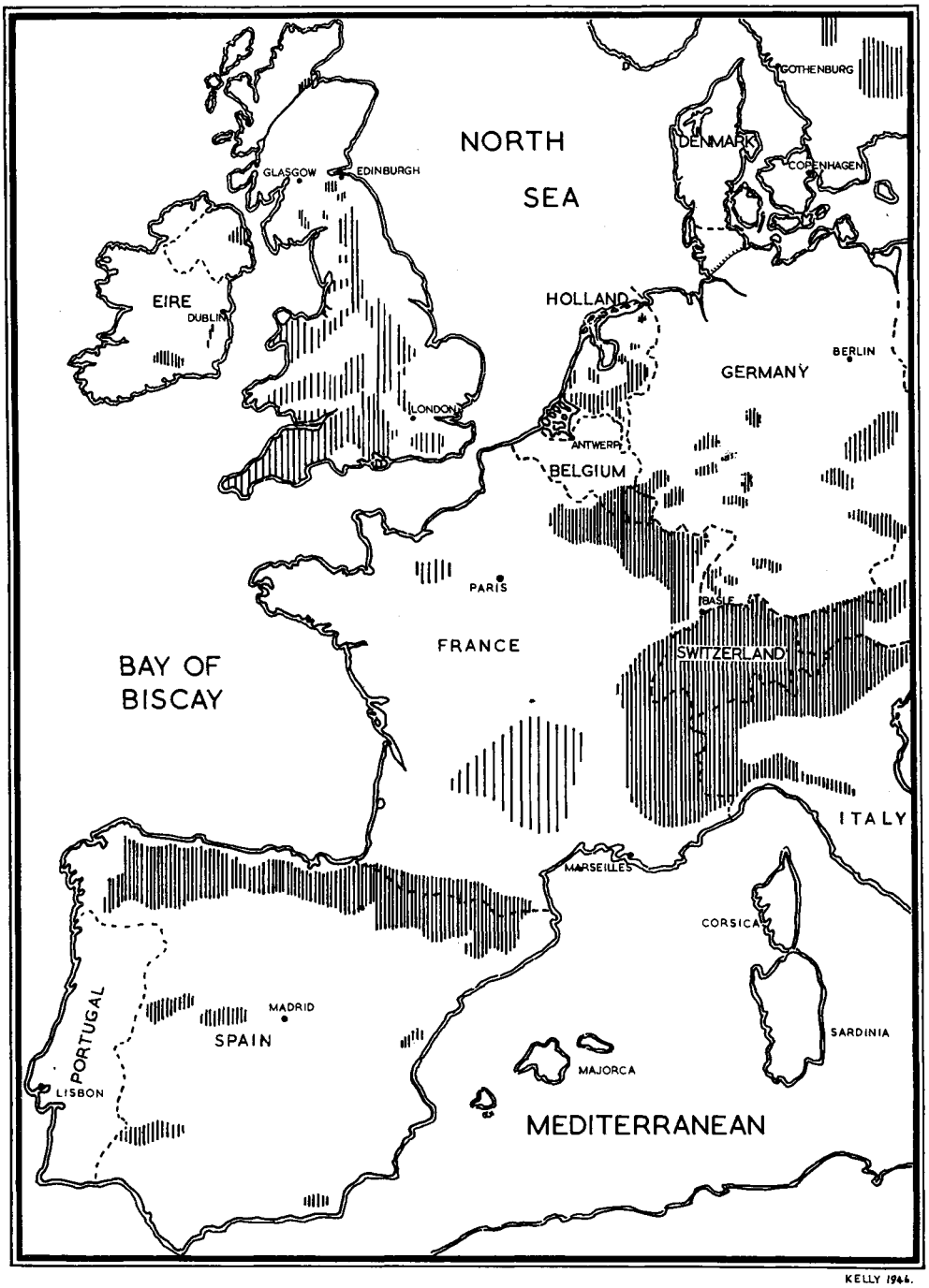


FIG. 34.—Europe: hatching indicates areas of endemic goitre.

The chief zones of goitre in France are in the east, extending from northern Alsace along the frontier to the Mediterranean coast, in a south-central zone covering the Auvergne and the Massif Central, and along the Pyrenees. At one time the districts of Luchon and Bigorre in the Hautes Pyrenées were among the most notorious endemics in Europe.

Goitre is still heavily endemic in the Sierras of central and western Spain. Indeed, in the Sierra de Gata is the area of Las Hurdes, some 175 miles due west of Madrid, which is one of the most notorious goitre centres of the world. In its wild and inhospitable valleys goitre is rife, and a very high proportion of the population is cretinoid. Cases of idiocy, deaf-mutism, and dwarfism abound. Not a single man from the district has ever been passed fit for military service because of the prevailing low stature and mental hebetude (Kelly, 1946).

Goitre is, of course, still endemic in Switzerland, though its severity has been much lessened since the introduction of iodized salt (Lauener, 1939). Its use is not, however, compulsory, and there is still a considerable incidence of goitre especially among the lower social classes.

PERCENTAGE OF GOITRE AMONG SWISS ARMY RECRUITS, 1924–25

(FROM STINER'S DATA, 1928)

North-West Cantons		*North-Central Cantons*		*North-East Cantons*	
Basel	20·7	Aargau	38·5	Schaffenhausen	46·5
Solothurn	24·6	Zürich	54·3	Thurgau	56·4
Neuchâtel	20·9	*Central Cantons*		Appenzell	63·4
South-West Cantons		Bern	39·5	St. Gall	56·3
Fribourg	35·5	Luzern	42·0	Glarus	41·1
Vaud	17·4	Zug	45·4	*South-East Cantons*	
Genève	25·8	Schwyz	19·4	Grisons	31·8
Valais	43·8	Unterwalden	45·6	Ticino	14·4
		Uri	41·0		

There are many clear references in the classics to the endemic in the alpine region of northern Italy. These early observers showed considerable insight for they even ascribed it to some peculiarity of the drinking water. Thus Pliny the Elder (*c.* A.D. 23–79) wrote in his *Natural History* (Book XXXVII, Section 44); " . . . varie genere aquarium juxta Alpis infestante guttura hominum."

In certain parts of central and eastern Germany, as well as southern Germany, there is considerable endemicity. Olesen (1933) reported 31·3 per cent. of female applicants for visas to the U.S. from Berlin, Breslau, Dresden, Leipzig and East Prussia, to be goitrous. The incidence of goitre in central Germany rose sharply during the war years especially among children (Grimm, 1948). This may be related to the greatly decreased consumption of sea-food. At Freiburg, in the Black Forest, Aschoff (1935) found that compression of the trachea by a goitrous gland was an important cause of neonatal deaths.

In some of the villages among the mountains of eastern Moravia, goitre is rife and affects as many as 80–90 per cent. of the inhabitants. In the Austrian Tyrol, also, goitre abounds: while motoring slowly through the market-place of a small village in the region of Salzburg we once counted twenty large goitres, evidently of the multi-nodular type. Goitre is very prevalent in Yugoslavia west of the River Drina, the incidence among the school children being anything from 15–70 per cent. Though goitre is not regarded as endemic in the Hungarian lowlands, a recent survey in one village showed that about half the inhabitants were goitrous (Oskó and Sós, 1948). In Rumania too, an incidence of 50 per cent. or more has been reported from

FIG. 35.—Consequences of iodine deficiency. A cretinous family compared with a man of normal stature. Danielopolu, D. (1937) *Les thyroidies endemiques et sporadiques*. Masson & Cie, Paris.

some districts, with associated cretinism, deaf-mutism, dwarfism and imbecility (Fig. 35).

Little definite is known concerning the incidence of goitre in Russia, though it is certainly widely endemic in the Caucasus and beyond, where, in eastern Turkestan there is one of the world's worst goitre belts. In fact, it was around Lake Issyk Kul about three hundred miles north-east of the Pamir plateau (Roof of the World) that Marco Polo noted and described goitres on his travels from Venice to the Court of the Grand Khan in China nearly seven hundred years ago. Writing of the people in the Yarkand he said, " They are, in general, afflicted with . . . tumours of the throat, occasioned by the quality of the water they drink."

Perhaps the most extensive and notorious goitre belt in the world is that stretching for 1,500 miles along the southern slopes of the Himalayas, where

the number of goitre subjects seeking treatment far surpasses 100,000 annually.

Passing eastward through Burma and south-west China, goitre endemics are encountered continually. Robertson (1941) states that the incidence of goitre in adults of both sexes in the labour gangs working on the Burma road often rose to 80 per cent. and averaged over 50 per cent. It was also noted during the second world war that the incidence of goitre in Yunnan province rose when, with the cutting of the Burma road, the supplies of sea salt were interrupted and use was confined to that from the local mines which was poor in iodine.

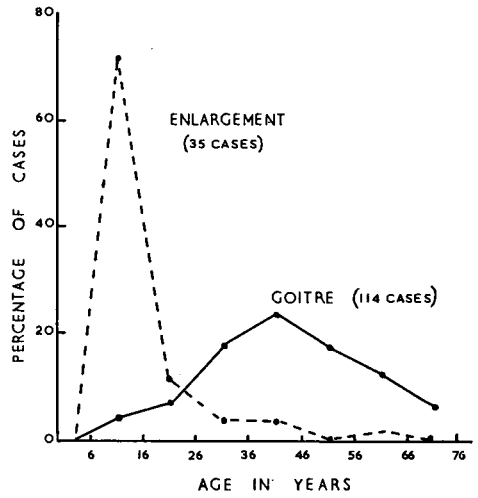


FIG. 36.—Percentage distribution, according to age of thyroid enlargement (slight diffuse hyperplasia) and established goitre in the village of Hook Norton. (Murray *et al.*, 1948.)

Small but important foci of goitre also occur in the East Indies, Australia and New Zealand. In New Zealand, the goitre surveys and iodine prophylaxis remain an example to the rest of the world.

Relationship of adolescent to established goitre. Murray *et al.* (1948), in a survey of a remote Oxfordshire village (Hook Norton) found 149 out of 575 subjects examined to be goitrous. In 35, the enlarged gland was soft, smooth and symmetrical, and in the remaining 114 it was either hard, nodular or asymmetrical (established goitre). The former type was found especially in adolescents, the latter occurred chiefly in adults (Fig. 36). The water supply of this village was " hard " and contained little iodine (1·5 micrograms per litre). The foregoing figures illustrate the association of a high incidence of adolescent and established goitre. However, not all adolescent goitres become established. The association depends, of course, on the fact that, in the last analysis, both depend on iodine deficiency, and the size of the gland during adolescent or adult life merely reflects the availbility of environmental iodine. Thus Ryle (1947) concludes:

" (i) The percentage incidence of visible glands in an adolescent population is a useful index of its iodine consumption and of the goitre hazard to which it is exposed in later life, whether we regard the clinical findings as an early sign of a specific deficiency—*i.e.* as pathological—or as expressing the more extreme limits of physiological variation or adaptation."

" (ii) Thyroid size (as has been amply demonstrated by others) receives a plus or minus bias inversely proportionate to the availability of iodine. In this country most adolescent enlargements can be regarded as slow temporal variants. But, since among children of the same age, living in the same locality and drinking the same water, cases with and without hyperplasia occur, we must also assume the operation of innate predisposing influences or species variations. The occurrence in English low-iodine areas of families without goitre and of other families with cases of goitre running through several consecutive generations supports this thesis."

" (iii) Where the percentage incidence of clinical hyperplasia exceeds, say, 5–10 per cent., there are good grounds for recommending the general use of iodized salt as a measure of social prophylaxis."

Sporadic or residual goitre. This may derive from one or a combination of the following factors, though it would be idle to deny that even sporadic goitre is independent of the iodine intake. In fact, of course, a diet rich in iodine will protect against many of the other factors which favour thyroid enlargement.

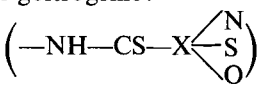
Diet. It has long been claimed that dietary factors are important in the aetiology of simple goitre and this view was greatly strengthened following the observation of Chesney *et al.* (1928) that a cabbage diet produced simple goitre in rabbits (" Cabbage goitre "). The administration of thiocyanates is also known to cause thyroid enlargement (Barker, 1936). Though Marine *et al.* (1932) believed that the cyanide linkage was responsible for cabbage goitre, subsequent workers have been unable to confirm this.

Intriguing observations on this subject have recently been made by Greer and Astwood (1948). A test dose of radioiodine was administered and its uptake by the thyroid determined by a Geiger-Müller counter placed over the neck. The food to be tested was then eaten in quantity and its effect on the uptake curve was determined in subsequent counts. A total of sixty-one foods were tested in a hundred different subjects. Contrary to expectations, cabbage interfered but little with the uptake of the iodine. However, another member of the mustard family, rutabaga (yellow turnip), was uniformly inhibitory (Fig. 37). White turnips also possessed considerable anti-thyroid activity as did strawberries and carrots. Mixed meals consisting of carrots, rutabaga, lettuce, pears and milk, resulted in moderate interference with iodine uptake by the gland.

Since cabbage, which is so active in rats and rabbits, exerted little effect in man, Greer and Astwood suggest that considerable species differences

may exist in the response to different foodstuffs. In general, the anti-thyroid activity of a given foodstuff is greatest when it is ingested in the raw state. The agents concerned are water-soluble and thermolabile.

What is the nature of the active compound contained in these foods? Exciting new data have been provided by the researches of Greer *et al.* (1949). Three types of compounds were known to be goitrogenic:

(i) Those containing a thiocarbonamide group  and including the thiouracils;

(ii) Derivatives of aniline, such as sulphaguanidine (not a proven goitrogen in *man*); and

(iii) Thiocyanate (goitrogenic action minimized by iodine therapy).

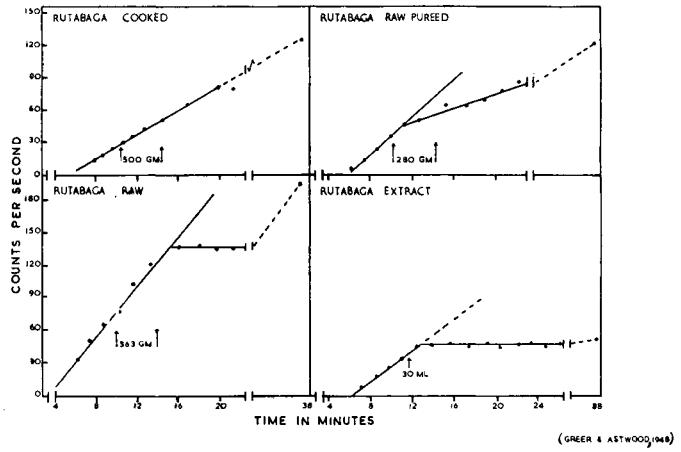


FIG. 37.—The effect of eating rutabaga on the uptake of radioactive iodine by the thyroid. Cooked rutabaga had no effect, 280 gm. of the raw puréed vegetable had a grade 2 effect, 363 gm. of raw chunks had a grade 3 effect, and 30 c.c. of a purified extract equivalent to 2,617 gm. inhibited the uptake completely for twenty-four hours.

Greer *et al.* found that the agent concerned in rutabaga (yellow turnip) is 1–5–vinyl–2–thiooxazolidone, which contains a thiocarbonamide grouping. In its pure state, it is slightly more active than propylthiouracil in man. This thiooxazolidone has also been demonstrated in the seeds of many other members of the cabbage family, namely white turnip, cabbage, kale, rape, brussels sprouts, broccoli and kohlrabi.

The thiooxazolidone does not occur free in active form in these foods. It is liberated by enzymatic action. Heating destroys the enzyme and prevents the goitrogenic effect. But gastric contents do not inactivate the agent. Nevertheless cooking these vegetables will prevent any goitrogenesis since no enzymes capable of forming thiooxazolidone from its precursor exist in the body.

Greer *et al.* conclude that if these goitrogenic foods are taken in the usual amounts they are unlikely to prove harmful but that if they form a large part of the diet, they may inhibit thyroxine synthesis and so cause thyroid enlargement.

It should be mentioned here that the foods which contain most iodine are, in order of merit, fish and what may be termed " sea-food ", green vegetables, wholemeal products, milk, meat and root vegetables. In a normal, well-balanced diet the greatest contribution to the iodine intake is made by milk followed by vegetables (Osmond and Clements, 1948).

It has long been known that diets containing an excess of liver are goitrogenic in the experimental animal. This question is reviewed by Hou (1940), who has shown that the agent responsible for the thyroid enlargement is alcohol-soluble: but again its precise nature is unknown.

Aetiological role of infections. McCarrison (1935) considered that toxic substances in the food and drinking water were responsible for goitre. He demonstrated that goitre can be produced in experimental animals by keeping them in unhygienic conditions and in man by administering the sediment from impure water.

It is also known that infective and toxic agents cause reactive hyperplasia by raising the demand of the body tissues for thyroid hormone (Cole and Womack, 1929). It is thus not surprising that the goitre which is liable to develop in experimental animals kept in dirty cages can be prevented by increasing the amount of iodine in the food. It would thus be as correct to say that toxic and infective agents increase the iodine requirements of the body, as that they are goitrogenic.

Geology, mineralogy and soil in relation to goitre. Murray *et al.* (1948) surveyed the frequency of goitre in the U.K. in relation to the calcium, fluorine and magnesium in the drinking water. From the calcium and magnesium contents, the total " hardness " of the water was determined. Most of the English waters analysed were hard, whereas those in Scotland were soft. Examination of the iodine content showed that the English waters were nearly always richer in this factor, yet in spite of this, the incidence of goitre in England was higher. The data thus strongly suggest that hardness of the water supply interferes with the availability of ingested iodine.

Many laboratory workers have designed experiments to elucidate the relationship between calcium intake and thyroid function. Marine (1935) concludes that a high calcium intake aggravates the effect of a goitrogenic diet. When the dietary calcium of rats on a low iodine intake is raised there are an increased iodine excretion and a fall in the iodine content of the thyroid gland (Simpson, 1947).

An excess of fluorine in the food and drinking water leads to disfiguring mottling of the teeth (dental fluorosis). Wilson (1941) was struck by the fact that where dental fluorosis existed in India, goitre was also endemic. Similarly, Steyn (1948) thinks that the combination of a high fluorine and calcium content of the drinking water is probably responsible for the high endemicity of goitre in the north-western part of Cape Province (South

Africa). In the affected areas, there is no lowering of the iodine content of the water and Steyn postulates the existence of a fluorine-iodine antagonism in the body, resulting in an endogenous iodine deficiency.

On the other hand, May (1940) determined the fluorine content of fifty-one waters from regions of Bavaria with a high incidence of goitre and was unable to show any correlation between the two factors. Murray *et al.* (1948) were also unable to come to any definite conclusion on the matter. It is true that in certain regions of the U.K., fluorosis and endemic goitre are associated (Bromehead *et al.* 1943): but the association is not consistent. Indeed, the U.K. is an unsuitable area for such a study, since the water fluorine is almost universally low and where it is raised, there is often a sufficient intake of iodine to outweigh any possible adverse effect of the fluorine.

Table IV shows the incidence of goitre in relation to geological formation. Though goitre may occur on any geological formation, it appears to be uniformly more prevalent on carboniferous limestone. It is generally absent from chalky formations. Similarly there is a tendency to higher rates on the Old Red Sandstone, but it is virtually absent where igneous and metamorphic rocks predominate.

Of course, the important factor is the iodine content of the different soils and waters which are derived from these various geological strata, for it is on these soils and waters that plants, the lower animals, and man must subsist. The age of the formation is not a factor except in so far as the iodine content of the rocks may have been more leached by the percolating waters.

In general, soils reflect the character of the parent rocks producing them. If this rock contains excessive calcium, magnesium, fluorine or arsenic, these substances will be abundant in the overlying soil and will so influence the water supplies and vegetation as to cause a raised demand for iodine in the

TABLE V: CHARACTERISTICS OF IODINE-RICH AND IODINE-POOR SOILS.

IODINE RICH	IODINE POOR
Heavy textured.	Light textured.
Retain moisture; greater holding power for iodine.	Porous; iodine easily leached out.
Rich in colloidal and organic matter (humus).	Deficient in clay-colloids and humus.
Reaction acid rather than basic; lime is acid-soluble.	Tend to alkaline reaction; rich in lime.
Red and brown colour due to presence of colloidal iron.	Usually of light colour; grey clays and pale sands lacking iron.
Iron in ferric state.	Iron in ferrous state, if present.
Mainly (but not exclusively) originate from igneous rocks.	Mainly (but not exclusively) originate from sedimentary rocks.

animals subsisting on them. Moreover, the character of the parent rock determines the texture of the soil. Heavily textured clays and loams retain their natural iodine much more efficiently than light sandy soils. Table V shows the main characteristics of iodine-rich and iodine-poor soils and Table VI shows that goitre increases as the soil iodine decreases.

Heredity. It is probable that inherited or constitutional liability to simple goitre exists in some subjects, though this hereditary predisposition cannot

TABLE VI: GOITRE INCREASES AS SOIL IODINE DECREASES

Locality in Switzerland	Geological System	Microgrammes of Iodine per Kilogramme of Soil				Percentage of Goitre.
		HCl Soluble.	HCl Insol.	Total	% Soluble.	
EFFINGEN	White, upper Jurassic, "Malm" corresponding to upper Oolitic clays (Purbeck and Kimeridge) of British system.					
Effingen Rock—Unaltered		3,700	1,700	5,400	68·5	1·0
,, ,, —Marl		5,600	2,230	7,830	71·6	
,, ,, —Soil		7,100	4,800	11,900	59·7	
HORNUSSEN (7 miles north of Aarau)	Brown, middle Jurassic, clay corresponding to lower Oolitic clays (Oxford and Gt. Oolite) of British system.					
Dogger (Great Oolite)—Rock		730	100	830	88·0	12·1
,, ,, ,, —Debris		1,050	1,250	2,300	45·7	
,, ,, ,, —Soil		2,710	2,230	4,940	54·9	
HUNZENSCHWIL	Tertiary: Miocene, Richly fossiliferous marly and limestone deposits of central Europe. Represented in N. Africa, India, New Zealand, N. and S. America, but not in Britain.					
Marine Mollasse: Sandst.—Unaltered		110	590	700	15·7	76·2
,, ,, ,, —Clay soil		110	510	620	17·7	
Lower Freshwater Mollasse—Unaltered		90	230	320	28·1	
,, ,, ,, —Sand		140	310	450	31·1	
KAISTEN	The Kaisten beds belong to the Middle Trias or, "Muschelkalk" which includes two series, *viz.* Schlern and Mendola dolomites lying above the lower Muschelkalk. The beds are flaggy marine limestones, dolomites and marls.					
Upper Dolomite Rock—Unaltered		320	100	420	76·2	61·6
,, ,, ,, —Weathered		240	80	320	75·0	
,, ,, ,, —Soil		510	310	820	62·2	
Muschelkalk Rock—Unaltered		390	40	430	90·7	
,, ,, —Weathered		370	170	540	68·5	
,, ,, —Soil		780	1,190	1,970	39·6	

be so clearly demonstrated as that to thyrotoxicosis (Bartels, 1941: Martin and Fisher, 1945). Where the iodine content of the food and drinking water is grossly deficient, goitre may be nearly 100 per cent. endemic. Where the deficiency is moderate, nearly all the members of some families may be goitrous, though neighbouring families, of comparable social and economic status and drawing their water from the same source, may be unable to record a single case. As Murray *et al.* (1948) point out, human subjects fit into a continuous spectrum at one end of which is a high inborn liability and at the other end a high resistance to the development of the disease. The intensity and duration of exposure to iodine deficiency produce variable effects depending on the subject's location in this biological spectrum.

It is known that endemic goitre tends to show itself in a higher percentage among the children of parents both of whom are goitre-bearers than when only one parent is goitrous, and that the incidence is least when both parents are free from goitre. When several generations of goitrous parents have interbred, goitre becomes firmly established in the offspring, and cretins or cretinoid children begin to appear among them. When goitrous parents migrate from endemic areas the children born subsequently may be free from the disease, and the goitrous tendency disappears in the course of one or two generations.

Age-Incidence. Endemic goitre is least prevalent during the first year of life, and does not become common until between the seventh and tenth years, after which there is a fall in the incidence until puberty, when a considerable rise occurs, especially among girls.

This brief statement of the age-incidence must be qualified considerably where the endemicity is high. In such districts goitre may be so rife that a normal thyroid gland is not easily found even in childhood, and the small symmetrical goitre of the English school child is replaced by the nodular, adenoparenchymatous variety typical of foci of high goitre incidence. Certain physiological factors affecting the total iodine content of the thyroid gland are important in the pathogenesis of simple goitre. Variations of iodine content with age run parallel with changes in total thyroid weight. Thus there is a gradual increase in the iodine content of the gland up to puberty, at which stage there is a particularly rapid increase (Nosaka, 1926). The content reaches its maximum in the adult and remains fairly constant until the age of fifty, after which there is a gradual decline. It is clear therefore that a higher iodine intake is necessary during the years of puberty and adolescence, if physiological requirements are to be met, and the percentage iodine content of the gland is to remain above the critical level at which work-hypertrophy supervenes.

The total iodine content of the gland is also of great importance during the later months of pregnancy and during lactation. Iodine is constantly present in the foetal thyroid from the fourth month, from which age the gland probably elaborates its characteristic hormone. This involves a constant call on the mother's blood inorganic iodine. Iodine is present in high concentration in the colostrum and when free lactation is established

the total quantity eliminated rises steadily and may reach 30–40 micrograms daily (Elmer and Rychlik, 1934). Thus in the absence of a sufficient reserve of iodine, the prolonged depletion during the second half of pregnancy and lactation may cause the iodine content of the maternal thyroid to fall below the critical level so that simple goitre develops.

Sex. In children up to about ten years the incidence in the two sexes is almost equal. There is a rapid rise in the proportion of females affected at and after puberty, so that in parts of Egypt the proportion is eighteen females to one male (Dolbey and Omar), though it may approach equality in certain areas of high endemicity.

Social status and occupation. " Labourers " are said to be more liable to the disease. In Lanarkshire, MacKenzie (1899) found that 98 per cent. of the endemic goitres were in " labourers " and miners. It is most common in the rural " working "-classes probably because of the distance from the sea and the scarcity and higher cost of fish in these areas.

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CHAPTER V

SIMPLE GOITRE—PATHOLOGY

Parenchymatous Goitre — Colloid Goitre — Nodular Goitre — Radio-iodine Studies of Thyroid nodules — Single Adenomata — Thyroid Cysts — Degeneration Cysts — Retention Cysts — Chemistry of Simple Goitre — Pathological Anatomy.

No description of the pathology of endemic goitre can be accurate which fails to emphasize that there is no single fixed type of the disease. In certain districts where the endemicity is high and the disease has prevailed for many generations, profound changes occur even in the thyroid of infants. Thus Aschoff (1935) states that about 9 per cent. of still-births and neonatal deaths in the Freiburg area are due to goitrous compression of the trachea.

Usually the degree of degeneration of the thyroid increases with the severity of the endemicity and the age of the patient, and *vice versa*, the consequence being that, where the incidence is not very high, small, smooth, and soft goitres preponderate in children and young adults, and nodular and cystic varieties occur in middle-age and later life. In districts of high endemicity, nodular and cystic varieties may be seen in infancy or early childhood. Correlated with these differences, cretinism is rare where endemicity is low and common where it is high.

The following three groups of simple goitre deserve separate consideration, though there are certain transitional types which make it certain that they represent stages or degrees of a common disease.

I. **Parenchymatous Goitre.** (*Struma Parenchymatosa Diffusa et Nodosa.*) This term should be reserved for a type of goitre resulting from increase in the epithelial elements of the thyroid gland without any appreciable colloid accumulation. It is a rare variety in England and Wales, both among endemic and sporadic cases, but it occurs occasionally, though the changes may be purely focal. In areas of high endemicity, *e.g.* in parts of Switzerland, it is common, especially in children, or even as a congenital lesion. The gland is moderately enlarged and firm, its vascularity slightly increased, and on section shows the pale, fleshy appearance which is characteristic of certain hyperplastic goitrous glands. *Microscopically*, there is little or no colloid present, the follicles are greatly increased in number, the cells are often subcolumnar or columnar in type, and there may be reduplication or infolding of the epithelial lining of the follicles similar to that seen in certain stages of primary thyrotoxicosis (Graves' disease). In most specimens the follicles are uniformly small in size, but in certain cases there may be scattered large irregular follicles among the smaller ones; solid cellular, trabecular and tubular areas also occur.

This parenchymatous goitre is seldom seen after puberty, because by that time it is usually converted into the colloid or nodular form. Parenchymatous goitres rarely reach any considerable size, but when they do so, they cause pressure on the trachea or oesophagus. In the newly-born, as already noted, parenchymatous goitre may cause suffocation: it may embrace the pharynx and oesophagus to form a retrovisceral or circular goitre; the trachea is sometimes compressed antero-posteriorly. The *iodine content* of parenchymatous goitres is always reduced, both relatively and absolutely, as compared with the normal thyroid.

In addition to diffuse parenchymatous goitre there are closely allied forms in which a nodular structure can be detected, though it may be inconspicuous. Many types of goitre occur intermediate between the diffuse parenchymatous form already described and the two that follow, so that the pathological structure is often more complicated than the descriptions given under the three main headings would imply.

II. **Colloid Goitre.** (*Struma Colloides Diffusa.*)—This type is common in areas of low endemicity, such as the Central European plains, in England and Wales, and in many parts of Africa, etc. Unlike the preceding type, the total iodine content of these goitres is equal to, or greater than, that of a normal gland, though bulk for bulk the percentage is less. Functionally, the gland appears to be satisfactory, for in such patients as have colloid goitre evidence of deficient thyroid activity is rare. Occasionally it is associated with hyperthyroid phenomena, usually of a mild or transitory type, though exceptionally a severe grade of secondary thyrotoxicosis may supervene.

Colloid goitre develops usually at or near puberty, but in certain endemic areas it is the most common congenital form. It may also occur during childhood and adolescence or later, but it is very rare to meet with colloid goitre in its typical form after the age of thirty.

Colloid goitres, though generally small and rather soft (*e.g.* the goitre of puberty in areas of low endemicity) may reach a very large size.

Colloid goitres have a rather pale pinkish or pinkish-mauve colour, and appear slightly translucent owing to the large amount of colloid they contain. They are, when moderate in size, flabby in consistence, but in the larger specimens the high degree of tension within the follicles results in a very solid, firm type of goitre, though less so than is general in hyperplastic glands. The true capsule is only slightly thickened, but the general connective tissue stroma of the gland is increased, resulting in conspicuous pseudo-lobulation in the older specimens. In advanced cases this fibrous stroma cuts off and encapsulates more or less rounded masses of parenchyma, so that transitional forms between the true colloid type and the nodular goitres can be traced. On cutting through the gland the honey-like, sticky, fluid colloid oozes from its surface. The vascularity of such goitres is often diminished, but exceptions occur, chiefly between puberty and adolescence, when the enlarged, tortuous arteries, especially at the upper pole, may give rise to conspicuous pulsation.

Substernal prolongations of the lateral lobes are very frequent in the larger colloid goitres, and they may also extend both upwards and backwards, almost or entirely surrounding the pharynx and oesophagus.

Histologically, the whole goitre can be seen to be formed of greatly distended follicles, the cells lining which are flattened. The nucleus and protoplasm of the cells show many of those appearances which are commonly regarded as indicative of cellular activity. The *follicles* themselves are often enormous, but, while usually fairly regular in shape, wide variations in size occur. We have examined specimens in which the diameter of many of the follicles exceeded 1,000μ, but more commonly they range from 150–500 μ. Hummock-like projections are occasionally found on the walls of the larger follicles. These hummocks consist of masses of follicles, mainly of small size and sometimes devoid of colloid contents. At the sites where the hummocks occur the follicular cells themselves are often columnar in type. The hummocks are probably newly-formed follicles which have arisen from the activity of the epithelium of the original follicle into which they project (cf. Chapter I).

The *colloid*, in all forms of colloid goitre, is semi-liquid and abundant. It stains uniformly and rather palely in most of the specimens and fills the vesicle. Occasionally histological evidence of physiological activity may be observed, but more commonly this is entirely lacking. In some inactive follicles the colloid becomes solid and hard, stains deeply with eosin, and, in sections, has a tendency to shrink and to fragment. Exceptionally, lymphorrhages are found in the stroma: fibrous and hyaline changes may also occur. Arterial degeneration is common.

Orator and Walchshofer (1927), working with material from Steiermark, were able to trace by histological methods the various transitions from the solid parenchymatous goitre of infancy and early childhood. They found that the former type, after the age of four, tended to develop lobules which, while solid at the periphery, had a central area of small follicles devoid of colloid, and that at puberty this central area became the site of a large colloid follicle, the peripheral follicles meanwhile acquiring colloid contents but remaining comparatively small in size.

Involution from a colloid to a normal gland is conceivable in the lesser degrees of the disease, but it seems probable that the majority of the larger colloid goitres develop eventually into nodular (adenomatous) goitres, as the former is so rarely seen after the age of thirty and the latter is the characteristic goitre in endemic areas in and after middle age.

Vascular goitre and *fibrous goitre* are terms which have been used to describe degenerate colloid or nodular goitres in which, in the one, there appears to be an excessive blood supply, and, in the other, an accumulation of fibrous tissue in the stroma. They are not to be regarded as specific varieties of goitre.

III. **Nodular Goitre.** (*Struma Nodosa, Multinodular Goitre*). This variety, which goes under the names of struma nodosa, adenoparenchymatous goitre, adenomatosis, and multiple adenomata, is the common form of endemic

goitre, though it is seen also as a sporadic condition. It occurs with great frequency in all endemic areas in patients over the age of thirty, but it may be found in children or infants in centres of high endemicity, especially where the disease has existed for generations. In endemic areas of recent development diffuse nodular goitre is seldom seen in young people, the colloid variety being the common type.

This nodular goitre produces a swelling which may be either roughly symmetrical, when the nodules are small and evenly scattered throughout its substance, or conspicuously asymmetrical, when one or more of the nodules increases greatly in size. When the whole gland is small, careful palpation is needed to detect the nodules, or they may be found only on cutting the gland open; in most cases the irregular outline of the gland indicates its nature. The adenomatous nodules may develop very strikingly in one lower pole, and as a result a large mass may be formed extending downwards into the thorax; if this tumour possesses only a narrow pedicle it may form a true intrathoracic goitre. Large nodules may also form in the upper pole, though this is rarer. If an adenomatous mass extends forwards in the gap between the infrahyoid muscle it may eventually draw out with it a long pedicle of skin and superficial tissues. A pendulous tumour thus develops, extending well on to the chest wall. Retropharyngeal, retro-oesophageal, retrolaryngeal, and retrotracheal extensions of the goitre may result from irregular development of one or more of the adenomata.

Macroscopical Appearance. On section, the naked-eye appearances vary according to the stage of the disease. An increase in the amount of connective tissue is always found, but in some specimens it may be very conspicuous, forming a tough, fibrous framework between the nodular masses of which the gland is composed; it may even be so tough as to resemble cartilage in texture, and calcareous deposits or actual bone formation may occur within its substance. The arteries often show the changes of endarteritis obliterans.

The adenomatous masses enclosed by the fibrous septa may be of almost uniform size, but far more often there is a wide range of variation in size, from a fraction of an inch up to some inches in diameter. The nodules may be of a pale yellowish-pink, semi-translucent appearance, indicating a colloid structure, or uniformly pale and opaque due to a parenchymatous microfollicular structure, or there may be degenerative changes, especially in the larger nodules. Haemorrhages are common, resulting in patches of a deep red or orange colour, with many intermediate shades of brown or yellow. Cyst formation is frequent, the cyst wall being generally formed of ragged remains of adenomatous tissue, though in some instances it may be quite smooth, when all macroscopic trace of the original solid material from which the cyst was derived has disappeared. In most cysts the contents are watery and brownish, but clear fluid or gelatinous colloid material is sometimes found. Cholesterin crystals in large numbers are generally present in the fluid contents of cysts. Large nodules often show a conspicuous, radiating, scar-like mass of fibrous or hyaline tissue near the centre; this is due to the imperfect blood supply to this region in the larger tumours. Opaque

yellowish-white foci of calcification may be seen in the connective tissue between the nodules and often in the nodules themselves; the latter may, in advanced stages, consist almost wholly of this calcified material. Small spicules of bone, and even large bony masses (Seelig, 1925), may exceptionally be met with.

Microscopically, the appearances correspond with the gross pathology. The stroma shows great overgrowth of the fibrous elements, and hyaline and calcareous, or even osteoid, changes occur in it. The structure of the nodules varies very widely, both within the individual nodules and in the different nodules found in each goitre. Oedema and mucoid degeneration are both common. Usually the nodules have the structure of colloid adenomata, with follicles often of enormous size, flattened epithelial cells, little evidence of secretory activity, and deeply staining colloid. The peripheral follicles tend to be smaller than those nearer the centre of the mass. The fibrous tissue which delimits the nodules contains in its meshes flattened and atrophic follicles, a fact which provides an indication of the method by which the nodules originate. Other nodules may have the structure of solid, colloid-free adenomata, the cells being arranged either in the form of numerous empty follicles with or without obvious lumina, or in long, more or less parallel columns. There are often large areas in these nodules in which the parenchyma is replaced partly or wholly by poorly-staining hyaline or granular connective tissue. Sinus-like blood-vessels, often of considerable size, may be found in the more degenerate nodules.

Evidence of cellular activity and of hyperplasia in the follicles may be detected in certain of the nodules, or it may be more generalized. The appearances closely resemble those seen in certain colloid goitres already described, viz., hummock-like formations in the wall of the follicles, consisting of small and, at first, empty follicles. The epithelium of the main follicle at the site of the hummock is often columnar in type. In rarer cases the hyperplasia may be of a more widespread nature, so that one or more nodules exhibit a structure which approximates to that seen in certain parenchymatous enlargements of the gland in infancy and childhood, and is not unlike those found in certain phases of primary toxic goitre (Graves' disease). In some such specimens there are to be found small cysts containing a papillary development from the lining epithelium, which may fill the whole cyst cavity with a branching structure made up of epithelial cells, often columnar in type, supported on a fine connective-tissue skeleton.

Just as with diffuse goitres, these nodular goitres are best classified on the basis of the size of the follicles they contain or the presence of solid-celled adenomata, *i.e.* on the degree of cellular and follicular differentiation (Wegelin, 1926).

Radio-iodine studies of thyroid nodules. Reference will be made later on to radio-iodine studies in nodular toxic goitre (Chapter XI). Dobyns and Lennon (1948) have recently published evidence that the functional capacity of thyroid adenomas is with few exceptions closely related to their degree of cellular differentiation. Ninety-four cases of nodular goitre were studied

and the usual assumption is made that the affinity for radio-iodine indicates the degree of function of the thyroid tissue. Slices of the nodule with some of the adjacent tissue were laid on photographic emulsion. The degree of exposure of the emulsion opposite the nodule is proportional to its concentration of radio-iodine, and consequently its functional capacity. The histology and function of different nodules and of the paranodular tissue may thus be compared. The solid embryonal adenoma and the struma trabecularis et microfollicularis show little affinity for the radio-iodine (" cold " nodules). Struma micro- et macrofollicularis absorbs and synthesizes the iodine in organic combination much more readily. Indeed, nodules with mixed micro- and macrofollicular hyperplasia may show great affinity for the radio-iodine and be productive of thyrotoxicosis (" hot " nodules), but this is not invariably so. In fact the presence of considerable hyperplasia is compatible with very little uptake of radio-iodine. Dobyns and Lennon's data suggest that, in this event, there is usually considerable irregularity in cell height and structure. Such nodules shade off into the adenocarcinomata.

Where the follicles are very large (struma macrofollicularis) there may be little uptake of radio-iodine. The tissue concerned may be considered to be in a state of hyperinvolution. Such nodules are described by Dobyns and Lennon as " over-ripe ".

Using a directional counter, Dobyns *et al.* (1949) have estimated the function of single thyroid nodules prior to surgical excision. When the ratio of the counts per minute from the nodule to the counts per minute from the extranodular tissue exceeds one the nodule is overactive, when it is less than one, the nodule is underactive.

Thus " hot " (hyperactive) and " cold " (undifferentiated or hyper-involutional) nodules can be distinguished. A patient with a " hot " nodule in the gland can still be euthyroid, if the nodule is small and if pituitary inhibition has resulted in inactivity of the remaining thyroid tissue. But if the " hot " nodule is large it will usually cause thyrotoxicosis.

The *blood supply* of large nodular goitres is often enormous, though the intraglandular vessels frequently show degeneration and obliterative changes. In some of the largest specimens which we have removed, the inferior thyroid artery has equalled the common carotid in size. The same condition of arterial enlargement has also been noticed by de Quervain (1926) in cretin goitres. Terry and Delamere (1924) found evidence of a rich anastomosis between the vessels supplying the adenomata in nodular goitres, the vessels tending to assume a radiating arrangement, though the branches anastomose freely among themselves. The larger vessels generally are healthy, but the smaller ones are poor in muscle fibres.

The *stroma* of the nodules is often increased by dense fibrous tissue, which may form an obvious white central stellate scar, or in rare cases may replace the adenoma by a solid pseudo-fibromatous structure which, however, reveals on section traces of its adenomatous origin. The stroma frequently undergoes hyaline and mucoid degeneration, and the latter is not infrequent even in the epithelial cells. Fatty, calciferous, ossific, and granular degenerations also

occur in various combinations: and, in addition, all forms of inflammation, both acute and chronic, may affect nodular goitres.

Single Adenomata. Single adenomata are apparently rare in endemic areas, but among sporadic cases single, well-encapsuled adenomata and cysts are very common, the remainder of the gland being healthy.

Such tumours have complete capsules, differing in this respect from the adenomatosis of nodular goitre, in which imperfect encapsulation of the smaller nodules is the common condition. The appearance of single adenomata, both macroscopically and microscopically, does not differ from that of the more obvious nodules met with in the diffuse variety of the disease. The capsule of the adenoma is composed of fibrous tissue, and may show hyaline, mucoid, calcareous, or osseous, degenerative changes. The intra-adenomatous stroma is well developed; its central portion, poorly supplied as it is with nourishment, often undergoes hyaline or fibrous degeneration, and a white, almost translucent scar, with radiating septa passing outwards from it towards the periphery, is sometimes visible. In colour the adenoma is often variegated from pale yellow through brown to deep purple. One or more cystic cavities may develop, and if they coalesce a large single cyst forms, with a capacity of up to a pint or more. The fluid within the cyst may be quite clear, but it is sometimes dark in colour, and may contain cholesterin crystals. Either the cyst is smooth within or remnants of the solid material of which the whole originally consisted project from its wall. The parenchyma and the stroma of adenomata are liable to degenerative changes similar to those already described in connexion with the diffusely nodular forms of goitre.

These single nodules, occurring in otherwise perfectly healthy glands, are probably true benign new growths arising from pre-existing follicles (Cattell and Eckerson, 1936; Boyd, 1938). The degree of epithelial follicular differentiation within the nodule is variable, as in the nodules of generally nodular goitres. Every stage from the solid embryonal type to the macrofollicular colloidal adenoma may be found.

Thyroid Cysts

Cysts of the thyroid are of two types, viz.:

(*a*) DEGENERATION CYSTS
(*b*) RETENTION CYSTS

(*a*) *Degeneration Cysts.* These, the common cysts of the thyroid, are the result of degeneration and liquefaction in solid adenomata. They often reach a large size, and in nodular goitres may be multiple. It is, however, unusual to find more than one to be large.

The various stages in the transformation of a solid adenoma into a cyst may sometimes be followed in a single nodular goitre. The softer and more vascular adenomata frequently show haemorrhages into their substance, and, as these extend, more and more of the originally solid tissue becomes converted into liquid.

The *wall* of the cyst may be thin, its inner surface being smooth and trabeculated, or thick from the formation in it of laminated fibrous tissue. In most cases the nature of the cyst may be detected by observing that small masses of adenomatous tissue remain attached to its inner surface. Usually these remnants are visible on careful inspection by the naked eye, but in some microscopical examination is necessary. If the cyst wall is thin, the fluid contents give to it a characteristic bluish colour before it is opened, unless it happens to be buried deeply in thyroid tissue; if thick-walled it is opaque. Calcification and sometimes ossification may occur in the wall of the cyst.

The *contents* of degeneration cysts vary greatly. Sometimes the cavity is filled with a firm, semi-translucent, jelly-like material, resembling colloid which has been deprived of some of its water. In other cases the cyst contains colourless or faintly yellow, limpid fluid, with or without a small amount of coagulum. If haemorrhage has occurred into the cyst cavity—a common complication—altered blood is found, and the contents may assume shades of brown and red. Shimmering cholesterin crystals may be present, often in great numbers. In old-standing cases the cavity of the cyst may be occupied by a solid or pultaceous mass of yellowish, cheesy material containing lime salts and therefore opaque to X-rays. Rarely, a single stone may fill the interior, and even more uncommonly a number of small mulberry-like calculi may occupy the cyst cavity. Suppuration may also occur as a rare event spontaneously, the pus either being sterile or containing pyogenic organisms of low virulence.

(*b*) *Retention cysts* are caused by the fusion of distended colloid-containing follicles; it is very doubtful whether a cyst of clinical importance could arise from the distension of a single follicle. Retention cysts are usually thin-walled, and contain colloid. They seldom reach a size greater than a walnut. Papillomata sometimes develop inside small retention cysts, and by their continued growth may fill the cyst cavity or distend it still further. The condition may be multiple, but does not appear to be related to the papilliferous carcinomata.

Spontaneous haemorrhage into degeneration cysts is not uncommon. It is probably due to the bursting of a vessel in the soft and degenerate adenomatous tissue which so often lines the interior of the cyst wall. Though described as spontaneous, there may be a traumatic factor, or the haemorrhage may follow excitement or physical or mental strain. In one case which came under our observation, the patient, who had a thyroid tumour of moderate size, was called upon to reply to certain pointed criticisms at a company meeting, and made a somewhat impassioned defensive speech. On his return home he felt a constriction of the neck and had to loosen his collar; he noticed that the tumour had greatly increased in size. Operation revealed that a large haemorrhage had occurred into a thyroid cyst.

Plummer and Broders (1933) designated as " acute capsulitis," a syndrome characterized clinically by painful acute enlargement of a thyroid nodule, and pathologically, by congestion, oedema, and intense lymphocytic

infiltration of its capsule, and haemorrhagic or necrotic degeneration of its substance.

Chemistry of Simple Goitre. There is a noticeable increase in the amount of silica, magnesium, calcium, phosphorus, and chlorine in goitrous glands, particularly in the old-standing nodular varieties.

The iodine content of the various forms of simple goitre has been worked out in a few districts, but comprehensive figures are not available. No final conclusions applicable to goitre generally are therefore legitimate. It has been shown too that the iodine content of the thyroid is not a sure indication of its thyroxine content, and therefore estimates of the functional capacity of this or that type of goitre based purely on the iodine content are most unreliable.

In general, it may be stated that in pathological thyroid glands, whether of the so-called simple or the toxic variety, there is a percentage deficiency in iodine. The deficiency is greatest in hyperplastic glands, such as are seen in infants in areas of high endemicity, and least in the symmetrical goitres containing abundant colloid material in a fluid state. The *total* iodine content, however, of twelve goitrous glands in Freiburg was found by Baumann to be slightly greater than that of healthy thyroids from the same district, and Jansen and Robert (1927) found a considerably increased total amount in goitres from the neighbourhood of Munich. Marine (1930) states that the percentage of iodine in adenomatous nodules is less than that in the surrounding thyroid tissue.

The ratio of thyroxine to total iodine is reduced to the region of 14 per cent. compared with the normal figure of approximately 30 per cent. (Elmer, 1932). The concentration of tyrosine is comparatively high (Cavett, 1936) and it is suggested that there is interference with the conversion of tyrosine into diiodotyrosine. This agrees with the primary deficiency being one of inorganic iodine. The blood organic iodine is also on the low side of normal so it is clear that the low thyroid iodine concentration is not due to excessive elimination.

Le Blond *et al.* (1946) in their radioiodine study of nodular goitres occurring in a goitre belt found that most of the nodules were functionally less active than the paranodular tissue as indicated by a low iodine content, a sluggish uptake of radio-iodine and a feeble turnover of the iodine into hormone precursors. The difference was most striking in a case of " foetal " adenoma but it was also marked in four goitres with colloidal nodules.

Pathological Anatomy. Small parenchymatous goitres may produce severe pressure, leading in the congenital forms to grave dyspnoea; but as a rule they are not productive of serious symptoms. Occasionally these solid goitres extend backwards behind the pharynx and oesophagus or between the pharynx and larynx and give rise to a " circular " type of goitre associated with both dyspnoea and dysphagia. The compression of the trachea is often in an antero-posterior direction.

Colloid goitres when soft and of small size rarely press seriously on the neighbouring structures, but larger ones, especially during the years which

intervene between puberty and adolescence, may so compress the trachea that it becomes scabbard-shaped, the narrowing corresponding with an area of from one to two inches below the cricoid cartilage. Intense stridor and dyspnoea, sometimes leading to fatal results, may follow this type of compression, which is relatively commoner in males. The onset may be sudden and there may be but little warning. The exact mechanism of the compression is not fully understood, because it is not always found in association with very large goitres, but may occur with small goitres or with those of moderate size. A severe cold or some similar catarrhal condition may precipitate the dyspnoeal attack. The tracheal compression has been ascribed to atrophy of the tracheal rings, though the existence of this is denied by Berry, and his opinion is supported by direct inspection of the trachea in our own cases.

The trachea is, however, known to be softer and more compressible in young people, and it may be that once the scabbard deformity is produced its rectification is prevented by the very nature of the tracheal wall, much as a thin celluloid ball will resist indentation up to a certain point, but, once effected, restoration of the spherical shape becomes impossible.

A colloid goitre frequently assumes the "circular" form, extending behind the pharynx and oesophagus until the two lobes actually meet or perhaps overlap. It is particularly the upper poles of the gland which show this tendency, which has to be allowed for when attempting to dislocate these poles during operations: the finger has to be thrust upwards deeply behind the pharynx to achieve the desired end.

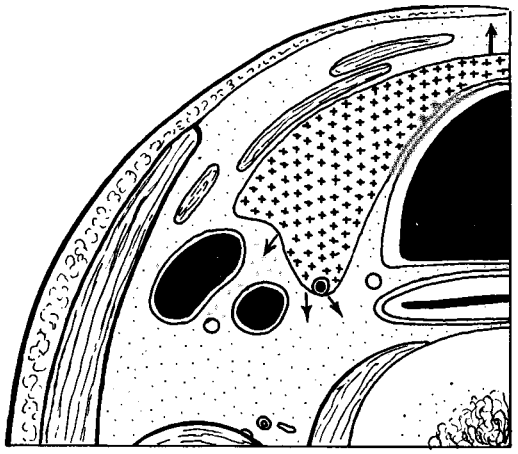
In goitre the lateral ligaments of the gland are thickened and so, in spite of their greatly increased weight, the lateral lobes remain firmly attached to the tracheo-laryngeal junction. This is a fixed point about which, at operation, the lobe can be elevated and turned inwards, as it were on a pivot. In goitre, also, enlargement takes place from this site (Fig. 38). The enlarging gland displaces the carotid sheath backwards and laterally and extends into the retro-pharyngeal and retro-oesophageal space. Here it comes up against the unyielding vertebral column, hence the tendency for such "circular" goitres to displace the viscera forwards.

The lower poles of colloid goitres often extend down to, or behind, the clavicles and sternum, so that the swelling in the neck assumes a truncated shape, being wider below than above. The lower poles may extend a considerable distance into the thorax, and the goitre thus becomes substernal, but, except in heterotopia of the whole gland, true intrathoracic colloid goitres do not occur.

Large colloid goitres displace the internal jugular veins outwards, the middle thyroid veins tethering the two together, but the carotid artery is displaced backwards and outwards, since it is freer to move independently of the goitre. The important nerves of the neck are seldom seriously affected. Deep grooves are, however, often made in the surface of the gland by the infrahyoid muscles, which become tightly stretched as the goitre enlarges.

It is often difficult during operations to dissect the muscles cleanly away from the goitrous tissue.

With cystic and solid adenomata, both solitary and diffuse, the degree and type of pressure vary considerably. Bilateral compression associated with more or less lateral displacement, or even actual torsion, of the trachea may occur in the diffusely nodular type of enlargement, whereas in the single adenoma the trachea is often kinked or bent, with one side flattened or concave and the other convex. Gross displacement of the whole larynx and trachea to one side or the other is seen less often than in malignant goitre.



TRANSVERSE SECTION THROUGH
LOWER CERVICAL REGION

FIG. 38.—Transverse section through lower cervical region. The arrows indicate the directions in which the gland enlarges when goitrous.

A single adenoma, if it should happen to lie postero-laterally, may press on the oesophagus sufficiently to interfere with swallowing. If, in addition, secondary inflammatory changes affect the adenoma in this region, it may become adherent to and subsequently by its growth stretch and paralyse the recurrent laryngeal nerve.

It is common to find single tumours and cysts developing from the lateral lobe and nearer the lower than the upper pole. As it enlarges, the contractions of the sternomastoid muscle tend to force the tumour downwards and inwards, so that sooner or later it pushes the infrahyoid muscles forwards and becomes prominent above the sternum. The adenoma may eventually occupy a symmetrical position and appear finally to have originated in the isthmus.

If an adenoma develops near the lower pole, especially in a short neck, it may soon dip entirely behind the sternum and clavicle and give rise to the most common type of intrathoracic goitre.

In very rare instances an adenoma insinuates itself behind the larynx or trachea and comes to occupy a position between the respiratory and alimentary passages. Very large cysts and adenomata may also involve, either by direct pressure or by the supervention of inflammatory changes, the sympathetic or the vagus nerve.

"*Goitre plongeant*" is a term sometimes used to describe intrathoracic or retrosternal forms, but it is better to restrict the name to those adenomata which, while the patient is in repose, lie immediately behind the sterno-clavicular joint. On coughing or swallowing they rise and are revealed in the neck as small or moderate-sized tumours. Should any sudden increase in the bulk of such a nodule occur, *e.g.* following a haemorrhage into its substance, it may no longer be able to move upwards on coughing and, becoming impacted, may produce grave and urgent dyspnoea.

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CHAPTER VI

SIMPLE GOITRE—CLINICAL FEATURES

Clinical Features — Pressure Signs — Cough — Stridor — Alterations in Voice — Pressure on Oesophagus — Dysphagia — Pressure on Arteries, Veins, Nerves — Recurrent Laryngeal Paralysis: Sympathetic, Vagus, Cervical or Brachial Plexus— Methods of Examination of Thyroid Enlargements — Size — Examination of other Structures in the Neck — Consistency — Mobility of the Tumour — Movements on Deglutition — Skiagraphy in Simple Goitre — Functional tests in Simple Goitre.

Murray *et al.*, 1948, classify the goitres of children and adolescents as follows:

(i) Visible to the trained observer, but soft, smooth and symmetrical.

(ii) Conspicuously enlarged (visible plus) but showing no palpable asymmetry, firmness or nodular change. This type is sometimes referred to as the " Rossetti " neck.

(iii) Showing a degree of firmness, asymmetry or nodular change, which can be regarded as definitely pathological.

The small, smooth and symmetrical enlargement in young children is a parenchymatous goitre. Its consistency is rather firmer than the more colloid goitre of adolescence. In adults most goitres are established and fall into Group (iii), or are of the large, soft, diffuse colloid type. The diffuse colloid goitre, if large, may persist unchanged well into the fourth decade.

In extremely large colloid goitres a diffuse and finely nodular surface may be felt, corresponding to an increase in the connective tissue which tends to break up the parenchyma into more or less rounded masses; these are visible to the naked eye on examining the cut surface. In the nodular goitre proper the irregularity of the surface may be very conspicuous, and in extreme cases gross asymmetry results from the unequal size of the masses in the two lobes. Some nodules may fluctuate, owing to the softness of their contents or to cystic degeneration. A hard nodule may be due to a thick or tense capsule or to calcification or even ossification in its substance.

Even very large goitres may cause little or no discomfort, the patient presenting for cosmetic reasons (Fig. 39). However, a variety of pressure signs may develop.

Pressure Signs—Pressure on the Trachea is common with all varieties of simple goitre. Its degree and extent vary with the firmness of the gland and its rate of growth, and also with the age of the patient, for in children and young adults the trachea seems specially susceptible to pressure of a bilateral type. Occasionally, as in the cases quoted below, the degree of tracheal compression appears to be out of all proportion to the size or firmness of the goitre. The exact site of compression is not constant, but it is usually found about 1 to 2 in. below the cricoid cartilage, being, however,

lower in the long-necked than in the short- or bull-necked. Nodular goitres may also give rise to lateral displacement and kinking of the trachea, simple in type with single adenomata, but sometimes resulting in double or triple curves with the larger and more diffusely nodular types. Antero-posterior compression, though less common than in malignant and inflammatory goitres, does occur in simple goitre.

The larynx is seldom seriously affected by simple goitre, but when very large a single adenoma will displace the whole larynx to one side and rotate it away from the affected lobe.

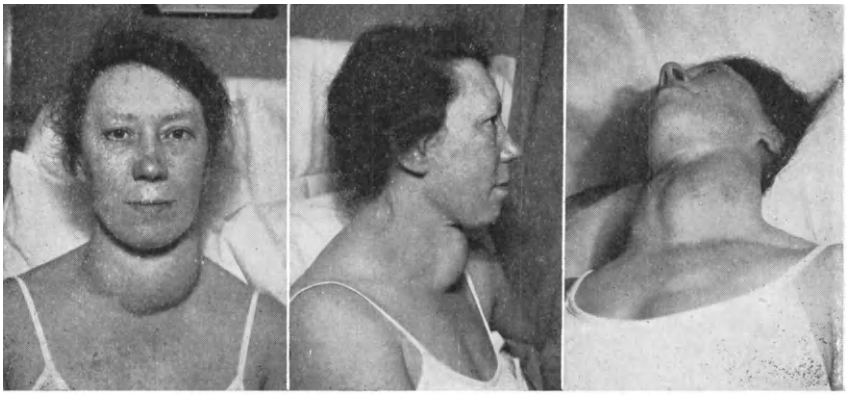

FIG. 39.—Simple (non-toxic) nodular goitre: The patient, aged 43, had had a goitre since the age of 18. There were no symptoms apart from slight dysphagia. There was a deeply placed nodule on the right side, extending retrosternally. Basal metabolic rate estimations, plus 5 per cent., and plus 1 per cent. A goitrous mass weighing 410 gm. was resected.

Recurrent attacks of bronchitis, tracheitis, and laryngitis increase the severity of the dyspnoea associated with the tracheal compression. In extreme cases death from suffocation results.

Cough is a common result of pressure on the trachea. It is met with in both bilateral and unilateral tracheal compression. Usually the cough is of a dry and spasmodic type. When due to intrathoracic extension of the goitre, it is frequently nocturnal and may be associated with severe asthmatic attacks, which have frequently been confused with ideopathic asthma. When bronchitis and tracheitis are superadded, cough is more obtrusive and associated with sputum characteristic of the various stages of these diseases.

Stridor is met with, especially in bilateral compression. It may be absent when the patient is at rest, and evoked only by physical exercise or excitement. Occasionally merely raising the arms above the level of the body will bring out stridor which was previously unnoticed. It is usually inspiratory, but may exceptionally be both inspiratory and expiratory.

Alterations in voice occur occasionally, even when there is no laryngeal paralysis, in both unilateral and bilateral thyroid enlargement. A peculiar creaking quality is not unusual with large goitres, and in other cases the voice may be weak and aphonic, on the one hand, or harsh, on the other. Sudden and unaccountable " breaks " in the voice may also be met with. It must not be forgotten that laryngitis and bronchitis may accompany any large goitre and take a share in the causation of alterations in the voice.

Pressure on Oesophagus—*Dysphagia*—This is a decidedly rare feature of simple goitre. Colloid goitres, even when large and of the retro-visceral or circular type, seldom produce any real difficulty or pain on swallowing. Occasionally an adenoma or tense cyst, lodged between the trachea and oesophagus, may give rise to true dysphagia, the site of obstruction being visible under radiological examination. In the severe grades of pressure produced by intrathoracic goitres, dysphagia is more common, and may be serious, but in general it is extremely rare for a simple goitre to be associated with a degree of dysphagia sufficient to interfere directly with nutrition. By contrast, it must be admitted that dysphagia is often complained of by patients with small soft goitres which from their size and physical characters could not conceivably press on the oesophagus. In such patients radioscopic examination shows that there is no delay or other modification in the act of swallowing, and the dysphagia is clearly of a functional character.

Pressure on Blood Vessels—(i) *Arteries*—The common carotid arteries are displaced backwards and outwards by large simple goitres, though the postero-lateral aspect of the latter is often deeply grooved by the vessels. The wide separation which frequently occurs between the carotid artery and the internal jugular vein is the result of the anatomical differences in the connexion existing between these structures and the goitre. Usually there is no branch passing directly from the common carotid artery to the gland, so that the former is in no way tethered to the latter, but is free to move away when the goitre enlarges. Its backward movement, however, is checked by the spine, so that the artery is displaced outwards as well as backwards by large goitres.

(ii) *Veins*—The internal jugular vein receives the middle thyroid veins and usually, in addition, the superior thyroid vein, so that these, especially if short, tether the vein to the enlarging gland, to the outer surface of which it often becomes closely apposed. This displacement and separation of the great vessels of the neck has to be remembered, especially during surgical operations.

In addition, the larger simple goitres may press sufficiently on the internal jugular and subclavian veins to cause actual cyanosis and even oedema of the face, neck, and upper limb. Dilatation of some of the superficial veins in these areas is, however, more usually met with. In large impacted intrathoracic goitres the veins of the chest may exhibit dilatation and varicosity resembling the " Medusa head " seen on the abdomen in advanced portal cirrhosis, and due similarly to the opening up of collateral venous channels.

necessitated by the obstruction in the main veins returning blood from the head, neck, and upper limbs.

Pulsation, thrills and bruits are sometimes detected over simple goitres. They are due to abnormally large and tortuous or degenerate thyroid arteries, and are therefore localized expecially to the sites where those arteries enter the gland. They are not characteristic of any particular type of simple goitre, though they are rather common in large, degenerate cretin goitres. In certain rapidly developing colloid goitres in young adults pulsating vessels (branches of the superior thyroid artery) may also be detected near the upper poles, where the vessels generally are more easily palpable. Pulsation, thrills, and bruits are of course, more commonly met with in toxic goitres, especially of the primary group, but no definite distinction between simple and toxic goitre can be made on this score.

Pressure on Nerves—Simple goitre may give rise to paralysis, partial or complete, of one of the main cervical nerves lying in relationship to the gland, but such paralyses are to be considered exceptional and, to a certain extent, accidental.

(i) *Recurrent Laryngeal Paralysis*—Interference with the recurrent laryngeal nerve occurs when inflammation or calcareous degeneration takes place in some part of the goitre and spreads beyond the true thyroid capsule. These changes are seen most often in association with degenerate cysts and adenomata in nodular goitres.

In our experience the resulting paralysis is invariably unilateral, very gradual in onset, and at first intermittent. The voice is weak and harsh, and with it there may be a brassy cough. Laryngoscopy usually reveals a complete unilateral abductor paralysis. In rarer cases the paralysis is due to stretching of the nerve over a rapidly enlarging nodule or a cyst into which haemorrhage has occurred. It is by no means invariable for the paralysis to disappear after the removal of the goitre which caused it.

Systematic laryngoscopic examination reveals that in simple goitre weakness of one vocal cord, associated with complete lesions of the recurrent laryngeal nerve, is more common than is usually suspected and with it the voice may be unaffected.

(ii) *Sympathetic*—This nerve is also, as an exceptional event, paralysed by a simple goitre. The pathological processes involved are probably similar to those described for recurrent laryngeal paralysis. The greater rarity of sympathetic paralysis is the result of the less intimate association between the thyroid gland and the nerve. The usual phenomena are narrowing of the palpebral fissure and diminution in the size of the pupil on the side corresponding to the lesion.

(iii) *Vagus*—Pressure by a simple goitre on the vagus trunk sufficient to produce unequivocal symptoms is exceedingly rare, but we have seen two cases which exhibited this phenomenon. One of them was in a male patient, aged fifty-four, with a huge adenoma of the left lobe. Periodical attacks of bradycardia followed by syncopal seizures occurred. These symptoms ceased abruptly with the removal of the tumour, which at the operation was seen

to be displacing the whole carotid sheath and its contents. Cornioley and Second (1929) record a somewhat similar case in a male.

(iv) *Cervical or Brachial Plexus*—In simple goitre neither of these plexuses is likely to be affected unless inflammatory complications be superadded, when pain referred to one or other of them has occasionally been noted. In firmly-wedged intrathoracic goitres pain due to pressure on the brachial plexus has been recorded, and even weakness of the limb, the result of interference with the motor fibres. The phrenic nerve is said to be sometimes paralysed in cases of intrathoracic goitre, but we have not met with such a case.

Methods of examination of Thyroid Enlargements. Good illumination, complete exposure of the head, neck and chest and muscular relaxation are the essentials for success in the diagnosis of thyroid enlargements and their differentiation from other cervical swellings. Murray *et al.* (1948) recommend that the patient be seated on a swivel stool adjusted to an appropriate height: " In this position the neck is first inspected at rest, and on swallowing, with the head at a natural angle. Care should be taken to distinguish a prominent cricoid cartilage from the isthmus. The gland is next palpated in the region of the lateral lobes with the flat of the finger-tips of both hands. The isthmus can be most conveniently palpated with the flat of the thumb, the fingers being placed behind the neck. The swivel stool is then turned and the neck is inspected in profile. In this view, true thyroid fullness appears as a gently rounded convexity of varying degree in place of the more usual straight line from the larynx to the suprasternal notch. The stool is then turned further and the gland finally palpated from behind with the finger-tips of both hands."

The size, symmetry or otherwise, consistency, nodularity and other characteristics of the goitres should all be noted at the time. A diagrammatic record of the clinical features of the goitre should be kept as a routine (Fig. 40).

Unilateral enlargements of the gland may be rendered prominent and easily palpable by pressing back on the unaffected side with the ball of the thumb. By this manoeuvre the trachea is displaced to the affected side and the nodule is thereby pushed up under the skin.

Size. There is no objective and accurate method of recording the size of a goitre. Circumferential measurement with a tape-measure placed round the neck over the most prominent part of the tumour is at best approximate.

Examination of other structures in the neck. No examination is complete which fails to include a careful survey of the structures immediately related to the goitre, namely the trachea and larynx, the recurrent laryngeal nerve, the oesophagus and the great veins of the neck. The cervical lymph glands draining both lobes and isthmus must also be palpated systematically in every case. The possibility of intrathoracic extension should be considered and, if thought necessary, excluded by radiography.

Consistence. Parenchymatous goitres are firm in consistency; small colloid ones are soft and doughy; large colloid goitres may feel almost hard, owing to fibrosis and to the distension of the follicles with colloid,

while nodular goitres are of varying consistence, hard and soft nodules being found scattered irregularly through the gland.

Calcification and ossific changes may affect any old-standing goitre and modifiy the consistence accordingly. The presence of a stony-hard mass in a goitre, especially when associated with pressure phenomena, will raise a suspicion of malignancy which may only be allayed by skiagraphy.

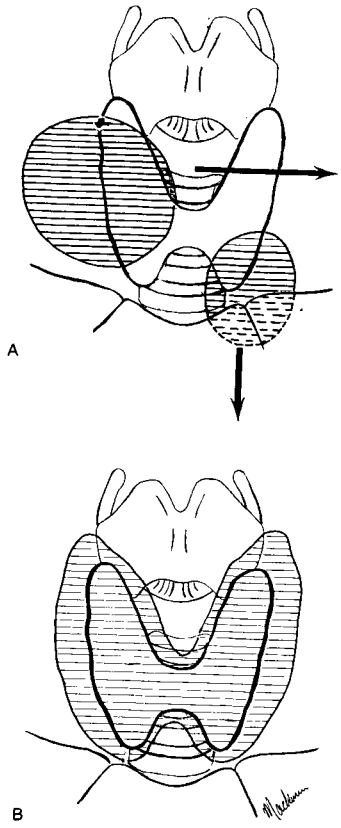

FIG. 40.—Method of recording clinical pathology of the goitre. A. A large nodule in the right lobe is displacing the trachea to the left and a nodule on the left is extending retrosternally. B. Diffuse goitre is present, enlargement is graded roughly as slight (+) moderate (++) and considerable (+++).

Cystic swellings, unless so exceptionally large and salient that they can be examined for translucency by transmitted light, are very difficult to differentiate from certain solid adenomata. If a cyst has thick fibrous or calcified walls the translucency test fails.

The shape and position of the tumour will generally suffice to prove its goitrous nature. Parenchymatous and colloid goitres may be sufficiently irregular to obscure the original thyroid contour completely.

A *single adenoma* is occasionally mistaken for a colloid goitre when the former has assumed a position in or near the middle of the neck, a tendency which, sooner or later, nearly all such tumours have. The goitre at first appears to be symmetrical in shape, but its adenomatous nature can be recognized by noting that the upper border of the tumour is rounded and convex, while that of a colloid goitre is concave. In addition, if the observer seats himself behind the patient and palpates the two sides of the neck simultaneously, fingers in front of and thumbs behind the sternomastoid muscles, it may be possible to feel that the adenomatous mass is on one side of the trachea and that the other thyroid lobe is normal. The displacement of the trachea to one side by such an adenoma or cyst may also be detected in this way.

Mobility of the Tumour. The degree of fixation between simple goitres and the larynx and trachea varies, but as a rule a certain amount of movement between them is possible. Inflammatory changes may considerably modify this mobility. On the other hand, an adenoma or cyst may acquire a pedicle of such length that the tumour migrates downwards in the thorax and loses all obvious external association with the thyroid, or hangs down over the chest wall as far as the patient's waist, carrying with it an attenuated pedicle of skin.

Movements of Deglutition. Demonstration of the existence of this movement is perhaps the most valuable diagnostic feature for simple goitres, though it is not necessarily confined to them. It is the outcome of the close association between the thyroid and the larynx and trachea, which are pulled upwards with the hyoid bone during swallowing. All thyroid tumours must therefore move in this way unless they are of an infiltrating character and have invaded the surrounding structures to such a degree that the upward movement is lost. The largest simple goitres may fail to show the movement, but, even when this is so, careful palpation over the mass during the act of swallowing will reveal a peculiar vibration, tug, or thrill, which indicates that the larynx is moving, or is being drawn on, underneath the bulky tumour mass. It must be remembered that upward movement of a tumour on deglutition does not prove anything more than that the tumour is connected with the larynx and trachea. Pathological swellings which develop on the outer surface of the larynx, *e.g.* chondromata of the thyroid, cricoid, or tracheal cartilages, will therefore exhibit the same phenomenon, but such swellings are rare, and their peculiar position and characters usually enable the distinction from goitrous enlargements to be made with ease. Exceptionally, *enlarged lymphatic glands* acquire adhesions to the larynx or trachea, and in shape, size, and movement on deglutition may more or less closely simulate thyroid swellings. Most commonly such glands are tuberculous and tend to become adherent to the skin and sooner or later to discharge their softened contents through sinuses, so that the distinction from a thyroid swelling is then made without much difficulty. From time to time fibromata, lipomata, and sebaceous cysts are met with which have acquired adhesions to the trachea and larynx, and by the

similarity of their movements during the act of swallowing may resemble goitrous enlargements.

Skiagraphy in Simple Goitre. Properly orientated skiagrams will reveal:

(*a*) the position of the trachea in relation to the tumour. Palpation may give an indication of the degree of displacement of the trachea, but it is rarely possible to gauge accurately the degree to which the trachea is flattened or distorted. This information is of great value in deciding on the necessity for operation, in planning its scope, and in selecting the mode of anaesthesia.

(*b*) The presence, size, and extent of retrosternal or intrathoracic goitre.

(*c*) The presence of calcification, ossification, etc.

Functional Tests in Simple Goitre. Basal metabolic estimations (Chapter XVI) in simple goitre reveal figures within a range of from 15 per cent. below to 15 per cent. above the normal level. If the result in a given case is below or above these limits it is to be regarded as evidence of either a defective or a toxic condition, thus excluding the case from the category of simple goitre. There are, however, certain cases on the borderline, on the one hand, between diminished functional activity and the normal or euthyroid state, and on the other between the euthyroid and the thyrotoxic, which have to be treated on their merits. In a certain number of goitres, especially in adolescent girls, the figures obtained by this test tend to approach or slightly exceed the higher limit given above. In this class of case there may be certain other features suggesting a mild degree of thyrotoxicosis, *e.g.* moderate tachycardia, excessive sweating, and tremor, but they are usually of a transitory nature and do not become established as cases of frank thyrotoxicosis. By contrast there are many cases, especially in areas of high endemicity, in which the B.M.R. figures tend to be low. In a few of them the basal rate may fall below the normal by as much as 15 per cent. or more. Such cases are to be regarded as *hypothyroid*, in contrast to the common *euthyroid* status of the simple goitre case.

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CHAPTER VII

SPECIAL TYPES OF SIMPLE GOITRE—TREATMENT OF SIMPLE GOITRE

General Phenomena associated with Simple Endemic Goitre — Simple Goitre associated with Acute Dyspnoea — Simple Goitre and Pregnancy — Intrathoracic Goitre — Intrathoracic Goitre Proper — Mediastinal Goitre — Goitre Plongeant — Substernal Goitre — Mechanism of Production of Intrathoracic Goitres — Pathological Anatomy — Incidence — Age and Sex — Signs and Symptoms — Dyspnoea — Diagnosis of Intrathoracic Goitre — Prognosis and Treatment — Prophylaxis of Simple Goitre — Iodine as a Prophylactic — Methods of Prophylaxis — Dangers of Iodine Prophylaxis and Treatment — Thyroid Preparations and the Treatment of Simple Goitre — Radiation Treatment of Simple Goitre — The Surgical Treatment of Simple Goitre — Single Adenomata or Cysts — Prophylactic Operations on Thyroid Adenomata — Cosmetic Indication for Operation on Simple Goitre.

General Phenomena associated with Simple Endemic Goitre. Frank cretinism and myxoedema occur in areas of high endemicity. There is also ample proof that the incidence of deaf-mutism is greater in districts with an iodine-poor water supply (Murray and Wilson, 1945). Of course, unless cretinism is treated early and continuously, idiocy follows. Thus the most striking ravages of iodine deficiency are cretinism, idiocy and deaf-mutism (Fig. 41).

Of greater social and economic importance, however, are the more insidious consequences of mild thyroid deprivation. They receive little attention but *in toto* they cause considerable interference with health and efficiency. Eason (1939) includes among them mental and physical lethargy, constipation, sluggish skin action and catarrhal disorders. King and Herring (1939) affirm that the hypothyroid state is the chief factor responsible for sterility and abortion in women. Kemp (1939) has produced data suggesting that iodine deficiency and consequent mild hypothyroidism are also important causes of still-births.

TABLE VII
(*From Shee*, 1939)

	Intelligence			Total	Percentage with poor intelligence
	Good	Fair	Poor		
Normal Thyroid	416	212	95	723	13·14
Slight Goitre	342	187	108	637	16·95
Established Goitre	66	53	37	156	23·72

Classical writers refer to goitre-producing waters as causing stupidity in those who drank them. Shee (1939) assessed the intelligence of schoolgirls in the endemic of South Tipperary, and his data (Table VII) suggest that there is a clear relationship between goitre and mental backwardness.

In endemic areas there is also definite retardation of physical growth (Stocks, 1927). Iodine prophylaxis continued over a period of three or four years was shown by Stocks to cause a significant increase in growth rate.

FIG. 41.—Consequences of iodine deficiency. The family of goitrous parents; four of the children are deaf-mutes. Danielopolu, D. (1937) *Les thyroidies endémiques et sporadiques*. Masson & Cie., Paris.

On the other hand, where the iodine deficiency is mild, adolescent goitre may be associated with a height above average for the age; rapid growth during adolescence may place increased demands upon the thyroid gland.

Simple Goitre associated with Acute Dyspnoea. In addition to the forms of dyspnoea which have already been described in connexion with nodules both single and multiple, cysts, retrosternal and intrathoracic goitre, and malignant disease, there is a type which in Great Britain is found almost exclusively in cases of diffuse colloid goitre. The condition is rare, and we have had only three cases under our own care.

The persons affected have comparatively small or moderate-sized bilateral colloid goitres, and the degree of dyspnoea apparently bears very

little relation to the actual size of the gland, but is undoubtedly due to a rapid increase in its bulk, associated with either a widespread distension of the follicles with colloid or oedematous changes in the gland.

In some cases the goitre has existed for months or years without respiratory disturbance, and the attack of acute dyspnoea follows a simple cold or some other trivial illness; in a few the goitre appears to be of recent origin and the dyspnoea is progressive; in others, periodic attacks of acute dyspnoea occur, but subside temporarily, only to be followed by more severe paroxysms. In all such cases with acute dyspnoea, immediate surgical intervention is indicated.

It has been proposed to treat such cases by tracheotomy, but this usually fails to relieve the condition because the site of the tracheal compression is often considerably lower than that at which tracheotomy is feasible. A comparatively long segment of the trachea is involved, so that unless special tracheotomy tubes, such as König's, are available, it is very unlikely that the dyspnoea will be relieved; added to which the difficulties of exposing the trachea, due to the mass of vascular thyroid tissue which has to be divided before this structure can be reached, make it an extremely hazardous and sometimes a prolonged operation. In our opinion it is infinitely more satisfactory to carry out a thyroidectomy, freely dividing the infrahyoid muscles so as to facilitate the rapid dislocation of the lateral lobes. As soon as this step is accomplished the patient will almost invariably begin to breathe comfortably.

Attempts have also been made to relieve the condition by the passage of an intratracheal tube. The difficulty of introducing such an instrument into a cyanosed patient who is using the accessory muscles of respiration, and in whom attempts to extend the neck produce an alarming increase in the dyspnoea, sometimes precludes the use of the method. There is no difficulty, however, in passing such a tube once the dyspnoea has been relieved by the dislocation of the lateral thyroid lobes. The tube then permits the operation to be completed without undue haste.

Simple Goitre and Pregnancy

Lawson Tait (1875) first described the step-like enlargement of the thyroid with each pregnancy. In women whose thyroids were previously normal, slight visible and palpable enlargement during pregnancy is common, but it is not always progressive and may disappear in the later months.

It is probably incorrect to speak of such slight enlargements as goitres, though it must be admitted that it is difficult if not impossible to define the point at which such enlargements pass out of the physiological into the pathological category. A few simple goitres undoubtedly do develop for the first time during pregnancy, even outside endemic goitre districts. They may be of the diffuse colloid type, but in England and Wales are more often localized or simple adenomata, and while they may become stationary, or even appreciably smaller, after delivery, they often continue to grow, and to behave as do most adenomata of this type.

If the patient is already goitrous, the gland may not increase in size; von Graff (1914), however, found that in 38·5 per cent. it became larger. Gardiner-Hill (1929) noted progressive increases with each pregnancy, but could find no evidence of any lack of fecundity in women with simple goitre of the adolescent type, though in one of his hypothyroid patients there was a tendency to repeated miscarriages. In women with the adult type of simple goitre, fecundity was a little less than normal, and the result of multiple pregnancies was to increase the size of the goitre and diminish its functional capacity. Gardiner-Hill advises the administration of dried thyroid gland during pregnancy for the latter class of case in order to minimize the risk of myxoedema.

If a simple goitre increases sufficiently during pregnancy to cause severe pressure in spite of rest and treatment by dried thyroid gland or small doses of iodine, or by both combined, it may be necessary to operate. If such a course is decided on the treatment should be on exactly the same lines as for any other simple goitre of the same class.

Intrathoracic Goitre

Varieties

I. Intrathoracic Goitre proper.
II. Mediastinal Goitre.
III. Goitre Plongeant.
IV. Substernal Goitre.

This important clinical group includes those goitres, both simple and malignant, which are partially intrathoracic, and therefore more accurately described as *substernal* (a distinction which is not strictly observed by many writers on the subject), and those which are *mainly or wholly intrathoracic.* The latter group includes a smaller sub-group, sometimes referred to as *mediastinal,* in which the intrathoracic mass arises from the isthmus or from one of the lateral lobes and comes to lie in the mediastinal space medial to the great vessels and in front of the aorta. " Goitre plongeant," a term sometimes used to denote intrathoracic goitre, should be reserved for those special goitres, usually of small size, which are inside the thoracic cavity under normal conditions, but during coughing or straining are forced upwards into the neck. Occasionally intrathoracic goitres arise from the thyroid lobe on the opposite side of the neck, the vascular or thyroid tissue linking them passing sometimes in front of and sometimes behind the trachea.

Many—possibly the majority—of large symmetrical goitres send down prolongations on each side behind the sternum and inner ends of the clavicles, and thus become substernal. The larger goitres seen in primary thyrotoxicosis often have substernal portions.

Nodular goitres also may extend downwards on one or both sides of the trachea behind the sternum: such extensions consist mainly of nodular masses which by their growth and subsequent degeneration eventually

become so large and so modified in shape that they are incapable of moving freely during the act of deglutition, but remain jammed in the upper aperture of the thorax, displacing and compressing the various vessels and nerves which pass through this aperture, and finally destroying life by damage to the heart or respiratory organs.

Mechanism of Production of Intrathoracic Goitres. The bones, muscles, and fasciae of the neck, and the vascular pedicles, are so arranged that a goitre extends upwards, backwards, and laterally with some difficulty. Anteriorly, by stretching or separating the infrahyoid muscles, it may extend considerably, producing a conspicuous, bulging mass. It is, however, particularly in the downward direction that, aided by gravity and the respiratory movements, and unopposed by any powerful fascial or muscular barrier, extension of the mass is least obstructed. It must be added that, in connexion with the normal gland, small almost completely detached portions of thyroid tissue are to be found extending downwards along the lateral aspect of the trachea. Should nodularity develop in these paratracheal masses intrathoracic extension becomes almost inevitable. In exceptional cases intrathoracic goitres may develop in connexion with the rare accessory thyroid glands which occur in the mediastinal space as low down as the aortic arch.

Maclean (1928) quotes Bevan's case in which no thyroid tissue at all could be found in the neck, but the thyroid vessels ran downwards into the thorax to supply an intrathoracic goitre. This should be regarded as ectopia of the thyroid gland proper, rather than goitrous development in an accessory thyroid.

Rives (1947) has described as " mediastinal aberrant goitre " that type in which the goitrous tissue is wholly intrathoracic and has no connexion with the thyroid gland in the neck. Its blood supply may come from the thyrocervical trunk or directly from the subclavian artery or the aorta. Goitrous tumours of this kind may be found in the anterior mediastinum resting on the aorta or pericardium or in the posterior mediastinum extending as far down as the diaphragm. Transpleural thyroidectomy may be called for. Keynes (1950) reports two patients in whom enormous goitres were located in the posterior mediastinum. In each, the tumour was successfully removed by median sternotomy.

Pathological Anatomy. A well-developed pedicle of thyroid tissue carrying the blood supply to the intrathoracic tumour (usually from the inferior thyroid trunk) generally exists, but in old-standing cases which have been firmly wedged in position for years the connexion may be reduced to a fibrous one containing few, if any, vessels; or in very exceptional cases, it is said, no connexion with the thyroid gland whatever can be traced.

Intrathoracic goitres may be unilateral or bilateral; the former are commoner. If bilateral they are rarely symmetrical, one side usually greatly exceeding the other in size. Unilateral intrathoracic goitres are often associated with a conspicuous enlargement of the thyroid lobe on the side of the neck opposite to the intrathoracic tumour. This has in the past, especially

before systematic skiagraphy was practised, led to serious errors, the more obvious cervical mass being removed as the probable cause of the patient's symptoms; but the intrathoracic goitre, associated, as it often is, with little or no evidence of a goitre on the same side of the neck, was overlooked and the patient failed to gain relief.

The various structures in the upper part of the thoracic cavity are displaced and compressed, especially at the upper thoracic aperture, where the space available is least and the walls are almost entirely rigid. When the condition occurs in children definite deformity of the ribs and sternum may follow; but this is not seen when the goitre develops in older patients, although the manubrium sterni may be displaced forwards at its junction with the gladiolus. All the neighbouring structures are displaced or stretched, but they suffer in varying degrees. The trachea is compressed in bilateral cases; laterally displaced, narrowed, kinked, or even twisted into a sigmoid curve in unilateral forms. Antero-posterior compression is not unknown, even in non-malignant cases. Rare instances are said to occur where the trachea is stretched over the front of the tumour, which itself lies wholly posteriorly. The stretched or compressed trachea becomes tethered in such a way that the normal excursion of the larynx in the act of deglutition is diminished, and in extreme cases the larynx may be drawn downwards bodily towards the thoracic inlet. The compressible veins are affected earlier and more obviously than the more rigid large arteries. The recurrent laryngeal nerves are frequently damaged, and the sympathetic nerve is occasionally involved. The tumour is usually surrounded by a layer or series of layers of fascial or connective tissue which intervene between it and the compressed or displaced viscera, and it is seldom that any firm connexion is found to exist between the tumour and such structures as the lungs and pleura, the trachea, and the oesophagus. The blood vessels of an appreciable size which enter an intrathoracic goitre are derived wholly from the normal thyroid vessels, which pass downwards from the neck into the tumour: it is very rare indeed to find any exception to this statement. The great vessels of the neck may be displaced outwards and backwards or forwards, the latter being far commoner. If the intrathoracic mass is a development from the thyroid isthmus the main vessels lie behind the goitre, which may occupy a strictly median position. The tumour is often in contact with the aortic arch, which may even be displaced downwards or to one side.

The apex of the lung and the overlying dome of the pleura were pushed downwards and backwards into the thoracic cavity, and the goitre reached as low as the eighth rib in one case of our own series.

Incidence. Great confusion has been caused by the loose use of the term " intrathoracic " goitre, so that in certain reports the figures suggest a very high incidence of this type of goitre, while in others it is shown to be a rarity. If the strict definition be adhered to, viz., that an intrathoracic goitre is one which is wholly and completely inside the thoracic cavity, then, not 1 per cent. of all goitres come into this category. In Pemberton's

series only 0·6 per cent. were purely intrathoracic, but 13·5 per cent. were substernal. Sauerbruch and Felix (1927) mention fifty-five intrathoracic goitres in 1,500 cases in Munich, but of these apparently only ten were of the strictly intrathoracic type. Santy (1948) reported only six cases among 1,500 thyroidectomies and Welti (1948) in 6,000 operations for goitre has never used any other than the classical cervical incision.

Age and Sex. True intrathoracic goitres are extremely rare in children, though in Pemberton's series (1921) a case occurred at the age of fifteen. In Berry's series (1921) the average age in males was fifty-one and in females forty-six. Our oldest patient was seventy-seven, and in general it is a condition of late adult life. Pemberton's figures from the Mayo Clinic show that it is nearly six times as common in women as in men, though Berry's twenty-two cases comprised eight males and fourteen females. In our own series there were seven men and two women with impacted, completely intrathoracic goitres, and twenty-nine women and nine men with goitres mainly intrathoracic.

Signs and Symptoms. The condition is almost invariably slow in development, though when it occurs in the young it may have almost an acute onset. In one of our cases the patient had had symptoms for more than forty years; Pemberton (1921) quotes one of forty-eight years' standing, and Higgins (1927) one of over sixty years'.

The symptoms are mainly those due to pressure on the various structures already enumerated, and while toxic features are not unusual they rarely dominate the clinical picture. Higgins says that the average basal metabolic rate in his series was + 32 per cent., which would imply that toxic phenomena are the general rule; but it must be remembered that such patients are often intensely dyspnoeic. The figures obtained by careful observers are therefore frequently very high, as indeed they are in all dyspnoeic conditions, whether of goitrous origin or not. The frequent coexistence of pulmonary complications and pyrexia still further invalidates the figures obtained. Pemberton found toxic features in 25·4 per cent. of his series. The toxic symptoms, when they occur, belong to the secondary type: primary thyrotoxicosis in association with genuine intrathoracic goitre is probably unknown, tremor, tachycardia, and loss of weight and strength are the usual indications of thyrotoxicosis in association with intrathoracic goitre, and they are often complicated by the existence of cardiac and metabolic disorders, the direct and indirect results of the pressure of the goitre on the heart, great vessels, and respiratory apparatus.

Of far more importance clinically are the various *pressure effects.*

Dyspnoea is often severe and continuous, with exacerbations at night, but it may be spasmodic and closely resemble asthmatic attacks. One of our own patients had been treated for asthma for many years, and Lamson (1914) quotes a similar case, which was treated for ten years for asthma and underwent an operation on the nasal septum for its cure. It must not be forgotten that the converse error has been made, viz., asthmatic attacks have been erroneously ascribed to the presence of a substernal or intrathoracic

goitre and operations on the latter have failed to influence the asthmatic state. One such patient came under our observation, a young man, who at intervals had had two or three operations on a moderate-sized colloid goitre, but his asthma persisted and he eventually died of it.

Dyspnoea is often most severe at night just when the patient has settled down to sleep. During consciousness the head and neck are maintained in the position in which breathing proves to be easiest, but with relaxation of the muscular vigilance which accompanies sleep, severe suffocative attacks supervene, and the patient may learn to dread the nights and try to avoid sleep. Many patients prefer to spend the night in a chair with the head supported by pillows.

Associated with pressure on the trachea is a tendency to recurrent attacks of bronchitis. Cough may be extremely troublesome and is often spasmodic, and not always proportionate to the severity of the bronchitis or to the amount of tracheal compression.

Dysphagia is sometimes complained of, but usually partakes of the nature of a mild discomfort or a consciousness of the passage of a bolus through the narrowed part of the oesophagus. X-ray examinations may show that there is a slight holding-up of a barium pellet, but the more severe degrees of obstruction do not occur unless malignant changes have supervened and the wall of the oesophagus is definitely infiltrated.

Venous engorgement of the chest, and sometimes of the corresponding upper limb, the head, and the neck, is very commonly seen when the intrathoracic goitre is large, and especially if it is right-sided. This phenomenon is the result of pressure on the large veins, especially the superior vena cava, followed by the development of a collateral venous circulation *via* the superficial thoracic, the intercostal, and the azygos veins. The head and neck and upper limbs may be deeply cyanosed in severe cases, and, exceptionally, oedema may supervene.

Paralysis of the recurrent laryngeal nerves is more common than in the generality of simple goitres. Higgins states that in 13 per cent. of his series there was pre-operative evidence of paralysis of one recurrent laryngeal nerve. The paralysis usually corresponds to the side of the intrathoracic tumour and may be indicated by alteration in the voice and by stridor, but the former is often absent, even in complete unilateral paralysis, and the latter may be due to direct pressure on the trachea. It has been stated that left-sided recurrent laryngeal nerve paralysis may be associated with right-sided intrathoracic goitre, and also that right- and left-sided paralysis may occur in an alternating fashion. Bilateral paralysis has been recorded by Hubert (1923).

Sympathetic paralysis has been recorded by several observers, including Dittrich (1887) and Higgins (1927). Rachford (1920) described a case in which the *phrenic nerve* was paralysed.

Diagnosis. The existence of the above-mentioned pressure phenomena in a goitrous patient will strongly suggest the presence of a substernal or intrathoracic extension. The occurrence of some or all of them in the

absence of an obvious cervical goitre will necessarily raise the question of the existence of an intrathoracic or mediastinal goitre. When the pressure effects are associated with limitation of the upward movement of the larynx and trachea during the act of swallowing, and especially if the larynx lies lower down than normal, a correct diagnosis should be possible. When the intrathoracic tumour is firmly impacted a curious and characteristic tug or thrill may be felt during swallowing when the hand is placed over the thyroid lobe corresponding to the side of the tumour.

A persistent dry cough, stridor, or otherwise inexplicable dyspnoea, will also raise a suspicion of the presence of an intrathoracic goitre, and if to these be added tachycardia and other thyrotoxic phenomena (including an increased basal metabolic rate) arising in a patient who has no obvious goitre, the possibility of an intrathoracic goitre must not be overlooked.

Radiological examination will often establish the diagnosis, though it does not always permit a clear distinction from other intrathoracic and mediastinal tumours. If unilateral, the outline of the intrathoracic tumour is usually well defined (unless malignant changes and infiltration have supervened), and it is so clearly wedged into the superior thoracic inlet that its thyroid origin is generally obvious. Melville (1928) emphasizes the tongue-like extension from the neck into the thoracic shadow, and the downward displacement of the aortic arch. The trachea in such cases is seen to be displaced laterally, or deformed and curved in a bizarre fashion. It may be displaced forwards when the goitre lies in the posterior mediastinum (Keynes, 1950). Calcified areas may be seen in old-standing cases. A dense, uniform shadow is rare, and is suggestive of malignant changes in the goitre.

In bilateral cases the tumours are wedged into the superior thoracic opening and closely apposed to the trachea, which is bilaterally compressed or, when the tumours are of very unequal size, bent into sigmoid or other curves. Antero-posterior tracheal compression sometimes occurs, and may be detected in lateral radiograms. Pulsation is often noticeable on screen examination, but is not of the expansile type, though it may be difficult to detect this where the tumour is in very close contact with the aorta.

Differential diagnosis from intrathoracic aneurysms may not be easy. Tracheal tug may occur in both, and the pressure effects on the respiratory and vascular structures may be very similar in both. One of Keynes's patients (1950) had been irradiated in the mistaken belief that the large mediastinal shadow was a sarcoma.

In nearly all intrathoracic goitres the upper part of the tumour can, by careful palpation at the end of deep expiration or during the act of swallowing, be felt or seen in the neck, while other intrathoracic tumours do not appear in this way. Fluoroscopic examination will seldom fail to show movement of an intrathoracic goitre in a vertical direction accompanying the acts of swallowing and deep breathing, thus differing from that seen in other mediastinal and intrathoracic tumours or aneurysms, but the test fails when the goitre is firmly fixed in position.

Thymic tumours can usually be differentiated from their position and from the fact that they often have almost rectilinear outlines, the two lateral margins converging as they pass upwards towards the neck. This particular appearance is not seen in even the rare intrathoracic goitres which arise from the thyroid isthmus: the shadow in such cases occupies a position similar to that of the thymus, but lacks the characteristic truncated triangular outline.

Dermoid cysts of the thoracic cavity may be mistaken for intrathoracic thyroid cysts, but seldom occur exactly in the position of the latter, nor do they move on deglutition in the same way.

Prognosis. When operation is refused the outlook is extremely grave. In two such cases we have witnessed most distressing deaths from a combination of pulmonary and cardiac complications and exhaustion.

On the contrary, the relief afforded by thyroidectomy is dramatic. The previous disabilities of the patient are so obvious to him and his friends that the contrast is patent to all. The pressure effects, even when of long standing, usually disappear rapidly and the only permanent residuum which I have observed is paralysis of the recurrent laryngeal nerve, which seldom disappears if completely established before the operation.

Treatment. Surgical measures are imperative in every case of intrathoracic goitre. It is true that many patients have lived for years with such a condition, but the associated disability is usually a progressive and menacing one. The substernal prolongations of colloid and primary thyrotoxic goitres are influenced by dried thyroid gland and by thiouracil and iodine respectively, exactly as are the cervical goitres of the same class.

Operation. The details of this are given in Chapter XXVII, but it is important to emphasize the necessity for operating only after a careful preliminary investigation of the cardiovascular system, combined with skilled radioscopic examination. It is desirable that the operation be planned for the summer months if possible, because the danger of post-operative pulmonary complications is greater in the winter. Should such complications appear likely, a chemotherapeutic " umbrella " should be used prophylactically.

Prophylaxis of Simple Goitre. In sporadic goitre there seems so little evidence of any single cause, and the incidence of the condition is so capricious, that it is probably futile to attempt prophylaxis. Similarly, it cannot be over-emphasized that iodine is not a cure for established goitre. On the contrary, in areas of endemic goitre, prophylaxis is of prime importance, especially where the incidence of cretinism is also high. It is possible that the response to preventive medication is not quite the same in all endemic goitrous areas, differing, as we know they do, both in the percentage prevalence and in the types of goitre found. Prophylaxis during pregnancy is probably the most generally useful method in endemic areas. The primary stage of simple goitre is thyroid hyperplasia. If this can be prevented, especially in early foetal life, when it so often begins, we can entirely eliminate simple goitre and all its attendant ills.

Iodine as a Prophylactic. This method was instituted as far back as 1860 by Boussingault and Grange by the administration to school children in three departments of France of iodized salt; to it was added 0·01 gm. of potassium iodide daily, in the form of a tablet. These doses were excessive, produced toxic features, and caused the abandonment of the method.

In 1904 iodine prophylaxis was revived by Galli-Valerio, who obtained good results from the use of a drop of the tincture of iodine daily. A further stimulus to these preventive measures was given by Marine's work in 1914, by Ennis Smith's in 1917, and by Hunziker's in 1924, who experimented on members of his own family. Kimball and Marine's work at Akron, Ohio, in 1918, provided the most impressive proof that iodine can prevent endemic goitre and gave the greatest impetus to the wider adoption of iodine prophylaxis. Of 2,190 non-goitrous children who were treated with iodine only five were found to be goitrous at the end of a year, whereas of 2,305 similar children who were untreated 495 developed goitre. In addition to these prophylactic measures good results were observed in early cases of established goitre in school children. Parenchymatous and soft colloid goitres diminished in size or disappeared.

In Switzerland in 1928 following Eggenberger's work, iodized salt 1 : 100,000 was made compulsory for all domestic purposes throughout the Canton of Appenzell, and after a lapse of three years no congenital goitre was found among children whose mothers had used iodized salt during pregnancy. The Swiss Goitre Commission in 1923 recommended the general use of 1 : 200,000 iodized salt as a prophylactic; in addition, 1 mgm. potassium iodide weekly was to be given to those children who were already goitrous.

Table VIII shows the effect of iodine prophylaxis in the incidence of endemic goitre in various countries.

TABLE VIII

(*From Kelly*, 1946)

Place	Year Iodized Salt Introduced	Data Apply to	Goitre Incidence Per Cent.	
			Before Introduction of Iodized Salt	After Introduction of Iodized Salt
UNITED STATES				
Michigan State ..	1924	Schoolchildren	38·6 in 1923/24	2·9 in 1936
City of Detroit ..	1924	,,	35·0 in 1924	3·0 in 1930
Cleveland, Ohio ..	1924	,,	31·0 in 1924	7·7 in 1936
SWITZERLAND				
Canton Vaud ..	1924	Whole populn.	77·0 in 1924	21·0 in 1937
Canton Appenzell	1922	Recruits	7·0 in 1922	0·1 in 1938
Canton St. Gallen	1922	,,	4·0 in 1917	0·5 in 1938
City of Lausanne ..	1924	Schoolchildren	57·0 in 1924	1·0 in 1937
POLAND				
Kraków Province	1935	Recruits	17·6 in 1930/34	2·9 in 1937

Goitre prophylaxis yields its most striking results in new-born infants. Wespi-Eggenberger's results (1948) are in line with previous data. Potassium iodide was given either in solution or in common salt to 132 pregnant women during the last four weeks of pregnancy, and the thyroid findings in their offspring were compared with those of 836 women who served as controls. Over 91 per cent. of the infants whose mothers had received the prophylactic treatment presented a normal thyroid gland, and in the others the goitre was small. Of the offspring in the control group, however, 32 per cent. had small goitres and nearly 5 per cent. had goitres of medium or large size.

In 1946, Kimball urged the American Medical Association, the American Public Health Association and the Federal Food and Drug Administration to co-operate in giving the United States a standardized national salt containing 0·01 per cent. of potassium iodide, or its equivalent. Again, in 1948, Dr. Arnold Jackson of Madison, Wisconsin, President of the American Goiter Association, urged Congress to enact legislation making the iodization of salt in the U.S. a statutory obligation.

In Great Britain also, the Medical Research Council, in its Memorandum 18 (1948), state:

> The Goitre Sub-Committee of the Medical Research Council strongly urge the adoption of a national policy of adding a trace of iodine to all common salt consumed in the country. The proportion recommended is one part of potassium iodide to one hundred thousand parts of common salt. With an average daily intake of 10 gm. of salt per head, this would provide 0·1 mg. of iodide (equals 0·076 mg. iodine) per head daily. The extra retail cost per head for iodized salt would thus not exceed 4d. per annum.

Following this recommendation iodization of salt is likely to be introduced in the U.K. at an early date.

Experience in New Zealand has suggested that the dosage of iodine must be adapted to local factors such as an increased intake of calcium, which may interfere with the availability of the iodine. O'Shea (1946) states that in Tipperary " it is unlikely that an intake of less than 0·150 mg. of iodine daily would provide a sufficient margin of safety to cover both the normal and extra physiological requirements of the human body."

Large-scale iodine prophylaxis is now good public health practice in various parts of the world including Switzerland, Poland, the U.S.A., Australia and New Zealand (Fig. 42).

Methods of Prophylaxis. Health authorities in different countries have recommended the following methods of iodine prophylaxis:

(i) Iodized confectionery.
(ii) Iodization of the water supplies.
(iii) Iodized milk.
(iv) Iodized salt.
(v) Potassium iodide as a solution, or in tablet form.

GOITRE INCIDENCE

BEFORE AND AFTER INTRODUCTION OF IODIZED SALT

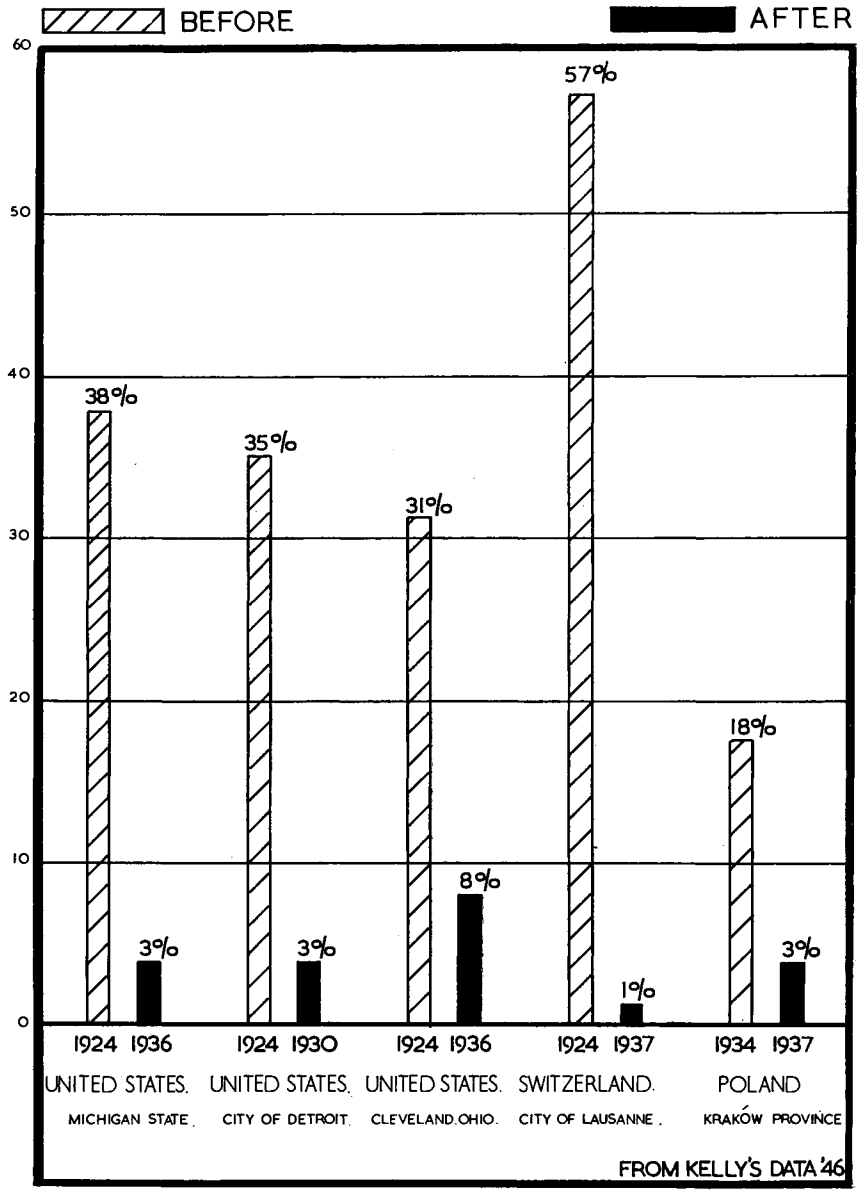

FIG. 42.

While any or all of these methods would be efficacious if carried out adequately, the use of iodized salt is found to be best as the additional iodine is taken without any special or conscious effort on the part of either the child or its parents. " In fact, iodized salt is now universally recognized by goitre authorities as the most convenient and the most effective vehicle for the administration of supplemental iodine " (Kelly, 1946). It is noteworthy that, as the result of surveys in Australia, potassium iodide was at first recommended and given in tablet form (Osmond and Clements, 1948) but it was subsequently found that its administration was being neglected by the parents and recently the Australian public health authorities have changed over to the iodization of salt. The proportions of iodide officially recommended in the U.S., Canada and New Zealand are approximately ten times as great as those in the European countries.

It is probable that the larger proportion is the more efficient. Iodine added to cooking salt tends to be leached during cooking, so that much of the iodine is lost. Moreover, the consumption of table salt is very variable and is taken in quite small amounts, especially by some children. Further, losses of iodide from the salt occur while it is stored in cartons before use. Iodide appears to migrate into the cardboard or fabric of the container. Exposure of the salt to sunlight also results in considerable loss of the contained iodine.

Dangers of Iodine Prophylaxis and Treatment. It is probable that with the low dosage recommended in Switzerland and those based on a similar scale, the risks of toxic or other unpleasant sequels to iodine prophylaxis for the populations concerned are trivial. The potential risk of iod-Basedow, or iodine-induced thyrotoxicosis, was formerly much stressed by German writers. According to this view the ingestion of iodized salt by goitrous subjects in an endemic area would supply the fuel from which the hyperplastic gland would manufacture an excess of secretion. Such fears have proved in fact to be groundless; the use of iodized salt has not increased the incidence of secondary toxic changes (Eggenberger and Messerli, 1938).

Thyroid Preparations in the Treatment of Simple Goitre. Marine (1926) advocated treating simple goitre by means of 0·1 to 0·2 gm. of dried thyroid gland daily for two weeks, followed after an interval of from one to two weeks by 2 to 4 c.c. daily of the syrup of hydriodic acid for a further period of from two to three weeks. He stated that by repeating these combined courses two or three times a year a considerable improvement may be effected. Our own experience with dried thyroid and with thyroxine in both sporadic and endemic cases in England has been rather disappointing: a few of the very small, soft goitres have diminished or disappeared, but in no instance has a large colloid or nodular goitre shown any significant diminution, though some few patients have admitted that they " felt better," a result probably to be ascribed to the stimulation of metabolism effected by the treatment.

Radiation Treatment of Simple Goitre. Because of the relatively poor uptake of radioiodine by simple goitres, radioiodine therapy does not offer

great promise of success. Nor is external irradiation to be recommended as the only cases in which it might be effective, namely the small parenchymatous goitres, are better treated with iodine.

The Surgical Treatment of Simple Goitre

The indications for operative treatment are:

(i) To relieve pressure.
(ii) To eliminate potential risks of malignant or toxic development.
(iii) For cosmetic purposes.

(i) **To Relieve Pressure.** This is by far the clearest indication for surgical treatment in simple goitre. When parenchymatous and colloid goitres are associated with moderate degrees of dyspnoea, medical treatment by dried thyroid gland, by iodine, or by both combined, may, without entirely abolishing the goitre, reduce its size sufficiently to eliminate all pressure effects. No operation is then needed. In the larger colloid goitres, however, especially if these be of long standing, little is to be expected from medical treatment, though it should usually be tried before surgical measures are adopted. When the patient is pregnant the influence of labour on any existing dyspnoea must be taken into account (Steiner, 1948); early strumectomy is advisable.

In the rare cases of acute dyspnoea, such as are recorded earlier in this chapter, to delay operation is to incur the risk of sudden death from asphyxia.

The *scope of the operation* to be employed for diffuse or *symmetrical goitres* is determined by the two necessities: (*a*) to remove the cause of the pressure and to prevent its recurrence, and (*b*) to conserve sufficient thyroid tissue to fulfil functional purposes. To do this it is necessary—

(1) To carry out a symmetrical operation: *operations for diffuse goitres must be bilateral.* The removal of a part or the whole of one lobe will sometimes afford immediate relief (although numerous exceptions occur), but the risk of continued growth of the remaining lobe, followed by displacement or distortion of the trachea and other structures, is so great that the invariable rule should be to extirpate portion of both lobes.

(2) To control the blood supply of the gland in such a manner that any recurrent growth will take place only in those situations where pressure effects are least likely to follow. This, in our experience, is best achieved (*a*) by systematic ligation of both inferior thyroid arteries, together with the removal of the greater part of the inferior portions of the lateral lobes and the whole of the isthmus; and (*b*) by conserving a strip of gland tissue on each side posteriorly for the protection of the recurrent laryngeal nerves, and in addition leaving a considerable amount of both upper poles intact. Should the latter enlarge, they are not likely seriously to compress the relatively rigid larynx. The trunks of the superior thyroid vessels are not tied, but their branches are necessarily controlled at the plane in which the section through

the gland is made. Ample blood supply to the remainder of the gland is provided for in this way and any sign of post-operative hypothyroidism is rare.

SINGLE ADENOMATA OR CYSTS. Here the indication is to remove the tumour together with a thick layer of the surrounding gland tissue, As Crile and Dempsey (1949) remark the danger is not that a discrete adenoma may become malignant but rather that it is already malignant. Therefore the operation should be designed so as to cure the cancer if it is present. In exceptional cases the tumour may be large enough to expand the whole lateral lobe, and then hemi-thyroidectomy with, if possible, conservation of a strip of thyroid tissue posteriorly is the operation of choice.

In NODULAR or ADENOPARENCHYMATOUS GOITRES which are causing pressure, discrimination is necessary to ensure the extirpation of the masses that are causing the trouble, while conserving the less degenerate portions in situations where they are likely to cause a minimum of trouble should they subsequently enlarge, a possibility which in this class of goitre in particular has to be faced. The operation must, as a rule, be bilateral, unless the disease appears to be entirely confined to one lobe, or one lobe and the isthmus, a rare but not unknown state of affairs. The general principles of the operation are similar to those for colloid goitre, viz. portions of both lateral lobes and the whole of the isthmus are removed. The parts conserved lie chiefly at the superior poles and in the region of the pyramidal lobe, which often appear to be less degenerate than the remainder of the gland. Both inferior thyroid arteries are tied in continuity, in order to cut off the blood supply and therefore minimize the risk of recurrent growth where it would be most likely to cause tracheal compression. A portion of the gland near the trachea on both sides is conserved in every case in order to protect the recurrent laryngeal nerve and the parathyroid glandules.

Much judgment is needed to preserve sufficient thyroid tissue, for as the whole of the gland is more or less involved in the adenomatous process it is necessary to conserve the less unhealthy and remove the more degenerate parts. The adenomatous masses often spread far back into the posterior portions of the lateral lobes, so that a mere shell of thyroid tissue lies behind them, and great care is then needed to avoid damaging the recurrent laryngeal nerves, which should always be clearly demonstrated by dissection.

(ii) **Prophylactic Operations on Thyroid Adenomata.** This indication is less urgent but hardly less imperative than the former. The risk of malignant changes in adenomata has been variously estimated at from less than 1 per cent. up to 25 per cent. The regional incidence of cancer of the thyroid may vary. Indeed published statistics suggest that it is far commoner in the U.S. than in the U.K. The differences seem too great to be explained solely on the basis of different microscopic criteria of malignancy. It appears from Graham's work that clinical examination is wholly unreliable in attempting to decide whether any given adenoma of the thyroid is simple or malignant; on the other hand it is generally agreed that the malignant adenoma is

a common type of malignant disease of the thyroid, and that its development is almost invariably preceded by a period of some years during which the tumour appears to be innocent in character.

A neoplasm should be suspected if the patient is under the age of 20, if the nodule is single and enlarging, and especially if there are pressure symptoms or recurrent nerve paralysis (Dailey *et al.*, 1949). In our experience more than one patient who has been advised to ignore an apparently innocent adenoma because of its small size and the absence of symptoms has subsequently sought advice owing to the presence of malignant changes in the tumour. The risk of malignancy in a single nodule is about three times greater in males than females (Cole *et al.*, 1949). The removal of small adenomata is almost entirely free from risk, and in our opinion they should be treated surgically.

Toxic phenomena are also known to develop in association with adenomata after a variable number of years (toxic adenoma). Such toxic changes often begin very insidiously, so that cardiac or other visceral degenerations

TABLE IX

INCIDENCE OF CARCINOMA IN NODULAR GOITRE (Cole *et al.*, 1949)

Author	Number of patients with nodular goitre (toxic and non-toxic)	Per cent. carcinoma in nodular goitre (toxic and non-toxic)	Number of patients with nodular non-toxic goitre	Per cent. carcinoma in nodular non-toxic goitre	Per cent. carcinoma in non-toxic single nodule
Brenzier and McKnight (1940)	2,324	4	—	—	—
Horn *et al.* (1947)	1,135	6.3	637	9.8	—
Crile (1948)	537	5.6	274	10.8	24.5
Ward (1947)	3,539	4.8	—	—	15.6
Cole *et al.* (1949)	663	8.0	285	17.1	24.4
Cope *et al.* (1949)	1,109	10.1	—	—	19.0

may be well advanced before the patient is fully aware of the deterioration in his condition. They are certainly more common in association with generalized adenomatosis of the gland, but are occasionally met with in localized adenomata. This fact provides a further argument in favour of the systematic removal of all thyroid adenomata, quite apart from the question whether all multi-nodular goitres should be so treated. In the latter group, especially if uncomplicated by pressure phenomena, there is a much greater reluctance on the part of the surgeon to interfere when the goitre is small, because the amount of healthy functional tissue available is very limited and consequently the margin of safety between euthyroidism and hypothyroidism is a narrow one. Nor is the risk of malignant degeneration so great in multinodular goitres (cf. table IX).

(iii) **Cosmetic Indication for Operation on Simple Goitre.** A large goitre, whatever its pathological character, is a disfigurement which, if incurable by medical means, is likely to cause chagrin to the patient. In the case of a

colloid, nodular, or adenomatous goitre, the considerations which have already been discussed in the two preceding sections will influence the surgeon's action, but if the tumour be caused by a single cyst or a calcified adenoma the risk of either malignancy or toxic development is small. If, then, the disfigurement is serious, especially in young patients, the surgeon is justified in acceding to a request for its removal, even when no definite surgical reasons for operation exist. Pedunculated tumours of the thyroid in elderly people also fall into this category.

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CHAPTER VIII

THE HYPOTHYROID STATES

Classification of Cretinism — Aetiology — Pathology of Thyroid Gland — Systemic Effects — Skeletal Changes in Cretinism — Diagnosis — Clinical Course and Prognosis — Myxoedema — Definition and Types — Spontaneous Myxoedema — Pathology of the Thyroid Gland — Systemic Effects of Myxoedema — The Tissue-Changes — Contrast with Thyrotoxicosis — Cutaneous Lesions in Myxoedema — Postoperative Myxoedema — Pituitary Myxoedema — Latent Hypothyroidism — Mixed Endocrinopathies, including Myxoedema — Diagnosis, Prognosis, and Treatment of Myxoedema.

Classification of Cretinism. Fabre (1857) said, " Goitre is the father of cretinism." As we have seen (Chapter IV) thyroid hyperplasia, leading to goitre, is the usual compensation, effected by the anterior pituitary, for deficiency of the hormone in the tissues. In adult life, such deficiency is not accompanied by conspicuous clinical changes unless it is marked. In infancy and childhood, on the contrary, even moderate degrees of thyroid insufficiency interfere considerably with normal physical and mental growth. The stigmata of cretinism develop in degree corresponding to the severity of the deficiency and the age of its onset. Consequently, in infancy and childhood, goitre and varying degrees of cretinism go hand in hand.

There is no hard and fast line between the various types of cretinism or between its sporadic and endemic occurrence. The following broad types are, however, distinguishable:

(i) Congenital thyro-aplasia, congenital cretinism.
(ii) Cretinism with congenital goitre.
(iii) Infantile or childhood cretinism.

The severity of the stigmata is greatest in congenital thyro-aplasia and least in infantile and childhood cretinism. Thus, in the latter, the child may have developed normally up to the time of onset of the disorder, or thyroid failure may be only partial. Such cases shade off into the very mild degrees of hypothyroidism seen with some endemic goitres.

Where the endemicity is severe and there has been much inbreeding, goitre may be congenital and cretinism develop very early in infancy. Total thyroid failure (congenital thyro-aplasia) is, however, more common as a sporadic event, suggesting an organ deficiency inherent in the individual.

Aetiology. Janney states that the parents of sporadic cretins are often goitre-bearers and suffer from thyrotoxicosis or from mild degrees of myxoedema. Ball and Morrison (1948) have recently reported a congenital cretin whose mother had developed thyrotoxicosis while pregnant. Congenital thyro-aplasia is sometimes a familial disease. Barrett (1919) recorded one family with six members affected and Bronstein *et al.* (1943) another in

which there were two cretinous brothers and four other members with goitre.

Cretinism associated with goitre, present congenitally or developing subsequently, is still prevalent wherever goitre is heavily endemic. It provides the most cogent argument of all in favour of efficient and persistent iodine prophylaxis.

The magnitude of the social and economic problem posed by cretinism is not generally appreciated. De Quervain (1930) stated that one in a thousand of the population in the Canton of Berne had to be provided with institutional treatment owing to cretinism, and that far more than this number lived outside institutions. In rural endemics, especially of the backward countries, the same high incidence obtains to-day.

The incidence of endemic cretinism is, however, low in the English-speaking countries. Jackson (1934) in a review of 512 cases, found that, in the U.S., cretinism had the same distribution as endemic goitre. Even though sufficiently rare to be labelled sporadic, cretinism could, therefore, be broadly related to the same causes as simple goitre. And, like simple goitre, its incidence had increased steadily since 1900, perhaps due to the too efficient (!) refining of the salt supplies. Similarly, in Great Britain, cretinism with or without goitre is rare.

Occasionally, cretinism crops up in association with goitre in the complete absence of any history of thyroid disease and where the family has for long resided in a non-endemic area, as in the case reported by Lerman *et al.* (1946). Thyroid degeneration may also occur in childhood from the destructive action of toxins and micro-organisms associated with the exanthemata and other infections.

Pathology of the Thyroid Gland. The thyroid changes are compensatory to the hormone deficiency and range from moderate, generalized hyperplasia to intense hyperplasia with considerable enlargement of the gland which may even cause respiratory obstruction in the new-born. Nodular degeneration occurs in those who survive and is characteristic of the cretin goitre. The nodules show the same cystic, calcific, and other changes found in the simple goitre of adults (Wegelin, 1927). Though areas of epithelial proliferation exist and though some of the adenomatous nodules contain normally-developed vesicles, their functional power is limited. Colloid is scanty and the cells appear largely effete.

Finally, where the gland loses its power to react by hyperplasia, it is extremely degenerate or aplastic. As long ago as 1888, The English Myxoedema Committee found that congenital cretinism is due to a chronic connective tissue overgrowth, leading to reduction in size of the follicles, degeneration and diminution of the number of cells, which are flattened and irregular in size and shape, round cell infiltration, and increase in the fibrous stroma, with the appearance of scattered lymphoid follicles throughout the gland. Small cysts, haemorrhages, adenomatous nodules, and calcified areas are also occasionally present. Aschoff, Wegelin, and others subsequently, have agreed with these findings.

Systemic effects. The general metabolic manifestations of cretinism are the same as those to be described in myxoedema but the systemic effects differ because of the earlier age of onset of the thyroid deficiency. Thus, there is striking interference with physical and mental growth, indicating the vital role of the thyroid hormone in early development.

There is a remarkable uniformity in the physical and mental characteristics of the congenital cretin, who is usually good-humoured and not mischievous. The child is ill-developed and learns to feed itself, walk, and to control the bladder and rectum much later than the normal child, if at all. It makes only inarticulate sounds, and often appears to be deaf, although the auditory apparatus is well developed anatomically. The sense of smell is not often affected. The cretin's head is small and round, and complexion pasty, the hair short, brittle, and scanty, the eyebrows and eyelashes deficient. The face is coarse, the lips are thick and parted, and the tongue, which protrudes between the lips, is furrowed and indented by the teeth. The abnormal size of the tongue is due to an increased amount of fat among the muscles and to oedema, and not to muscular hypertrophy. The nostrils are large and directed forwards. The ears are conspicuous and do not lie against the head. The chin recedes, owing to the ill-developed mandible. The neck is short and the head unsteady on it. The chest is relatively small, but the abdomen is protuberant and umbilical hernia common. The gait is waddling and uncertain, and there is a conspicuous lordosis. The upper and lower limbs are coarse and deformed. The hands are spatulate, the feet flat, and the legs often bowed. It was Curling (1850) who first noticed the symmetrical supraclavicular swellings in this type of cretin. Sporadic cretins are usually lethargic and prone to fall asleep. They may be too dull even to take food placed near them. The body temperature is subnormal; the muscles are flabby and infiltrated by fat. Breathing is often very much slowed. The genital glands and external genitalia are ill-developed, and in males the testes are often undescended; histologically, there is evidence of defective spermatogenesis and oögenesis. Pathological changes have also been described in other endocrine glands, *e.g.* fibrosis of the parathyroids and hypertrophy of the pituitary, but it is doubtful if these are really constant features.

The cretins of endemic areas vary greatly in the degree of physical and mental defect which they exhibit and in the extent to which these are combined, whereas in sporadic cretinism there is a peculiar uniformity in the physical and mental characteristics of the patient. In the milder degrees of endemic cretinism the variation from the normal may be slight and only discernible on careful examination; but the more severe grades simulate closely the condition described under sporadic cretinism as being due to congenital thyro-aplasia. The subcutaneous swelling seen in myxoedema and in sporadic cretinism is, however, often absent. De Quervain (1930) estimated the basal metabolic rate in the Berne Institute patients, and found it on the average considerably diminished. The mental and physical disabilities by no means run parallel: some cases occur which are mentally

about normal, yet the patients are typically cretinous in appearance, and vice versa.

The psychical condition in cretins who are not entirely devoid of mind is peculiar and differs from that of the ordinary mental defectives in asylums. The former have good memories for faces, but not the special memory for figures possessed by some idiots. They have the magpie habit of collecting all sorts of trifles. They are great optimists, and are not at all unhappy so long as they have food, tobacco, and little work. They have no sexual problem. Their motto is never to do to-day what can be put off until to-morrow. The optimistic attitude of the true cretin contrasts with the pessimism of the myxoedemic patient of later life, who is able to compare his present with his former state (De Quervain, 1930).

Skeletal changes in cretinism. The skeleton shows profound changes, due, according to Wegelin, to persistence of cartilaginous synchondrosis beyond the growth age, and to inadequate development of the primitive cartilage-absorbing medullary spaces. These histological changes in the skeleton are common to, though not equally developed in, all types of cretinism.

The skull is infantile, with widely open fontanelles and persistent sutures in the occipital bone, so that its four primitive parts are separate and distinct throughout life. The spheno-occipital synchondrosis persists, and the crista galli remains cartilaginous. The primary dentition is irregular in eruption, decay is early, and the deciduous teeth often persist for years beyond the normal time limit. The palatine arch is vaulted. These various skull changes are more pronounced in sporadic than in endemic cretins.

The ossific centres of the long bones appear late and develop slowly, or may cease growth entirely. In congenital cases the epiphyses may remain cartilaginous throughout life, while in the endemic type the variation from the normal is usually comparatively slight or absent. The shafts of the long bones, though short, are not so disproportionate in length compared with the spine as is usual in achondroplasia. The ridges and tubercles for the attachment of muscles, characteristic of normal bones, are ill-defined or absent, and the curves seen in such bones as the femur and radius are seldom present in the proper degree.

The spine shows persistent synchondrosis, and the epiphyses have abnormally small ossific centres. The intervertebral discs are relatively thick and the bodies of the vertebrae thin. The pelvis shows changes strictly comparable with the rest of the skeleton.

It is generally believed that the sex hormones promote closure of the epiphyses. The activity both of the gonads and the adrenal cortex is, of course, reduced in myxoedema but this may not be the whole story. Mussio-Fournier *et al.* (1948) have shown that myxoedema in adults may be associated with persistence of the epiphyses even though menstrual and other sexual functions have developed normally. It is thus possible that the thyroid hormone exerts a direct effect on the growth and maturation of the skeleton.

A characteristic dysgenesis, best and most constantly seen in the head of

the humerus and femur, has been described by Wilkins (1941). Instead of a single centre, there are multiple, irregular islets of ossification in these and other epiphysis. Later on, these foci gradually enlarge and fuse forming an irregular spongy or fluffy mass. Finally there is transition from the misshapen, spongy epiphysis to one of normal structure.

These appearances were constantly found in twenty-three hypothyroid children who were adequately X-rayed; Woolley and McCammon (1945) also stress that a hard, densely calcified, epiphyseal plate is regularly found.

Thyroid therapy quickly results in resumption of growth, the most striking changes being seen within two to six months after beginning treatment. Centres of ossification appearing soon after treatment show the characteristic stippled dysgenesis, but centres developing later are normal. Thyroid therapy brings about rapid ossification in those sites where it is overdue. The shafts of the bones also elongate and calcify normally.

The dysgenesis of hypothyroidism is often mistaken for the chondrodystrophy of Legg-Calvé-Perthes but the multiple stippling of the former is easily distinguishable from the destructive aseptic necrosis of the latter, which is also usually monarticular and shows no response to thyroid therapy. Mongolian stunting also fails to respond to thyroid extract.

Diagnosis. From mongolian idiocy the diagnosis is not difficult, owing to the characteristic facies and the greater physical activity of the mongol compared with the cretin. The basal metabolic rate is also greatly reduced in cretinism, ranging from minus 50 to minus 20. The sugar tolerance is increased and the blood cholesterol is raised. The uptake of radio-iodine by the gland is negligible in thyro-aplasia and when degenerative thyroid changes are marked, but may be much more rapid than normal where endemic goitre is associated with mild hypothyroidism (Hamilton and Soley, 1940).

Of twelve thyroid deficient children studied by Bronstein (1933), all had a raised blood cholesterol, which was quickly lowered by thyroid therapy. But the quickest and simplest test for hypothyroidism in children is probably a determination of the bone age by X-rays (Dutton, 1946).

Clinical Course and Prognosis. Untreated, many cretins die in infancy or early childhood and only in very rare instances do they survive to adult life, though in one or two cases they have lived to the age of thirty or slightly longer.

Cretins respond strikingly to thyroid therapy. The vital need is for early diagnosis, and prompt and continued treatment. Granted these, the prognosis is excellent. Thus Hochsinger (1938) reported a patient with congenital cretinism, who was observed continuously from the age of nine months to his forty-fourth year. He had developed normally and had a normal child. Deficiency symptoms appeared only when treatment was discontinued.

Usually there is some delay in recognizing and treating the cretin and then, even with thyroid therapy, development, especially of the mental faculties, is imperfect. There is marked recovery of the higher mental faculties parallel with improvement in the metabolic rate and electroencephalographic record during the early months of thyroid therapy but thereafter it ceases despite

continued treatment (Gantt and Fleischmann, 1948). Thus most of the series examined by Brown *et al.* (1939) still had intelligence quotients below 70. At maturity the mental age was seldom much above that of a child of ten or twelve years. Goodkind and Higgins' data (1941) were only slightly more favourable. All of the twenty-three hypothyroid children studied had been under thyroid therapy for from five and a half to twenty-four years, but seventeen had intelligence quotients below 90. A normal physique was, however, more often recovered.

Myxoedema

Definition and Types. The term, myxoedema, is applied to the condition which results from atrophy, destruction, or loss of function of the thyroid later in life than is the case in true cretinism. The following types are distinguishable:

(1) Spontaneous thyroid atrophy; spontaneous myxoedema.
(2) Post-operative myxoedema.
(3) The pituitary type of myxoedema; polyglandular insufficiency involving the thyroid.
(4) Localized pretibial myxoedema.

Spontaneous thyroid atrophy appears to be associated with a raised thyrotropic hormone content of the blood whereas in pituitary myxoedema the content is greatly lowered (de Robertis, 1948).

Spontaneous myxoedema. All gradations of thyroid insufficiency up to full-blown myxoedema occur, the mild or moderate degrees being often associated with goitre. The aetiology of spontaneous myxoedema is ill-understood. Its age incidence rises to a peak at about forty-five years and then falls (Dock, 1909). Several cases may appear in one family and instances of an hereditary tendency have been recorded.

Very occasionally thyrotoxicosis may give place to myxoedema when the thyroid burns itself out. This occurred in one of female twins, both of whom suffered from thyrotoxicosis (Rundle, 1941). The mother had myxoedema. Rarely iodine administration in hyperthyroidism may be followed by myxoedema, as in Hurxthal's case (1945).

Pregnancy is said to protect some females from incipient myxoedema, the disease establishing itself only after parturition or at the approach of the menopause, but in other cases pregnancy appears to aggravate the disorder. Infections, both acute and chronic, toxic states, pyschic trauma, and all other influences which tend to put a strain on the gland are possible causes of thyroid deficiency, but a clear history of even one of these is often absent.

Pathology of the Thyroid Gland. The English Myxoedema Committee, appointed in 1883, in its Report dated 1888 concluded that in myxoedema the thyroid is atrophied and devoid of functional tissue. The gland is often replaced by a mass of fatty connective tissue. There is thus a negligible uptake of iodine from the blood and complete failure of hormone synthesis and secretion.

Systemic effects. The lack of thyroid hormone depresses the activity of all the tissue cells. In fact, full-blown myxoedema converts the sufferer into a human vegetable, dull, apathetic, obese, and immobile (Fig. 43). Like thyrotoxicosis, the disorder is one of cellular chemistry; histological lesions are minimal. Thus, within a comparatively short time of commencing thyroid therapy, perception reawakens, the physical appearance is transformed, and normal activity is regained.

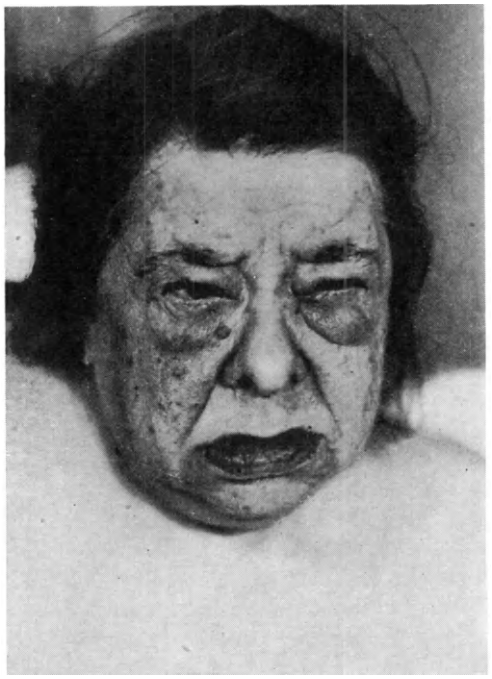


FIG. 43.—Spontaneous myxoedema. The patient, aged 73, presents the picture of gross myxoedema. She was drowsy; her speech was thick and indistinct and, in fact, a few stertorous snorting sounds were all that she could manage to produce. Her skin was everywhere dry and thickened and she had enormous supraclavicular pads. She died shortly after admission from bronchopneumonia. (Dr. R. Asher's case.)

The tissue changes. The nature of the tissue changes in myxoedema is of interest. Ord (1878) noted the characteristic, subcutaneous "pads" which, in his first case, appeared gelatinous on section. There has been much controversy ever since, as to the exact nature of these doughy subcutaneous swellings. It is now clear that the predominant change, both in the subcutaneous tissues and elsewhere, is a protein-rich oedema. Plummer (1940) estimates that there are about 6 kgm. of excess water in the tissues in spontaneous myxoedema.

In 1925, Boothby *et al.* injected thyroxine into one normal and two myxoedematous subjects and observed that the ratio of nitrogen to water lost was almost identical, namely, 1·9, 2·0 and 1·9 per cent. respectively. On the basis of these results they suggested that the oedema of myxoedema was an albuminous, colloid fluid with a nitrogen-water ratio identical with that of egg-white. Carl Voigt, as long ago as 1881, had introduced the concept of "circulating protein" and "tissue or organized protein". Boothby and his co-workers concluded that myxoedema involved an increase in the tissue protein to three or four times the normal level.

Byrom (1934), in an admirable study of the sources of the fluid and protein mobilized from normal and myxoedematous subjects by thyroxine administration, showed that there is an essential difference between the two groups.

In myxoedematous patients, the fluid and nitrogen are derived from extracellular and extra-vascular sources. In the normal subject, the intra-cellular stores are attacked directly.

> "It will be noticed that when a second dose of thyroxine is given (to a myxoedematous patient) six days after the first, the response more closely resembles that obtained in the normal subject. This suggests that the abnormal extra-cellular deposits have been largely dispersed by the first dose of thyroxine, and that the brunt of the second dose is borne by the normal cellular reserves."

Byrom admits that:

> "Implicit in the above reasoning is the assumption that the fluid loss observed is a consequence of destruction of suspended protein and the further corollary that the effect of thyroxine in the normal subject amounts to a piecemeal demolition of protoplasm to furnish protein for fuel, exactly as occurs in starvation."

Both assumptions are, however, in harmony with modern physiological teaching. He then advances his concept of the basic changes in myxoedema.

> "Protein occurs in the cellular milieu in two forms. A small amount is present in the circulating tissue fluids. There is secondly the mucinous ground substance which supports the cells and is present in some form of fixed colloidal gel.
>
> Myxoedema consists of an introduction of extra protein into this environment, and from the fixed appearance of the swellings, it seems probable that the condition is one of expansion of the ground substance into the circulating filtrates of the blood . . . the total volume of the (blood) plasma is diminished and its percentage protein content increased in untreated myxoedema. Both these changes suggest the presence in the extra-vascular fluids of a colloid which tends to abstract saline but not protein from the plasma . . . . The degree of disorganization of filtration across the capillary membrane, however, is small in comparison with the high concentration of the myxoedema protein. . . . The present results are entirely in harmony with Ord's original claim that myxoedema is a mucinous infiltration of the tissues . . . ."

Contrast of Systemic Effects with Thyrotoxicosis. The general metabolic effects of myxoedema are opposite to those of thyrotoxicosis and there is a similar contrast between the functional disturbances of the various systems in the two conditions. This is well illustrated by reference to the cardiovascular system. In myxoedema, the cardiac output per minute and per beat are both reduced and the volume flow of blood through the vessels is slowed to an extent never met outside congestive heart failure. Thus despite the low cellular metabolism the arteriovenous oxygen difference is increased (Stewart *et al.*, 1938). The blood volume is diminished (Gibson and Harris, 1939) and the rate of filtration through the capillary walls is decreased (White and Jones, 1939). The blood proteins are raised. All these findings are diametrically opposed to those in thyrotoxicosis (Chapter XII).

The impact of myxoedema on the heart is of peculiar importance to the clinician. The heart shadow widens progressively as shown by serial X-rays but returns to its original size with thyroid therapy. This was well illustrated in the case reported by Howell (1945). Such behaviour has earned the epithet, " accordion heart " in myxoedema. Similarly in Schnitzer and Gutmann's case (1946) the transverse diameter of the heart was 20·6 cm. before treatment and decreased to 12 cm. at the end of four and a half months' thyroid therapy. In this case 60 c.c. of clear straw-coloured fluid were aspirated from the pericardium early in treatment, and it is quite clear that some of the cardiac widening is usually due to such pericardial effusion. Protein-rich effusions also occur into the pleural and peritoneal cavities even in the absence of congestive failure (Marzullo and Franco, 1939; Mussio-Fournier *et al.*, 1946).

In myxoedematous patients with severe cardiac symptoms there is usually associated organic disease of the heart. Thus of twenty-four such patients studied by McGavack *et al.* (1945) only four had a purely myxoedema heart. Coronary and peripheral arteriosclerosis are frequent accompaniments of long-standing myxoedema, the association perhaps depending on the hypercholesterolaemia.

La Due (1943) has reported the pathological findings in a patient dying from heart failure in myxoedema, unassociated with other cardiac disease. The heart muscle was pale red and possibly a little soft, but there was no fibrosis or focal lesion. Sections of the heart muscle just beneath the endocardium, however, showed extensive hydropic degeneration of the muscle fibres and elsewhere the nuclei were pyknotic, and the cells pale and lacking in striation. There was no mucin-like infiltration; the appearances were rather those of oedema of the myocardium. The changes were non-specific, being found equally in control sections from elderly patients dying with heart failure.

The frequent association of coronary artery disease with myxoedema and the need for a cautious approach to treatment should be emphasized (Bartels and Bell, 1939). Injudicious thyroid therapy may precipitate coronary thrombosis.

Both myxoedema heart and coronary artery disease may contribute to

angina pectoris. Thus in a case reported by Beaumont and Robertson (1939) pain was finally present even at rest, before treatment. It was then relieved by thyroid therapy but increasing the dose caused it to reappear; the optimal basal metabolic rate was between minus 10 and minus 17 per cent.

Though dosage should not be excessive, especially at the beginning of treatment, thyroid extract is always indicated however severe the cardiac manifestations (McGavack *et al.*, 1945). Obviously, in patients with failure and oedema, the usual criteria of a therapeutic response, namely, changes in the metabolic rate, body weight, pulse, etc., are unsatisfactory but reliance may be placed on the blood cholesterol.

Stern and Altschule (1936) followed the blood picture in patients subjected to total thyroidectomy for congestive heart failure. Concomitantly with the fall in metabolism there develops a macrocytic, hyperchromic anaemia. A simple hyperchromic anaemia is also characteristic of spontaneous myxoedema. The mechanism of this anaemia has been well explained by Bomford (1938) and confirmed by Jones (1940). Because of the low tissue requirements of oxygen there are inactivity and atrophy of the red marrow. Sternal punctures show a subnormal percentage of nucleated cells. Thyroid therapy results in reticulocytosis. Clearly, therefore, the anaemia of myxoedema is not strictly comparable to the deficiency anaemias; it differs from them in that it is associated with a hypoplastic and fatty bone marrow. Rather it is a " physiological " adaptation to the diminished oxygen requirements of the tissues comparable to that following prolonged exposure to atmospheres with high oxygen tensions.

An interesting association is occasionally seen between the anaemia of myxoedema and hypogonadism. If the myxoedematous patient is elderly there is also frequently hypogonadism. In this event, thyroid hormone alone will not restore the blood picture to normal. Testosterone must be added. The erythropoietic response is then prompt and complete (Glass, 1943). Gordon *et al.* (1946) also showed that in thyroidectomized and castrated rats the combination of testosterone and thyroxine produced the most rapid recovery of the blood picture after bleeding.

About 15 per cent. of all patients with myxoedema develop psychoses, of which melancholia is the commonest. Short of psychosis, there is striking impairment of mental function, a general retardation of psychomotor activity being characteristic. The patient exhibits mental torpor, apathy, and a striking slowness of response to stimuli. These psychic manifestations respond very gratifyingly to thyroid therapy.

The gastro-intestinal features of myxoedema are of some interest. The mucosa throughout the alimentary canal is atrophic and the other coats are infiltrated by lymphocytes and plasma cells, and thickened by oedema. There is a general lack of elasticity and motility (Bastenie, 1946). The flow of digestive juices, including gastric hydrochloric acid, is reduced. There is diminution of peristalsis and the intestine becomes distended with the products of fermentation. The patient is constipated and the abdomen ballooned. Bastenie (1946) claims that megacolon develops in the course

of severe thyroid deficiency and that it, in turn, may give place to true paralytic ileus. In five autopsies on such subjects he found the colon to be enormously distended and elongated.

The intestinal paresis occurring in advanced cases may be chronic or acute; in the former there are gradually progressive constipation and abdominal distension, with bowel actions occurring at weekly or longer intervals. In the acute forms, abdominal distension occurs so rapidly that the physician is likely to suspect a cyst or tumour. Surgical exploration was fatal in two such cases quoted by Bastenie. However, even when the patient is *in extremis*, treatment with thyroid extract often brings prompt relief.

In myxoedema the face is puffy and pale yellow with a characteristic flush over the malar bones. The skin becomes dry, the hair coarse and scanty, and patchy alopecia develops. The nails are thickened, cracked and atrophic. The mucous membrane of the mouth, tongue, pharynx and larynx is swollen, and speech, singing and breathing are all affected. The patients do not sweat even in the hottest weather and pilocarpine is without appreciable effect on the sweat glands.

Cutaneous lesions in Myxoedema. Deposits of mucinous material take two forms: (i) localized pretibial myxoedema; (ii) myxoedema papulosum et annulare.

Localized pretibial myxoedema is discussed in Chapter XIV. It has recently been shown (Watson, 1946) that the glairy, gelatinous substance deposited in the skin in this condition is rich in the mucopolysaccharides, hyaluronic acid and chondroitin sulphuric acid. Localized pretibial myxoedema may develop either during the florid stage of thyrotoxicosis or long after effective control of the hyperthyroidism.

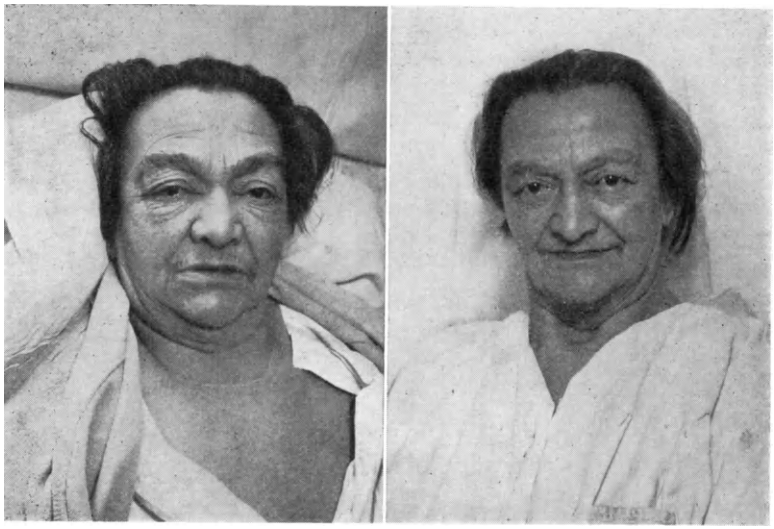
In myxoedema papulosum et annulare (Freudenthal and Braünauer, 1942) there are multiple small thickenings in the skin over wide areas of the trunk and limbs, which are similar in histology and chemistry to pretibial myxoedema.

Post-operative Myxoedema (cachexia strumipriva) (Fig. 44). This condition, first recognized almost simultaneously by Reverdin and by Kocher, follows total ablation of the thyroid in man. To this must now be added myxoedema resulting from excessive administration of antithyroid drugs or radio-iodine. The onset of post-therapeutic myxoedema is often delayed and insidious; the full-blown picture may not develop for months or years, if at all. Where it fails to develop, fragments of thyroid tissue may have escaped destruction or ablation.

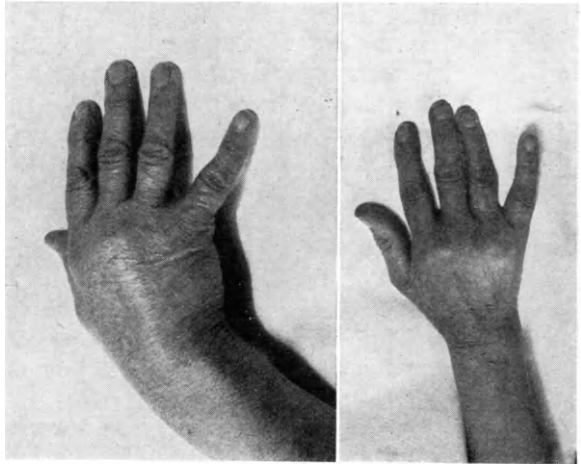
However, Hertzler (1935) and others have strenuously maintained that even after total thyroidectomy for goitre, it is exceptional for incapacitating hypothyroidism to develop.

The phenomena of hypothyroidism induced by complete removal of the normal gland in man have been exhaustively studied in patients so treated for chronic heart disease. The clinical features develop between the first and second months after the operation. There are the usual coldness of the extremities, dryness of the skin, absence of sweating, slowing of the rate of

hair-growth, and pallor. Between the second and the sixth post-operative months, about 90 per cent. of patients develop puffiness of the face and extremities, irritability, fatiguability, drowsiness, tinnitus and swelling of the tongue.



(*a*) *Before* (*b*) *After*



(*a*) *Before* (*b*) *After*

FIG. 44.—Post-operative myxoedema. The patient, aged 68, had a thyroidectomy for Riedel's struma in April 1937 and presented two years later with well-marked myxoedema (*a*). After two months' thyroid therapy there was striking improvement in her mental and physical state (*b*).

It should be emphasized, however, that metabolic levels of minus 20 to minus 25 per cent. may exist for a considerable time without clinical features of myxoedema, though the lower levels of metabolism, especially those below minus 35 per cent., are nearly always associated with obvious clinical signs. There are also mild anaemia, lowering of the free hydrochloric acid in the gastric secretion and characteristic changes in the electrocardiographic record and heart size (Blumgart and Davis, 1934).

Pituitary type of Myxoedema. Disease or destruction of the anterior pituitary results in partial atrophy of the thyroid gland as in Simmonds' disease. The thyroid usually retains some functional activity and hypothyroidism is therefore generally mild or moderate. The absence of trophic hormones from the anterior pituitary simultaneously affects the adrenals and gonads, and the patient manifests a polyglandular insufficiency.

Patients with pituitary myxoedema sometimes closely resemble those with ordinary myxoedema and it is very important for the physician interested in thyroid diseases to appreciate this and to be on the lookout for those of the former type because thyroid therapy will send them into a state of shock, which will prove fatal if such treatment is continued (Means *et al.*, 1940), but which responds to injections of gonadotrophic hormone and intravenous glucose-saline (Lerman, 1941). Tell-tale indications that myxoedema is of the pituitary type are atrophy of the breasts, vaginal mucosa and uterus in women and a eunuchoid habitus in men, scanty body hair and persistent hypotension. There may be a history of post-partum haemorrhage followed by failure of lactation, continued amenorrhoea, and loss of libido. The relevant laboratory procedures will quickly reveal the presence of disordered function of the other endocrines and the diagnosis will, in fact, seldom be missed if the possibility of pituitary myxoedema be kept in mind. There is less tendency for the converse to happen, namely, for spontaneous thyroid atrophy to be confused with Simmonds' disease, though this did occur in Chiolero and Meerwein's case (1939).

Latent Hypothyroidism. Degrees of hypothyroidism short of myxoedema are responsible for much ill-health because the true basis of the complaints is unrecognized and goes untreated. Such "masked" hypothyroidism (Rose, 1939) may be productive of manifold symptoms referable to the different systems. There are pain, soreness and stiffness in the muscles and joints, and backache. According to Hall and Monroe (1933) hypothyroidism is frequently a factor of importance in arthritis especially of the hypertrophic type. It is worth searching for, because its correction leads to improvement in the joint condition.

Chief among the genital complaints are amenorrhoea, oligomenorrhoea, infertility, menorrhagia or metrorrhagia. King and Herring (1939) have emphasized the frequency of abortion in women with hypothyroidism. In a sixty-three-year-old man with myxoedema reported by Marine (1939) there was advanced atrophy of the interstitial cells of the testes.

There may be anaemia and cardiac symptoms progressing to those of myxoedema heart. Achlorhydria, dyspepsia and constipation may also

derive from hypothyroidism. Possible mental changes include amnesia, depression, stupor, and dementia. Fenichel (1948) draws attention to chronic headache due to masked hypothyroidism. The headache is bilateral and may persist for weeks at a time. Associated features are asthenia, sensitivity to cold and a slow resting pulse rate. The basal metabolic rate is subnormal and the headache is relieved dramatically by thyroid therapy. These features were illustrated in the patient shown in Fig. 45 before and after thyroid therapy. In some patients with a mixture of general symptoms there may be a striking response to thyroid therapy even when the basal metabolic rate has been sensibly normal (Vandenberg, 1941).

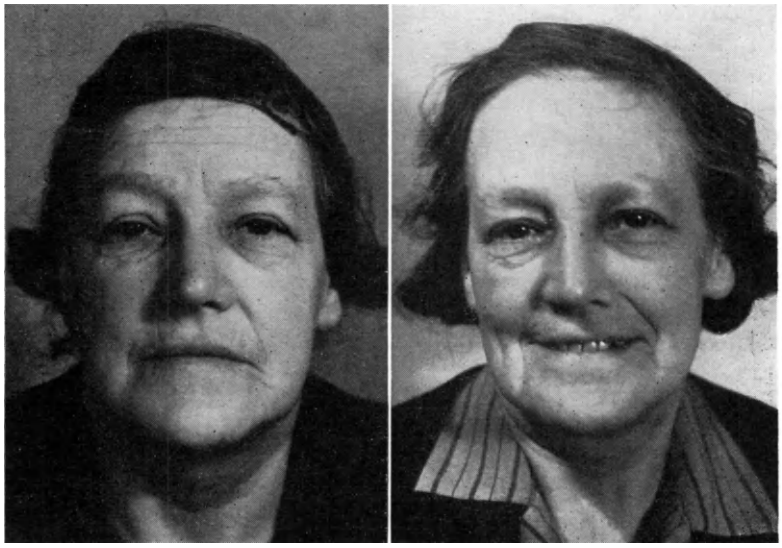


FIG. 45.—Mild hypothyroidism. She complained of tiredness, vague abdominal pains and increase in weight. She felt the cold and her voice had got deeper and thicker. With thyroid therapy her skin became normal in texture and elasticity, she lost all her symptoms, felt enormously improved in vigour and alertness. The serum cholesterol reading dropped from 440 mgm. per cent. to 223 mgm. per cent. (Dr. R. Asher's case.)

Other complaints deriving from hypothyroidism include vertigo, huskiness, weakness of the voice, blockage of the eustachian tube, degeneration of the eighth nerve, and swelling, catarrh and blockage of the various sinuses and foramina (McLaurin, 1945).

Mixed endocrinopathies including hypothyroidism. Some bizarre polyglandular dystrophies occur. Thus Hurxthal and Musulin (1945) report a woman with myxoedema who also suffered from hyperadrenalism. The basal metabolic rate was minus 33 per cent. and the blood cholesterol was raised. She had a profuse growth of hair on her face, chin and neck as well as on the upper part of the chest. The skin also showed areas of pigmentation.

Sixteen months after starting thyroid therapy all traces of the myxoedema, the excessive hair growth and the pigmentation had disappeared. In Kissin and Bakst's case (1947) myxoedema coexisted with hyperparathyroidism. Beaumont and Robertson (1943) and Miller (1946) have described a syndrome which they term " pituitary hypothyroidism with impaired renal function". In Miller's case it followed a penetrating gunshot wound of the brain, which was thought to have caused pathological changes in the pituitary body with consequent degenerative atrophy of the thyroid and abnormal renal function.

Diagnosis of Myxoedema. This is based not only upon the clinical features but also upon measurements of the radio-iodine uptake by the gland, the basal metabolic rate and the serum cholesterol. Associated diseases especially of the cardiovascular and endocrine systems must be sought for.

Prognosis. Untreated, the patient remains in an inert, torpid, semi-imbecile condition and though life may endure for many years its normal expectation is usually cut short by intercurrent infection, cardiac failure or ileus.

Excellent results follow systematic treatment with dried thyroid gland; the patients rapidly improve and may attain a degree of physical and mental activity almost indistinguishable from normal.

Treatment. Since the first brilliant result obtained by Murray (1891) in the treatment of myxoedema by preparations of the thyroid gland of sheep (carbolated glycerin extract given subcutaneously) progress has been made in many directions in treating cretinism on the same lines. H. Mackenzie (1892) and Fox (1892) were the first to administer the fresh gland by the mouth. In order to obtain the best results it is necessary to ensure that the preparations of the thyroid used are of standardized activity. It is also essential that the degree of thyroid deficiency should be calculated by basal metabolic rate estimations, in order to facilitate the restoration of an exact functional balance.

With the isolation of thyroxine by Kendall it was hoped that it would be possible to substitute the pure chemical compound for the usual dried thyroid gland. The high cost and the uncertainty of action of thyroxine when given by the mouth have, up to the present, interfered with its general use in the therapeutics of thyroid deficiency. Recent developments in the synthesis of thyroxine, however, indicate that it may soon be produced at reasonable cost and it is also clear that oral administration of thyroxine gives perfectly satisfactory results in myxoedema (Hart and Maclagan, 1950). A single daily dose of 0·15–0·3 mg. of l-thyroxine sodium is sufficient. It is freely absorbed from the alimentary tract and has the advantage that it does not require chemical or biological standardization.

In Great Britain the official preparation is thyroideum siccum B.P. (referred to here as dried thyroid). One grain of dried thyroid is equal approximately to 5 gr. of fresh sheep's gland. Tablets prepared from the dried gland remain fully potent for many months if kept cool and in stoppered bottles.

Repeated estimations of the basal metabolic rate in any cretin or myxoedematous patient are desirable, in order to decide on the appropriate dose of dried thyroid, to estimate the degree of improvement that follows, and as a check against inadequate or excessive dosage. The basal metabolic rate rarely falls below minus 42 per cent. in high-grade cretinism and myxoedema, and in the minor degrees of endemic cretinism the figures may approach, or even exceed, normal. It must be remembered that it is difficult to obtain in cretins with gross mental defect the degree of calm and co-operation which are so essential for the determination of strictly basal figures.

Winkler *et al.* (1945) claim that in any event the level of the serum iodine is a better indicator of the amount and accuracy of the thyroid dosage. In twenty-nine untreated patients with myxoedema the serum iodine averaged 1·3 gamma, with a range of 0·2–2·5 gamma per cent. as compared with a normal range of 3–9 gamma per cent. There was a close correspondence between the dose of thyroid extract given and the consequent rise in the serum iodine, 1 grain daily increasing the serum iodine by 2 gamma per cent. After adequate treatment the blood iodine in their own cases ranged from 3·0–6·7 gamma per cent. and averaged 4·8 gamma per cent.

Our routine in uncomplicated cases has been to start with a dose of 1 gr. thyroideum siccum B.P. daily and to increase this gradually to 2 gr. daily until the basal metabolic rate rises to normal. It is usually more convenient for patients to take the gland at bed-time. Murray advised diminution of the dose during hot weather and a slight increase in the cold part of the year. If pregnancy supervenes in the female he advised that the dose of dried thyroid should be increased by 25 per cent. The prophetic quality of this advice based on purely clinical observation is borne out by the recent work of Peters *et al.* (1948) (See Chap. XIV).

In elderly subjects or those with cardiac complications the initial dosage must be small ($\frac{1}{4}$–$\frac{1}{2}$ gr. of dried extract each night) and the patient should be largely at rest (Murray, 1930). The dose is gradually increased to 2 gr. daily at the end of six weeks, when it may be finally adjusted to the level of metabolism desired. A slightly *minus* level is often preferable (Hart and Maclagan, 1950).

The patient with myxoedema who is responding favourably to treatment is aware of increased warmth, and slight sweating. Objectively, there are moderate rises in pulse rate, temperature and the quantity of urine excreted and sharpening of the mental processes. If malaise, palpitation, aching pains in the limbs, loss of appetite, and diarrhoea and sickness occur it is an indication for a diminution of the daily dose. The basal metabolic rate should rise slowly, and the weight should not diminish too rapidly. The skin soon ceases to scale and becomes soft and elastic, and after a time hair begins to grow on the bald patches. The blood picture may slowly return to normal. If deafness has been a prominent feature if often improves as a result of treatment and psychoses also disappear. Sexual disturbances are among the earliest to improve.

Murray (1920) quotes his first case, which lived on for twenty-five years, and died at seventy-four from cardiac failure. De Quervain (1930) admits that thyroid medication in endemic cretinism is disappointing, but believes that iodine prophylaxis holds out considerable promise.

That myxoedematous patients can be kept alive and well for very long periods is shown by a case of Raven's (1924). This patient developed myxoedema in 1870 and died in 1924 at the age of ninety-four. Before the treatment was started she had been bedridden and imbecile for twenty years; after five weeks' treatment she had greatly improved, and within fifteen months her condition had become practically normal—she was happy, healthy and mentally alert. At first the patient was given 5 gr. of dried thyroid gland twice a week; later on this was altered to 1 gr. twice daily, a regime which she continued, though apparently not quite regularly, for the rest of her life.

Surgical intervention in goitre associated with cretinism aud hypothyroidism. The existence of pressure symptoms and possibly the grosser degrees of deformity justify the removal of goitres even when cretinism exists. Favourable results, not only in respect of pressure symptoms but in the direction of increased functional activity, have occasionally been claimed. There is, however, in our opinion, no possible justification for operations on the goitres of cretins in the hope of permanent improvement in function resulting. On the other hand, it is unjustifiable to allow these patients to suffer from the pressure effects of large goitres in the fear than an appreciable deterioration in function may follow partial thyroidectomy, since in any case thyroid medication will correct the adverse balance.

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CHAPTER IX

GRAVES' DISEASE — TYPES — NATURE — NOMENCLATURE — HISTORY

Graves' disease is one of the key problems of internal medicine. On the one side, it overlaps the toxic nodular goitres (Fig. 46). The precise relationship, for example, between secondary toxic goitre and classical Graves' disease is still not clear. On another side it merges into the anxiety states, autonomic imbalance and neurocirculatory asthenia. On still another, there

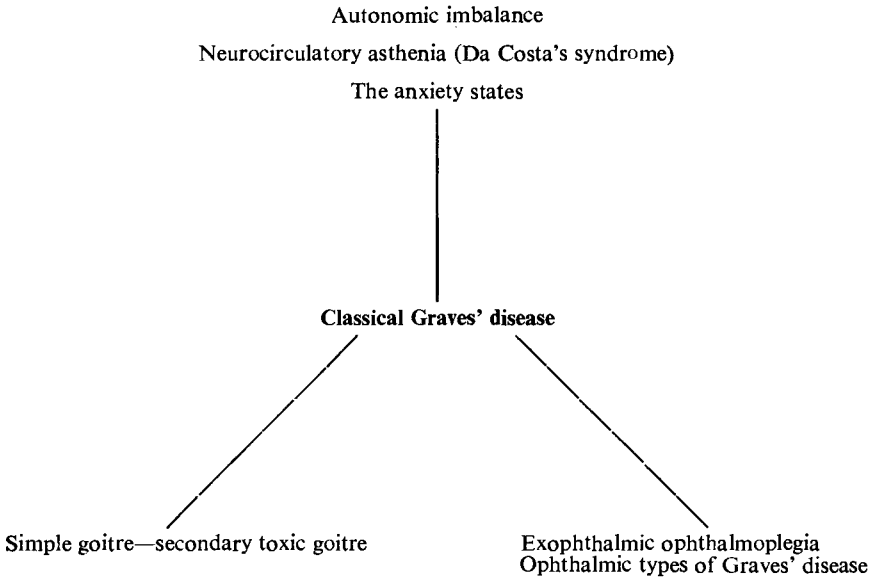

FIG. 46.

are the gross and intriguing conditions of exophthalmos and ophthalmoplegia which still baffle our comprehension. Beyond these there are even more obscure linkages with certain other endocrinopathies, and conditions characterized by thymic enlargement and myopathy.

Forms in which Graves' disease occurs. These are shown in Table X.

The expression " Graves' disease " is conveniently used in an omnibus sense to include all these types. Groups 1–3 suffer from thyrotoxicosis but in Group 4 goitre and hyperthyroidism may be entirely lacking, though the

eye-signs of Graves' disease are present. Variation in the natural history of thyrotoxicosis are shown diagrammatically in Fig. 48.

Components of Thyrotoxicosis. The central disorder in thyrotoxicosis is excessive thyroid secretion, and the structural correlate of this is hyper-

TABLE X

GRAVES' DISEASE

1. Classical Graves' disease, exophthalmic goitre, toxic diffuse goitre, primary toxic goitre (Fig. 47).
2. Toxic nodular goitre:
   (*a*) toxic adenoma, hyperfunctioning (" hot ") single nodule, 3 per cent. of thyrotoxics.
   (*b*) toxic multinodular goitre:
   - endemic—secondary to long-standing simple goitre—nodules are " cold ".
   - sporadic—may be secondary to simple goitre — but long-continued or intermittent thyrotoxicosis may result in nodularity (" hot " nodules).
3. Thyrotoxicosis factitia.
4. Ophthalmic types of Graves' disease (" exophthalmic ophthalmoplegia ") { spontaneous / post-operative

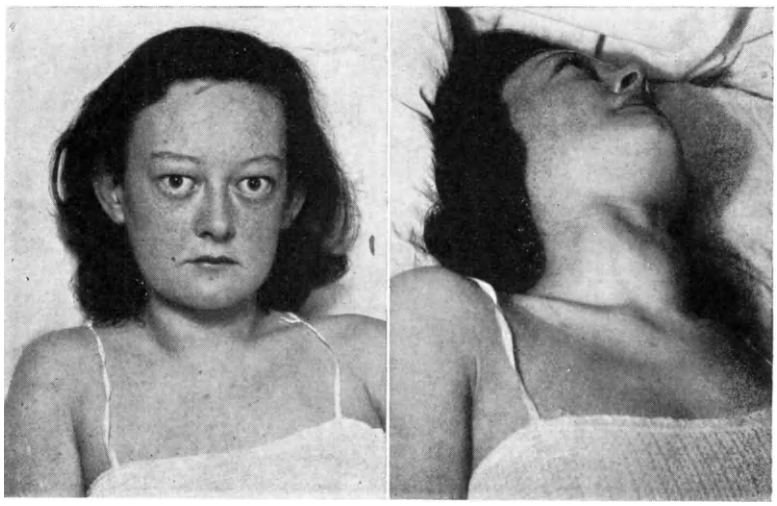

FIG. 47.—Classical Graves' disease in a patient aged 16. Prominence of the eyes and a lump in the neck had been noticed six months previously. She had become " nervous and jumpy " and had developed an " enormous appetite ".

plasia of the thyroid epithelium. Other more or less independent components are the ocular changes and a group of nervous manifestations termed by Rasmussen (1937) "the psychoneurotic syndrome." Both may persist virtually unchanged after the hyperthyroidism is eradicated. While of course some degree of thyroid intoxication is by definition essential for the diagnosis, the ocular and nervous components are inconstant and unessential. It is, however, doubtful whether the nervous phenomena form an integral or characteristic part of the syndrome.

Harington and his co-workers (1935) established the fundamental fact

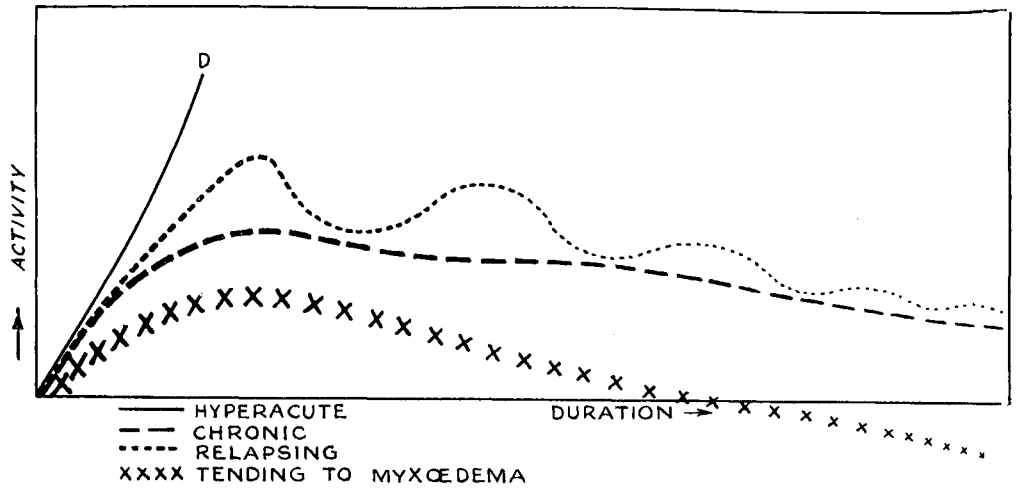

FIG. 48.—Possible variants in the natural history of thyrotoxicosis.

that the glandular secretion in thyrotoxicosis, though excessive in amount, is not qualitatively different from normal. This has greatly clarified the pathology of the disease, the elaborate dysthyroidism theory of Plummer being rendered invalid. But the precise amount of thyroid hormone passing into the circulation cannot be measured directly either in health or disease. Hence the expression "thyroid intoxication" cannot have an exact meaning.

Nomenclature. The term, "hyperthyroidism," is used here to signify both the excessive secretion of thyroid hormone and its systemic effects. These are summarized in Table XI. Hyperthyroidism thus describes one component of thyrotoxicosis and is best not applied to the patient's state as a whole. *The ocular changes* of Graves' disease include principally lid retraction, exophthalmos and lid protrusion, and ophthalmoplegia. In its classical or full-blown form, Graves' disease includes one or more of these ocular changes as well as goitre and hyperthyroidism. The following expressions are accordingly synonymous:

Exophthalmic goitre,
Graves' disease,
Parry's disease,
Basedow's disease,
Flajani's disease.

But there are also abortive forms, *Graves' disease without hyperthyroidism*, in which one or more of the ocular changes are present without hyperthyroidism. In these abortive forms the ocular changes are usually severe. Other expressions used to describe them are:

Exophthalmic ophthalmoplegia (Brain and Turnbull, 1938).
Malignant exophthalmos (Ruedemann, 1936).
Hyperophthalmopathic Graves' disease (Means, 1948).
Thyrotropic exophthalmos (Mulvany, 1944).
Ophthalmic types of Graves' disease (Rundle and Wilson, 1944).

TABLE XI

SUMMARY OF SYSTEMIC PATHOLOGY OF THYROTOXICOSIS

—	Thyrotoxicosis		Thyrotoxicosis plus local, associated disease.
	Slight	—→severe and prolonged	
1. Cardiovascular system	Tachycardia	—→auricular fibrillation, congestive failure, anasarca	Early cardiac breakdown, masked hyperthyroidism e.g. angina pectoris
2. Central nervous system	Hyperexcitability	—→acute thyrotoxic delirium	Organic reaction types of psychosis, if predisposition.
3. Endocrine system	Low sugar tolerance; other effects on adrenal and gonads		Diabetes, if diabetic anlage.
4. Muscular	Weakness	—→thyrotoxic myopathy	Relation to myasthenia gravis—periodic paralysis.
5. Bone	Decalcification	—→spontaneous fracture	—
6. Alimentary system	G.I. hypermotility	—→G.I. crises with vomiting and diarrhoea	—
Liver	Deranged glycogenesis	—→liver atrophy and necrosis	
7. Lymphatic	Lymphoid hyperplasia, thymic enlargement		—
8. Cutaneous	—		Localized pretibial myxoedema.

The term, " thyrotoxicosis," may be used to describe all patients with toxic goitre whether or not ocular changes are present. Patients with thyrotoxicosis may be classified as suffering from *toxic diffuse goitre* or *toxic nodular goitre*, on the basis of the clinical characteristics of the goitre itself and the history, for in the former there is usually no record of goitre previously (*primary thyrotoxicosis*) whereas, in the latter, goitre may have ante-dated by many years the onset of hyperthyroidism (*secondary thyrotoxicosis*). Ginsburg (1929) gives the following synonyms for secondary toxic goitre:

Enlargement of the Thyroid Gland in Connexion with Enlargement or Palpitation of the Heart	(Parry 1825.)
Constitutional Iodism	(Rilliet, 1860.)
Iodine Exophthalmic Goitre and Iodine Graves' Disease	(Trousseau, 1860.)
Formes Frustes of Exophthalmic Goitre	(Trousseau, 1862; Marie, 1883.)
Secondary Basedow	(Gauthier, 1893; Buschan, 1894.)
Basedowified Goitre	(Marie, 1897.)
Goitre Heart	(Kraus, 1899.)
Iodine Thyroidism	(Breuer, 1900.)
Struma Basedowificata	(Kocher, 1906.)
Basedowoid	(Stern, 1909.)
Toxic Adenoma of the Thyroid	(Plummer, 1913.)
Adenoma with Hyperthyroidism	(Plummer, 1916.)
Hyperfunctioning Adenomatous Goitre	(Plummer, 1921.)
Iodine Hyperthyroidism	(Jackson, 1924, 1925.)
Nodular Goitre with Hyperthyroidism	(Rienhoff, 1927.)

In toxic nodular goitre multiple nodules exist. Radioiodine studies of toxic nodular goitres occurring in a goitre belt have now shown that most of the nodules are functionally less active than the paranodular tissue (Puppel *et al.*, 1946).

Similar studies have enabled *toxic adenoma* to be definitely separated from the generality of toxic nodular goitres. It is a rare type; the nodule is over-active, the paranodular tissue, atrophied (Cope *et al.*, 1947).

Thyrotoxicosis factitia results from the excessive consumption of thyroid extract. Thyroid extract is being taken for obesity or the patient is a psychopath; consumption of the extract is then usually concealed or denied.

History. A study of the earlier literature reveals without a doubt that Parry, in 1786, was the first to recognize exophthalmic goitre. His description is exact and unequivocal. Graves' account, in 1835, of three cases is much less convincing and altogether inferior to Parry's, but Basedow (1840) deserves the credit for the fullest and most exact account of the disease which had up to that time been published; he also mentions a case referred to by Scarpa of Paris in 1821 and another described by Paula of Heidelberg in 1837.

The great importance of Parry's observations makes it desirable to include here an abstract of his writings.

Collections from the Unpublished Medical Writings of the late Caleb Hillier Parry, 1825

" *Enlargement of the Thyroid Gland in Connection with Enlargement or Palpitation of the Heart* "

CASE 1. There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed in that connection by medical writers. The malady to which I allude is enlargement of the thyroid gland.

The first case of this coincidence which I witnessed was that of Grace B., a married woman aged thirty-seven, in the month of August, 1786. Six years before this period she caught cold in lying-in, and for a month suffered under a very acute rheumatic fever; subsequently to which, she became subject to more or less of palpitation of the heart, very much augmented by bodily exercise and gradually increasing in force and frequency till my attendance, when it was so vehement, that each systole of the heart shook the whole thorax. Her pulse was 156 in a minute, very full and hard, alike in both wrists, irregular as to strength, and intermitting at least once in six beats. She had no cough, tendency to fainting, or blueness of the skin, but had twice or thrice been seized in the night with a sense of constriction and difficulty of breathing, which was attended with a spitting of a small quantity of blood. She described herself also as having frequent and violent stitches of pain about the lower part of the sternum.

About three months after lying-in, while she was suckling her child, a lump of about the size of a walnut was perceived on the right side of her neck. This continued to enlarge till the period of my attendance, when it occupied both sides of her neck, so as to have reached an enormous size, projecting forwards before the margin of the lower jaw. The part swelled was the thyroid gland. The carotid arteries on each side were greatly distended; the eyes were protruded from their sockets, and the countenance exhibited an appearance of agitation and distress, especially on any muscular exertion, which I have rarely seen equalled. She suffered no pain in her head, but was frequently affected with giddiness.

For three weeks she had experienced a considerable degree of loss of appetite and thirst, and for a week had oedematous swelling of her legs and thighs, attended with very deficient urine, which was high coloured, and deposited a sediment. Until the commencement of the anasarcous swellings, she had long suffered night sweats, which totally disappeared as the swellings occurred. She was frequently sick in the morning, and often threw up fluid tinged with bile.

She nursed for a year the child of her first lying-in, during which time she did not menstruate. Subsequently to that period she had five times miscarried, and for the last four months her menses had been irregular as to intervals, and defective in quantity and colour. Bowels usually lax, and more especially so for the last three weeks. It was directed that six ounces of blood should be taken from her arm, and that she should take twice a

day a pill consisting of dried Squill, and quicksilver triturated with Manna, of each one grain.

The bleeding almost immediately relieved the dyspnoea and stitches across the sternum. But the oedematous swellings were increased, and the urine did not exceed half a pint in twenty-four hours. She had been purged seven or eight times each day. Her pulse was 114, full and hard, and never more than six strokes without intermission. This was the state of symptoms on the 16th of August. The bleeding was ordered to be repeated and the pills to be continued.

I did not again see her until the 25th, when she had taken eight of the pills, which did not affect the mouth, but had produced seven or eight watery stools daily. The urine, however, did not amount to three ounces in the twenty-four hours, and was very high-coloured, and extremely turbid on standing, with a copious sediment. Her drink was about a quart in the day. Each systole of the heart shook the whole trunk of the body. The oedema had extended itself nearly to the navel.

The pills were repeated, and she was ordered to drink freely of a solution of supertartrate of Potash.

From this time no further application was made to me respecting this patient, who, probably, soon paid her debt to nature.

The vivid account of primary thyrotoxicosis or exophthalmic goitre includes references to irregularity of the heart's action, which appears to have been due to what would to-day be described as auricular fibrillation, and to the repeated miscarriages.

After describing two other similar cases, Parry proceeds:

My attendance on the three last patients having occurred at the same time, first suggested to me the notion of some connection between the malady of the heart and the bronchocele. I mentioned that opinion to Mr. G. Norman, surgeon, to whom I shewed the lady last mentioned. Shortly afterwards I expressed the same opinion to Mr. Cruttwell, surgeon, to whom it then occurred that he was attending a patient with a similar coincidence, and that in her the bronchocele succeeded to the affection of the heart. . . .

CASE 8. Miss P., of a gouty and nervous family, has had an enlargement of the thyroid gland for more than twenty years, which has very much increased of late. It commenced at sixteen years, after having been two years tolerably regular, but leading a sedentary life. It is not sore, but occasionally somewhat uneasy. She had no previous headache or giddiness, but frequent palpitation of the heart, sudden and violent. She is regular copiously, with no difference at these times.

Eight or nine years ago a pain came on in the right foot, across the small joints of the toes, with swelling, redness, and tenderness, continuing for five or six weeks, and becoming of a dark, livid colour; impeding her walking for a considerable time, without breach of the skin. From that period she has been subject to depression of spirits, and frequent headache, especially of late. The swelling began on the right side, and is now nearly equal on the left, but extending far upwards. Pulse 96, and soft. Carotids of moderate strength; the right, strongest. Palpitation less of late, but violent. Bowels tending to costiveness. Extremely nervous. She has taken Bark, Sponge, Calomel,

Antimony, Sarsaparilla, Soda, has tried sea-bathing, and used Mercurial friction, which made her faint. Vs. ad ℥ viij. Aloes Barbad. gr. j. vel. iss. h.r.n. Extr. Conii, q.s. ad nauseam ciendam.

The blood was not inflamed. A fortnight afterwards, the patient, who lives at a distance, says in a letter, " That the tightness and uneasiness in the swelled part are quite removed, but I cannot be certain the size is reduced. I have taken much exercise, and feel altogether improved by your remedies.—May 12, 1814."

This appears to have been a case of secondary thyrotoxicosis or toxic adenoma.

Basedow's Cases

CASE 1. A multiparous woman aged thirty-three, in whom he noted, among other features, exophthalmos, wasting, goitre, sweats, palpitations, rapid small pulse, shortness of breath, amenorrhoea and oedema of the extremities. Following treatment with iodine and digitalis, she improved and was able to go through two further pregnancies in five years, but the exophthalmos persisted.

CASE 2. In this case, also a woman, he noted obstinate diarrhoea, extreme wasting, exophthalmos, forcible heart impulse, inability to keep still, rapidity of speech, subjective sensation of warmth, unnatural liveliness, and a very large appetite which the patient satisfied indiscreetly. She slept with the eyes wide open, and by no effort could they be closed. She improved on Adelheidsbrunner water—a mineral-water rich in iodine.

CASE 3. A man aged fifty. In addition to the symptoms described in Cases 1 and 2, Basedow mentions that both eyes were lost as a result of corneal ulceration.

CASE 4. In this female patient he noted the change from a phlegmatic temperament to one of peculiar liveliness. She became impetuous in conversation. Her condition improved during pregnancy.

Flajani's name (1802) is sometimes associated with exophthalmic goitre, but his paper is inferior to that of any of the other three authors, and his patient did not exhibit exophthalmos. It would be difficult, therefore, to justify the term " Flajani's disease " as signifying exophthalmic goitre.

From Basedow's time until the end of the nineteenth century attention was concentrated mainly on the particular form of thyrotoxicosis which he and his two predecessors had studied, viz., exophthalmic goitre, but it has been overlooked by most writers, though not by Ginsburg (1929), that Parry, who, in 1814 (see Case 8, p. 144), described thyrotoxic phenomena associated with a nodular goitre in a patient who exhibited no exophthalmos, therefore deserves credit as the first writer to give an account of two types of thyrotoxicosis, although he did not himself name either or differentiate between them. Later in the century certain forms of thyrotoxicosis, which differed from ordinary exophthalmic goitre in the absence of some of the more prominent signs and symptoms were termed " formes frustes " by Trousseau (1862) and Marie (1883). These were further studied and re-named by Gauthier (1893) and Buschan (1894) " secondary Basedow," by Marie (1897)

" Basedowified goitre," by Kraus (1899) " goitre heart," by Kocher (1906) " struma Basedowificata," by Stern (1909) " Basedowoid," by Plummer (1912–21)) successively " toxic non-exophthalmic goitre," " toxic adenoma of the thyroid," " adenoma with hyperthyroidism," and " hyper-functioning adenomatous goitre."

Möbius (1886) was apparently the first to ascribe the disease to the abnormal thyroid itself, though Parry mentioned the possibility of the association but concluded that the gland acted as a sort of sponge to hold some of the excess of blood which he believed the brain to contain in this disease.

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CHAPTER X

THYROTOXICOSIS: NATURE AND CLINICAL FACTORS IN ITS AETIOLOGY AND PATHOGENESIS

Nature of Thyrotoxicosis — Geographical Distribution — Antecedent Goitre — Climatic Factors — Urban and Rural Influences — Prevalence — Sex Incidence — Age of Onset — Heredity — Constitutional Predisposition — The Autonomic Nervous System and Toxic Goitre — The Sympathetico-Adrenal System and Thyrotoxicosis — Has Thyrotoxicosis a Thyroid or Extra-Thyroid Origin? — What has Thiouracil taught us concerning Pathogenesis? — Significance of the Thyroid Stump — Dietary Influences — Neurogenic — Psychic Trauma — Infectious Disease and Toxaemia.

As Boyd (1947) remarks, " Graves' disease is an enigma and constitutes one of the most perplexing problems in the whole of medicine." Any study of the pathogenesis of thyrotoxicosis is as much an inquiry into the nature of the disease as into its causation. In fact, one of the greatest difficulties is to form an adequate concept of the syndrome.

Geographical distribution. The geographical factors in the pathogenesis of Graves' disease should be the subject of a co-operative study (Means, 1948). The disease is widespread, occurring in all countries and in all regions. There is also powerful evidence from goitre maps that endemic goitre predisposes to thyrotoxicosis. Campbell (1925) and McEwan (1938) in England, McClendon (1936) and Read (1939) in the United States and Wyndham (1940) in New South Wales, have made geographical surveys of the incidence of simple and toxic goitre. Each author found that the areas of highest incidence of thyrotoxicosis coincided with those of highest endemicity. Read's object was to compare the incidence of exophthalmic and endemic goitre, and consequently the correlation he found was not as close as that existing between endemic goitre and thyrotoxicosis, including the secondary forms.

Antecedent goitre. The geographical distribution of thyrotoxicosis is bound up with the problem of the role of antecedent goitre. There can be no doubt that simple goitre, endemic or sporadic, predisposes, or indicates a constitutional predisposition to thyrotoxicosis. Thus in a random series of 332 thyrotoxics the disease was of the secondary type in 21·5 per cent. (Rundle, 1941). Such a proportion, occurring as it did in London, a non-endemic area, constitutes conclusive evidence that goitrous subjects are particularly liable to develop thyrotoxicosis.

In many of our patients the previous goitre had appeared at puberty or during adolescence. It had then often subsided in adult life but the subsequent development of thyrotoxicosis indicated that the gland had remained a *locus minoris resistentiae*.

Anderson and Collip (1934) described an interesting experiment: A group of rats suffering from spontaneous goitre were injected with the same dose of thyrotropic pituitary extract as a group of control rats. The goitrous rats were much more susceptible and developed a hyper-acute form of thyrotoxicosis. This experimental result is highly suggestive, but it should be noted that Remington (1937) was unable to obtain confirmatory results with rats in which goitre had been induced experimentally.

The responsiveness of the thyroid epithelium to activating stimuli is variable. In simple goitre it is increased. By contrast, in certain subjects, the thyroid has an extraordinary resistance to anterior pituitary extracts. Thus Sharpey-Schafer and Schrire (1939) found that injections of thyrotropic extract restored the metabolism to normal in most cases of hypothyroidism but in some such cases even massive doses failed to evoke a response and biopsy of the thyroid isthmus showed the histology to be inactive and resting.

Climatic factors. Cramer's classical observations (1928) established that exposure to cold strongly activates the thyroid in experimental animals, which suggests that climatic factors may influence the incidence of thyrotoxicosis.

Mills (1930) by plotting the death-rate from goitre in Canada and the United States, found that it was low along the Atlantic seaboard and in the southern States, higher on the Pacific Coast and highest of all in the central northern States around the Great Lakes, which area is subject to the most violent fluctuations in temperature and exposed to the extremes of cold. It is also the region of greatest endemicity. Mills' table of mortality statistics shows similar differences to exist in Europe, the death-rate being lower, for example in Mediterranean Italy and Spain, than in more northerly England and Wales, and Holland. Sallström (1935) in careful goitre maps of Sweden, also found a distinctly higher incidence of thyrotoxicosis in the colder regions. Iversen (1948) suggests that the three exceptionally cold winters immediately preceding the thyrotoxic " epidemic " in Denmark (1941–45) may have played a part in its causation.

A seasonal variation in the intensity of thyrotoxicosis is suggested by Morgans and Trotter's data (1949) exacerbations being most frequent in the spring and least frequent in the autumn.

Urban and Rural Influences. Since his areas of highest mortality of thyrotoxicosis coincided with rural endemic areas McEwan (1938) was inclined to discount the importance of the stress and strain of urban life in pathogenesis. Other authors, including Mayo and Plummer (1925), Sallström (1935), Read (1939), have, however, found the urban incidence higher. Clearly, many factors are involved in this question.

Prevalence. The table (Table XII) appended gives the number of deaths from thyrotoxicosis at all ages for each year from 1931 to 1946 in England and Wales. It will be seen that on the whole there was a gradual increase from 1913 to 1924, except for a small fall between 1915 and 1918, and that this increase became very rapid from 1925 onwards right up to 1939. Since then there

has been a steady fall. This fall, coinciding exactly with a period of unparallelled stress for the civilian population, during the war years, is remarkable. A similar sharp decline in the prevalence of the disease occurred in Germany during the 1914–18 war (Jacobowitz 1932; Curschmann, 1922 and 1923). Curschmann related this decrease to severe under-nourishment in Germany

TABLE XII. DEATHS FROM THYROTOXICOSIS IN ENGLAND AND WALES.
(From the Annual Report of the Registrar-General)

Year	Deaths at all ages			Crude annual death rate		
	Male	Female	Total	Male	Female	Persons
1913	42	368	410	2	19	11
1914	38	434	472	2	23	13
1915	32	400	432	2	21	12
1916	47	399	446	3	20	13
1917	40	395	435	3	20	13
1918	46	357	403	3	18	12
1919	56	473	529	4	24	15
1920	46	464	510	3	24	14
1921	54	533	587	3	27	15
1922	63	591	654	3	30	17
1923	56	569	625	3	28	16
1924	46	574	620	2	28	16
1925	64	680	744	3	34	19
1926	84	743	827	4	36	21
1927	91	852	943	5	42	24
1928	119	933	1052	6	45	27
1929	128	936	1064	7	45	27
1930	112	1114	1226	6	54	31
1931	138	1162	1300	7	56	33
1932	165	1239	1404	9	59	35
1933	168	1244	1412	9	59	35
1934	181	1315	1496	9	62	37
1935	183	1378	1561	9	65	38
1936	207	1492	1699	11	70	42
1937	191	1482	1673	10	69	41
1938	196	1372	1568	10	64	38
1939	201	1378	1579	10	64	38
1940	163	1022	1185	9	47	30
1941	138	817	955	8	38	25
1942	113	752	865	7	35	23
1943	107	715	822	7	33	22
1944	84	573	657	5	27	17
1945	90	563	653	5	26	17
1946	75	590	665	4	27	16

during the blockade years but this explanation cannot be advanced to explain the decline in Britain during the recent war. The Registrar-General's figures from New South Wales (Australia) show a similar sharp fall in deaths from thyrotoxicosis since 1941 (Gibson and Poate, 1949).

Iversen (1948) on the other hand, in a valuable monograph, describes a sharp rise in the frequency of thyrotoxicosis in Denmark during the period 1941–45. During this Danish " epidemic," toxic nodular goitre became nine

times more frequent than in 1938, while the prevalence of toxic diffuse goitre was quadrupled. He concluded, after an exhaustive analysis, that dietary and climatic factors might have been involved in this remarkable increase.

Sex Incidence. Everywhere thyrotoxicosis is more common in women, but the exact proportion between the two sexes varies somewhat in different parts of the world. Figures for some of the bigger series are given in Table XIII:

TABLE XIII. SEX DISTRIBUTION IN THYROTOXICOSIS

Author	Date	Male	Female	Number in Series
Sattler	1909	1:	5·4	3,800
Cookson	1939	1:	8·5	400
Rundle	1939	1:	8·2	332
Iversen	1948	1:	7	1,832
Witzig (Switzerland) ..	1948	1:	4·4	594

The character of the case material obviously affects the ratio and since simple goitre predisposes to secondary thyrotoxicosis the incidence tends to become more equal in highly endemic areas (Witzig, 1948). Not only thyrotoxicosis but all diseases of the thyroid gland are more common in females, indicating some inherent predisposition to goitre in the endocrine equipment of the latter.

The frequent development of thyrotoxicosis in relation to one or other of the sexual epochs, stressed by Gardiner-Hill (1929), further emphasizes this relationship. The menopause is the epoch most commonly involved, and about a fifth of cases develop within two years of it (Rundle, 1941). Branwood (1949) claims that climacteric thyrotoxicosis is benefited by oestrin therapy. In our series of 332 cases, 36 per cent. were women of the active child-bearing age (twenty to forty years), but social status and child-bearing appeared not to be very important factors, for about half (58 per cent.) were, or had been married and about half (42 per cent.) were spinsters. However, it might be argued that there was a relatively high proportion of spinsters in the series, compared with that in the general population. Most (65 per cent.) of the married women had borne children normally. In occasional cases, the onset of thyrotoxicosis presented a striking association with marriage, pregnancy, or childbirth and in some there was a life-long history of menstrual irregularity, but all these features were variable and inconstant.

Age of onset. Most statistics relate to the age of patients on first attending hospital. Though it is commonest in middle life, thyrotoxicosis can occur at any age. Thus White (1912) described it in a foetus, Ellis (1935) reported its occurrence in infancy, and the Criles' account (1937) showed that juvenile thyrotoxicosis is essentially similar to the same disease in the later age-groups.

Such early occurrence must argue against an exclusively psychological origin of the disease.

Iversen (1948), emphasizes that the age distribution has changed markedly in the past few decades. Earlier statistics (Sattler, 1909; Mackenzie, 1916; Gardiner-Hill, 1929) regularly showed thyrotoxicosis to be a disease of young people affecting particularly the 20 to 40 age-group. Now, most series show the peak incidence to be in the 40 to 49 decade. Thus, in Cookson's (1939) series of 400 cases, only 37 per cent. were forty or younger, whereas 63 per cent. were over forty years. In our 1941 series, more than one-quarter of the patients were over fifty. Iversen's curve (1948) is valuable since it takes into account the population at risk in the different decades.

This changing distribution may depend on several factors but chiefly upon better recognition and diagnosis of the mild types of secondary thyrotoxicosis in older people. Much prominence has recently been given to these types in published writings (Lahey, 1931; Clute and Swinton, 1935; Cookson, 1939, and Hendrick, 1941).

Heredity. The hereditary factor in exophthalmic goitre excites much interest especially when the disease affects children (Dinsmore, 1941; Moolton and Bruger, 1942), or when many members of the one family are affected, as in the remarkable report of Boas and Ober (1946). In this family there were 143 blood relatives in five generations, eleven of whom had definite exophthalmic goitre; eight were females and three were males.

Thyroid disease looms large in the family history of patients with goitre. Thus, of sixty-nine patients with Graves' disease, Bartels (1941) found a history of goitre in 61 per cent. Similarly, there were eighty-eight affected relatives in the families of 201 goitrous patients examined by Martin and Fisher (1945). But the incidence has not always been found so high; it was 22 per cent. in our own series (Rundle, 1941).

Bartels detected a recessive characteristic for the inheritance of Graves' disease, partially sex-limited to women and with a manifestation in them of 70 to 80 per cent. Martin and Fisher corroborated and further clarified Bartels' observation. By separating patients with exophthalmic goitre from those with other types, a separation justifiable for the analysis, their evidence becomes very striking; patients suffering from exophthalmic goitre had more relatives with exophthalmic goitre than did patients with nodular goitre, by seventeen to two. They were able to conclude from their statistics that for exophthalmic goitre " there is evidence strongly suggestive of a single, recessive factor favourable to the disease and perhaps necessary for its occurrence, but this does not mean that all recessives develop the disease."

For nodular goitres, however, the case is altogether different, because of the important role of *extrinsic* factors, *e.g.* iodine deficiency, in the production of such goitres. To such factors all members of a family would tend to be exposed and might well respond by developing goitre. Hence in this group constitutional predisposition is less important (family history of 30 per cent. in Bartels' series) than in primary exophthalmic goitre (61 per cent.).

The small family tree shown (Fig. 49) illustrates the intriguing possibilities that arise. The mother was myxoedematous and had twin daughters, one of whom developed exophthalmic goitre which remitted under iodine therapy. Typical myxoedema then gradually supervened. A few years later the second twin developed exophthalmic goitre. Because of their similar behaviour, the possibility arises that the two are uniovular twins. All three subjects—the mother and her two daughters—belong to the same blood group, group B. Incidentally, the first twin affected illustrates the rare type of Graves' disease which remits spontaneously and gradually gives place to myxoedema.

Constitutional predisposition—the autonomic nervous system and toxic goitre. It has often been claimed that there is a characteristic constitutional

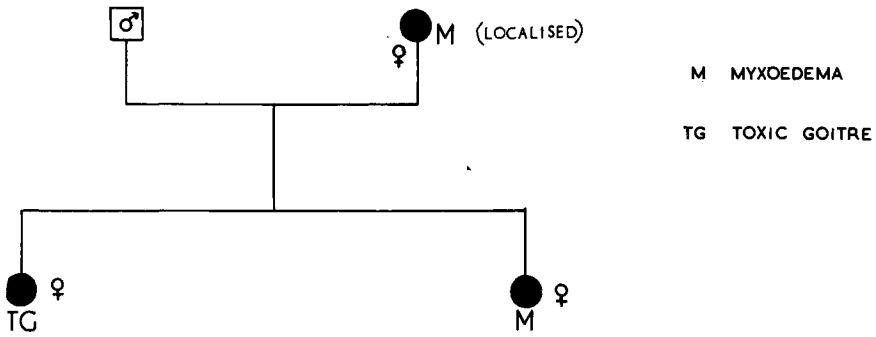


FIG. 49.—The Ansell-Gibbs-Miller family (Rundle, 1941).

background in Graves' disease (Chvostek, 1917; Warthin, 1928). Best known, perhaps, is Warthin's emphasis on a fundamental, youthful build, " rapid functional reaction," a " thymic-lymphatic constitution," and hypoplasia of the adrenals, heart and blood vessels.

In addition to these physical changes, many writers since Noorden, jr. (1911), Kessel and Hyman (1923) and de Courcy (1928), have postulated the existence of a labile and unbalanced autonomous nervous system with the sympathetic component dominant. This concept of a basic autonomic imbalance reaches its frankest expression in Moschcowitz and Bernstein's paper (1944). They state that neuro-circulatory asthenia (effort syndrome) provides the background of Graves' disease and is responsible for the symptoms persisting after thyroidectomy. In brief, many authors favour the concept of thyrotoxicosis as a general neuro-endocrine disorder in which thyroidectomy removes the most important of the glandular components, leaving untouched the fundamental disorder.

Without doubt, follow-up studies show that there is a comparatively

heavy incidence of nervous disorder and persistent symptoms after thyroidectomy. Martin (1948) has analysed thirty-three patients to determine the nature of these residual symptoms. He was able to group them as:

(i) Constitutional (these ante-dated Graves' disease and persisted after thyroidectomy); (ii) Residua of Graves' disease (these developed during the disease and persisted afterwards); (iii) Symptoms consequent on Graves' disease plus thyroidectomy (these arose after thyroidectomy); doubtless, any major illness followed by an operation would suffice to cause emotional symptoms, including nervousness, palpitation, lassitude, tremor, etc., in many female subjects; (iv) Symptoms originating independently of both Graves' disease and thyroidectomy. It should be noted that many of these post-operative symptoms may equally well exist in such conditions as anxiety states, the menopause, cardiac neurosis and chronic invalidism. Martin could find no evidence of any common or constant underlying personality, but the proportion of his patients with emotional instability and constitutional symptoms seems very high and we are not told how it compares with that in a control series interrogated by the same method.

We have made careful notes of the physique in our own thyrotoxics and have found no evidence that any particular type is more prone to thyrotoxicosis than another. Herbivorous, asthenic and hypoplastic persons occurred in the same proportions as in a large series of controls. The unique records of Fitz (1944) also provide valuable evidence. He observed thyrotoxicosis develop in thirty-three people on whom he had conducted routine medical examinations over a period of twenty years. He considered that there was nothing in their physique or constitution by which it could have been predicted that such a fate would overtake them. He concluded that Graves' disease was " a medical misadventure that may befall anyone, at any time."

The sympathetico-adrenal system and thyrotoxicosis. Crile (1928 and 1935) and others, have contended that thyrotoxicosis is due fundamentally to a disorder of the sympathetic nervous system and the adrenals. Crile based this opinion upon the work of Goetsch (1918) and upon the similarity between the experimental effects of thyroxine and adrenaline, the former having, however, a longer latent period and a more prolonged action than the latter. He removed portions of the adrenal glands in patients with exophthalmic goitre, and claimed results in accord with his hypothesis.

Much of this thinking has undoubtedly been based on the fallacious belief that the ocular phenomena of Graves' disease are produced by sympatheticotonia. Though stimulation of the cervical sympathetic trunk does cause exophthalmos in some animals, the same is not true in man (Unverricht, 1925; Mutch, 1936; Pochin, 1939a). In fact the sympathetic theory of origin of the eye signs must be quite abandoned in view of present evidence (Pochin 1939 a and b).

On the other hand, there is increasing evidence, summarized by Means (1949), that the secretory activities of the thyroid gland and the adrenal cortex are delicately interrelated. The one appears to protect against overproduction of hormone from the other. Thus, in myxoedema, the adrenal

cortex seems to be underactive whereas in thyrotoxicosis, it works overtime. The combination of Addison's disease and thyrotoxicosis may prove rapidly fatal as in Houston and Price's cases (1948). Recent advances in knowledge of the pituitary-adrenal hormones promise to throw much light also on thyroid-adrenal relationships.

Has thyrotoxicosis a thyroid or extra-thyroid origin? Janney (1922) ascribes the purely thyrogenic theory to Rehn (1884). It was based on the striking contrast between the symptoms in thyrotoxicosis and those in myxoedema and upon the conspicuous relief following thyroidectomy, particularly in toxic nodular goitres. This contrast, however, applies only between myxoedema and the hyperthyroidism component of Graves' disease.

One type of thyrotoxicosis, namely that resulting from a hyperfunctioning adenoma, is clearly thyrogenic. The paranodular tissue, in fact the whole of the uninvolved gland, is inactive and even atrophic (Cope *et al.*, 1947). The adenoma, like any other new-growth, functions autonomously but the rest of the gland is normal and does not. Inactivity and atrophy occur in it because the anterior pituitary is depressed by the excess of thyroid hormone in circulation.

It is true that exophthalmic goitre has been reported to develop in association with thyroid medication (Moorhead, 1931; Brain, 1936; Brunn, 1945; Lous, 1945), but such an event is very rare, considering the multitude of patients receiving such medication for obesity and other conditions; it may thus be coincidental. In some of the patients, thyrotoxicosis has without doubt already been present when medication with thyroid extract was misguidedly instituted.

Clear evidence for an extra-thyroid origin of classical Graves' disease is provided by the behaviour of the ocular manifestations, particularly the exophthalmos and ophthalmoplegia. These appear to be little influenced by thyroidectomy and may progress steadily afterwards, or they may even arise quite spontaneously as in the ophthalmic forms (cf. Chapter XV). It is noteworthy that thyroid feeding causes enophthalmos in the experimental animal (Pochin, 1944).

What has thiouracil taught us concerning pathogenesis? When thiouracil is given to normal human subjects the elaboration and secretion of thyroid hormone are halted, the level of oxidative processes in the tissue cells falls, the anterior pituitary is activated, and thyrotropic hyperplasia follows in the thyroid gland. A considerable goitre may develop. If, in thyrotoxicosis, there existed a similar equilibrium between the output of thyrotropic hormone and that of thyroid hormone, inhibition of thyroid secretion by thiouracil therapy should regularly result in further thyroid enlargement. In point of fact, the goitre becomes smaller or remains stationary in two-thirds of patients on antithyroid therapy. Enlargement regularly occurs only if the dosage is excessive and the metabolism is pushed down to hypothyroid levels. It is thus possible that only in the event of overdosage does the anterior pituitary come into action at all.

A further fascinating problem is posed by the fact that provided the metabolism is maintained at a normal level with thiouracil for a period of some six months, cessation of the drug then results in a very high percentage of permanent, or at all events very prolonged, remissions. Why does the mere fact of maintaining metabolism normal for a period " cure " the disease? Certainly spontaneous remissions would not normally develop in such a high percentage of cases in so short a time. It is possible that some vicious circle, concerned in the causation and maintenance of hyperthyroidism, is broken by a period of euthyroidism. It is conceivable that surgery acts in a similar fashion. At all events, it is remarkable that such a relatively crude method as subtotal thyroidectomy should give consistently satisfactory results.

Significance of the thyroid stump. Halsted, as long ago as 1896, showed that a similarly extensive resection of the normal thyroid in the experimental animal results in its rapid re-growth and this has been abundantly confirmed by Marine (1932). It is therefore remarkable that re-growth of the thyrotoxic gland is not more common. This is particularly so in view of the histology of the " thyroid stump" (Figs. 50a and b). For the first few weeks after thyroidectomy there is considerable oedema and desquamation of the follicles, particularly near the line of section, but hyperplasia and hypertrophy of the cells persist unchanged often for many years (Rienhoff, 1934; Roussy, Huguenin and Welti, 1934). Does this mean that some abnormal extrathyroid stimulus is still operating?

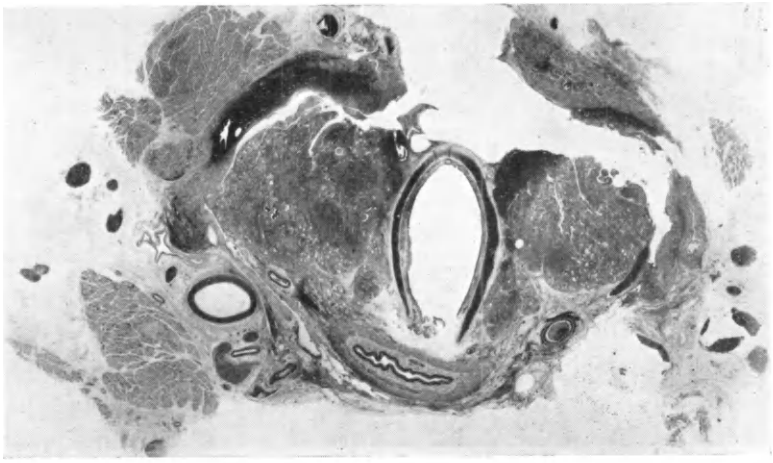
Dietary influences. As is well known, dietary factors have a powerful influence upon thyroid function. Malnutrition causes significant falls in metabolism (Benedict *et al.*, 1919; Loewy and Zuntz, 1916) and a sharp decrease in the frequency of thyrotoxicosis was associated by Tallquist (1922) and Curschmann (1922a) with the hunger-blockade of Germany in World War I.

A very high fat or protein diet will produce histological evidence of thyroid activation in the experimental animal (McCarrison, 1922; Paal and Kleine, 1933) but Remington (1938) claims that such diets are poor in iodine and that this is the actual factor responsible for the hyperplasia. Various investigators have claimed that vitamin-deficient diets are associated with thyroid enlargement in the experimental animal but the evidence remains doubtful. On the other hand, following the original observation by Chesney, Clawson and Webster (1928) and work by numerous subsequent investigators, the strumogenic effect of plants belonging to the *Brassica* genus has become well established (Cf. Chapter IV).

Iversen (1948) found that the onset of " epidemic " thyrotoxicosis in Denmark in 1941–42 coincided with the cessation of imports of soya bean meal, which is rich in antithyroid factors. It is possible, he thinks, that many mildly toxic goitres previously adequately controlled by these substances in the diet then " escaped " and gave rise to symptoms.

Neurogenic. It may now be taken as established that the hypothalamus is the central co-ordinating mechanism of the autonomic and endocrine systems (Beattie, 1938) and it has been suggested, (Morley, 1936) that

thyrotoxicosis is primarily a hypothalamic disorder. Interesting recent data concerning the possibility of neurovascular transmission of stimuli from the



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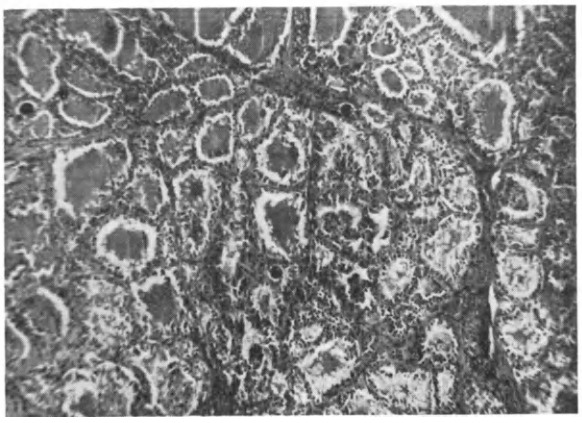

b *× 120*

FIG. 50 *a* and *b*.—Thyroid "stump" from a patient aged 25 who died four days after thyroidectomy for severe Graves' disease. The gland remnants show hyperplasia (Fig. 50*b*). In a similar patient dying from acute appendicitis, persistent hyperplasia was found four months after thyroidectomy.

hypothalamus to the anterior lobe of the pituitary via the hypophyseal blood vessels, have been presented by Harris (1948). However, it must be admitted that the evidence is scanty and circumstantial. Thus, lid retraction similar to that in Graves' disease may occur in cases of post-encephalitic

Parkinsonism and Polzer (1938) has reported the occurrence of Graves' disease as a complication of the striatal and mid-brain disturbances which follow encephalitis. Similar cases have been reported by Mandel (1940). The experimental work of Schittenhelm and Eisler (1932), Sturm and Schneeburg (1933), Löhr (1937), and Pighini (1935) suggests that iodine and the thyroid hormone may be selectively absorbed by, and functionally related to, this part of the central nervous system.

Langdon Brown (1923) advanced a stimulating concept of thyrotoxicosis as a manifestation of dissociation on the vegetative level of the neuro-endocrine system. In this sense the thyrotoxic state could be regarded as an endocrine mania comparable to hysterical twitching.

Psychic Trauma. It is an intriguing fact that psychic trauma is associated with the onset of symptoms in a comparatively high percentage of cases. Marañon (1921) emphasized that patients often volunteer the information that some major shock, worry or stress, seemed to bring on the illness. If closely and sympathetically questioned, about 40 per cent. of patients will describe a psychic trauma associated with the onset of thyrotoxicosis (Eason, 1927; Gardiner-Hill, 1929; Rundle, 1941). Among women, domestic difficulties associated with frequently recurrent pregnancies, marital infidelity, sexual incompatibility, disorders of the genital apparatus, anxieties over the health or upbringing of children, or, conversely, worry over persistent sterility or a series of miscarriages, may be traced in an appreciable percentage of the cases. In men, too, assiduous questioning may extract information as to nervous strains and stresses, either of a sexual nature or, more often, related to business and financial matters.

Such associated psychic trauma will often not be elicited except by very patient and sympathetic questioning. Yet its evocation and treatment by reassurance or otherwise are of great importance. Otherwise, mere control of hyperthyroidism will confer only partial relief. The psychic factors will continue to operate and produce untoward symptoms, anxiety, or frank hysteria, in the post-operative period.

War-time stresses are commonly cited in patients with thyrotoxicosis (Rabboni, 1947). Bereavement may be an additional factor in patients involved in a " bomb incident " (Prunty, 1949). But, astonishingly enough, there occurred a steady fall in the death-rate from thyrotoxicosis in England and Wales during World War II, despite the fact that the urban population was subjected to unprecedented stresses and traumata. The average death-rate for the years 1943–45 was less than half that during 1936–38. Among military personnel also Graves' disease was seldom encountered (Means, 1948).

Whatever rôle psychic trauma has in the pathogenesis of Graves' disease there can be little doubt that a sudden shock may greatly aggravate the disease when it is already present. Several of our patients have cited some specific shock or fright such as witnessing a fatal street accident, the fracture of a limb, having been bitten by a dog and so forth, as initiating the illness. It is probable that in most of these patients subclinical thyrotoxicosis has already

existed. Two good examples of this have come under the revisor's observation. The one was a man aged forty-five who was involved in a street accident in which he had sustained a fractured femur. After being maintained in skeletal traction for two months, his medical officer reported that Graves' disease had developed. Careful inquiry, however, showed that there were already symptoms of Graves' disease before the accident and that a continuous tachycardia had existed unchanged since his admission, within an hour of the accident. In a second patient, a woman aged forty-two, there was a history that the gas-oven had exploded in her face and set fire to her hair. She was brought to hospital for emergency treatment and while still under supervision about a fortnight later was noticed to have Graves' disease. But again inquiry revealed that not many months before, she had been in a goitre clinic for investigation but had been discharged without treatment because her metabolism test was almost normal. Incidentally, in this patient, thyrotoxicosis recurred twice after subtotal thyroidectomy and the ocular manifestations eventually became very severe. Finally, at a third operation, all remnants of gland tissue were removed, but because of her excitability, marked vaso-motor reactions and exophthalmos, she continued to present the picture of active Graves' disease. Four years after her first attendance she developed pre-tibial myxoedema.

While there seems little doubt that a sudden shock may greatly modify thyroid activity, how such psychic disturbance operates is quite unknown. Here then, is a problem in psychosomatic relations involving the central representation of the thyroid, and possibly also, that of the anterior lobe of the pituitary.

Infectious disease and toxaemias. It is a fact that patients often relate the onset of their symptoms to one of the acute infectious diseases, such as influenza or tonsillitis. Gardiner-Hill (1929) estimated that in women, infectious diseases are the exciting factor in 20 per cent. of cases, and that in men they are even more important relatively. But it is doubtful whether such acute infections are more than coincidental. A debilitating illness like influenza may cause exhaustion in the patient already suffering from mild and unrecognized thyrotoxicosis. The exhaustion symptoms then determine her attendance at hospital. Joll (1939) calls attention to the fact that during and after the great influenza endemic in 1917–1919 there was but an insignificant rise in the incidence of thyrotoxicosis. On the other hand, acute tonsillitis may run a fulminating course in a patient with full-blown Graves' disease and similarly such an infection may precipitate thyrotoxic crisis.

Many authors have stressed the importance of obscure foci of sepsis in the aetiology of primary thyrotoxicosis but we think that they play an altogether unimportant part in its causation. While it is doubtless true that many patients with thyrotoxicosis may be found to harbour one or more such foci, there is no evidence that they are more common in thyrotoxic patients than in the general population. Such septic foci should be dealt with on their own merits and (unless eradication is urgently necessary as in

acute appendicitis) only after full control of thyrotoxicosis. Thus in a child, reported by Farquhar (1948), excision of infected tonsils, after thiouracil control, resulted in distinct further improvement.

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CHAPTER XI

THE THYROID GLAND IN THYROTOXICOSIS

Toxic Diffuse Goitre: Pathological Anatomy — Histology — Effect of Therapeutic Agents — Thiouracil — Toxic Nodular Goitre — Lymphoid Hyperplasia — Clinical Features.

The central lesion in thyrotoxicosis is thyroid hyperplasia associated with excessive secretion of thyroid hormone. Hyperplasia is seen microscopically to assume three main forms which may co-exist in the one section. They are:

1. Papilliferous hyperplasia.
2. Macro- and microfollicular hyperplasia, and
3. Regenerative epithelial hyperplasia.

The thyroid gland is enlarged and its enlargement presents three forms: (i) Toxic diffuse goitre, (ii) toxic multi-nodular goitre, and (iii) toxic adenoma. In the first all types of epithelial hyperplasia occur, but in the second and third only micro- and macrofollicular hyperplasia are found, with but few exceptions.

In recent years radioactive iodine has been used to trace the uptake of iodine and its synthesis into thyroid hormone within the gland. The physiology of these processes has already been discussed in Chapter I. The gland's natural avidity for iodine is greatly increased in thyrotoxicosis. As in the rat's thyroid, activated by thyrotropic hormone, so in thyrotoxicosis, all the steps of iodine uptake, hormone synthesis and hormone release, are accelerated. In a word, there is an exceedingly rapid turnover of iodine, with the result that in spite of its increased avidity, the iodine content of the whole gland is lower than normal.

The location of injected radio-iodine may be determined by radioautographs. A tracer dose of radio-iodine is injected forty-eight hours or so before thyroidectomy. Microscopic slices of the fresh gland are then laid on a photographic emulsion. The resulting radioautographs are compared with the histology when the same slices are stained. At forty-eight hours, as in normal glands, nearly all the radio-iodine is present in the colloid. The activity of nodules in the thyroid can also be estimated by their uptake of radio-iodine and by this technique much light has been throw non their functional significance in the two forms of toxic nodular goitre.

1. **Toxic diffuse goitre—pathological anatomy.** The goitre is " thyroid-shaped "(McCarty, 1912). Its surface is smooth with only such irregularities as arise from a slight exaggeration of the normal contours. Its size varies very greatly, but seldom reaches that of a moderate colloid goitre, and it is

never so small as to be of the dimensions of a normal gland. Most goitres from thyrotoxicosis of the primary type weigh from 60 to 150 gm. The increased vascularity of the gland which is such a prominent feature during life is not always conspicuous after removal from the body, though the main vessels can be seen to be enlarged to a greater or lesser extent. Contrasted with the softness of the normal thyroid or the adolescent colloid goitre, there is a distinct solidity about the diffusely thyrotoxic gland. On section, the parenchymatous tissue stands out very clearly. It is of a uniform colour, though in different specimens it may show shades of red, brown, yellow, or grey, according to the degree of hyperplasia, vascularity, and colloid content. The characteristic translucence of the colloid goitre is absent, but colloid-

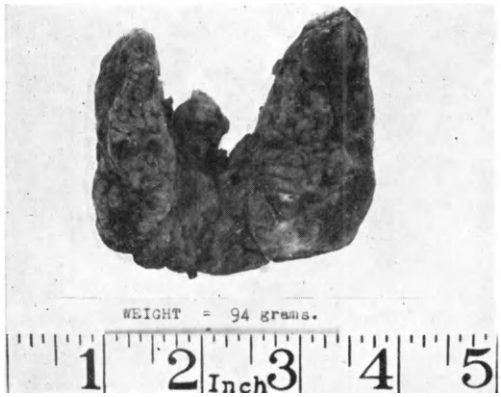

FIG. 51.—Diffuse hyperplastic goitre of primary Graves' disease. Note fleshy cut surface and grain. From a woman aged 46 who had developed a goitre eight years previously following her son's death. It enlarged progressively and had produced severe thyrotoxicosis for two years prior to her admission. (Rundle, 1948.)

containing follicles may be present in considerable numbers. During the cutting-up of the gland an abnormal toughness due to increased fibrosis may be detected, but it is not invariably present in the earlier stages. The gland retains its shape, and is not easily deformed by the fingers or the pressure of the knife.

The variations from this common type are numerous. The gland on section may have an appearance like that of uncooked meat, and is then less firm in consistence; Broders (1935) likened it to beefsteak (Fig. 51). In other specimens, especially when the disease is of long standing, the cut surface may, while retaining its general uniformity, be of a dull yellow colour and the thyroid tissue very friable. The stroma of the gland in such specimens is increased in thickness, but is softened by degeneration. In still more advanced cases the fibrous stroma stands out in the form of strands of varying thickness which surround masses of parenchyma, giving them an

appearance of complete encapsulation and resembling in miniature the nodular changes which supervene sooner or later in all simple goitres, both endemic and sporadic. Actual cysts and colloid adenomata may be found in patients prepared for operation with iodine. They are also a regular feature in all pathological thyroid glands of long standing.

The solid, opaque parenchyma may not be uniformly distributed throughout the gland tissue, but may exist as small scattered foci amidst tissue

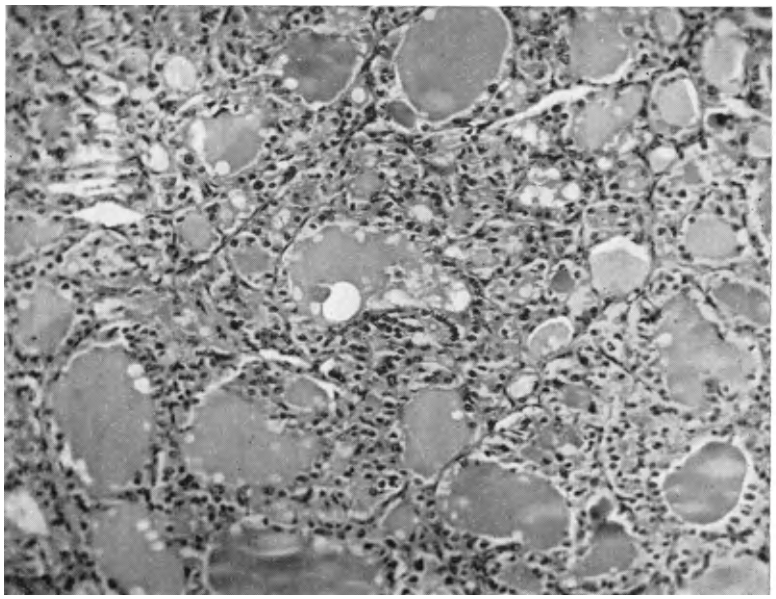

FIG. 52.—Microfollicular type of hyperplasia: pre-operative iodine therapy has resulted in colloid storage in some follicles but not in most. (× 150.) (Rundle, 1948.)

which resembles that of a colloid goitre. The name " focal Graves' disease " has been applied to this type, but it is a little doubtful whether it is ever found as a primary condition, *i.e.*, irrespective of involutionary changes due to natural processes or to iodine medication.

Histology. Greenfield (1893) was one of the first to describe the thyroid hyperplasia of exophthalmic goitre.

Great variations in the microscopic structure of the gland are found, corresponding with the different macroscopic appearances above mentioned. The most characteristic change is an increase in size, and especially in height, of the epithelial cells (Abel, 1940). They are pale and extensively vacuolated (*cf.* Figs. 3–4, chapter I). The nucleus is enlarged and vesicular, the Golgi apparatus hypertrophied (Welch and Broders, 1940).

PAPILLIFEROUS TYPE OF HYPERPLASIA

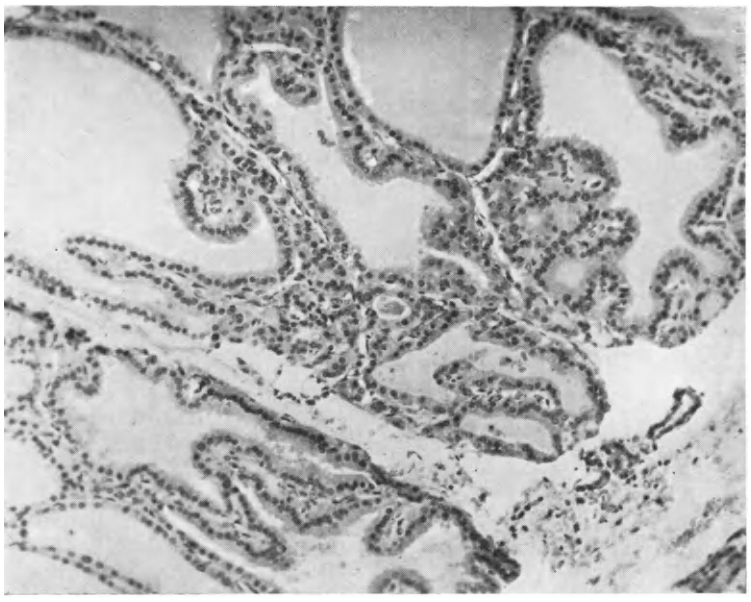

FIG. 53.—Papilliferous type of hyperplasia: The follicle on the left and below is in process of obliteration. (× 150.)

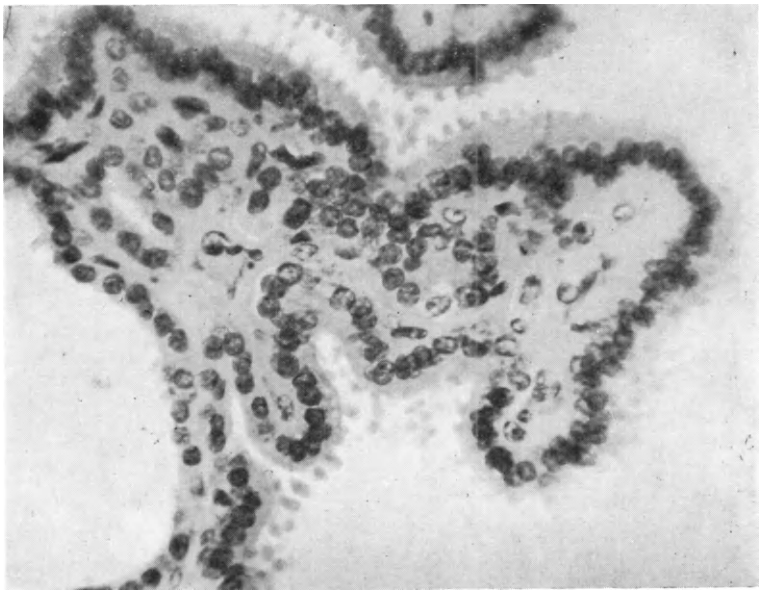

FIG. 54.—Showing structure of papilliferous ingrowth. (× 500.) (Rundle, 1948.)

Instead of the rather small follicles commonly found in the normal thyroid, most of the follicles are enlarged (macrofollicular hyperplasia). This enlargement has been demonstrated by measurement (Wilson, 1927; Jackson, 1931); but the size of the follicles still falls far short of that predominating in colloid goitre. Where hyperplasia is very intense the corresponding follicles are often smaller than usual (microfollicular hyperplasia) (Fig. 52).

In other areas the follicles enlarge and their epithelial lining becomes infolded, sometimes to such an extent that an appearance of intrafollicular papillomata is produced, and the groups of follicles in section exhibit a lace-like structure which in some cases is very striking (papilliferous hyper-

REGENERATIVE TYPE OF HYPERPLASIA

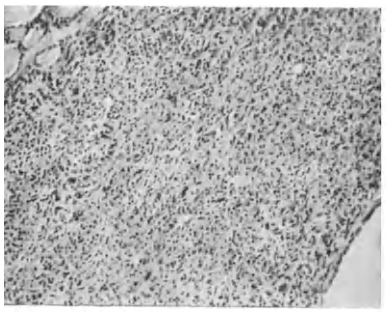

FIG. 55.—Area of regenerative epithelial hyperplasia: Note colloid-containing follicles in the top left and bottom right corners, and absence of encapsulation. (× 150.)

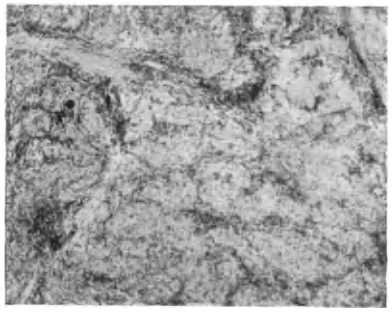

FIG. 56.—Extensive area of regenerative epithelial hyperplasia. Note absence of colloid-containing follicles and the presence of considerable lymphocytic infiltration, tending to delimit the glandular units. (× 65.)

plasia) (Figs. 53 and 54). In extreme examples the appearance may be reminiscent of papilliferous adenocarcinoma.

In papilliferous hyperplasia, the direction of growth is centripetal, in the micro- and macrofollicular types, it is centrifugal. In 1931, Moritz demonstrated that hollow or solid epithelial buds grow out from foci of mural hyperplasia into the perifollicular space, separate off, and continue to form new generations of satellite follicles.

When centrifugal proliferation is very intense, follicle formation may be lacking, the epithelial cells occurring in solid sheets. Even the cell boundaries may become indistinguishable, the nuclei being merged in a syncytium-like arrangement (regenerative epithelial hyperplasia) (Figs. 55, 56, 57 and 58). This striking type of hyperplasia is rare and Broders (1939) warns pathologists against mistaking it for carcinoma.

Effect of therapeutic agents. (i) **Iodine.** In Rienhoff's investigation (1925) a series of untreated thyrotoxics were submitted to hemi-thyroidectomy; then for the first time they were given iodine and after a full response the

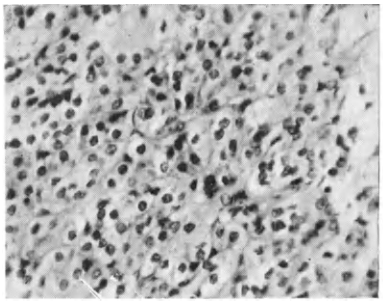

FIG. 57.—High-power view of the section above (FIG. 55). Note columnar arrangement of epithelial cells. (× 500.)

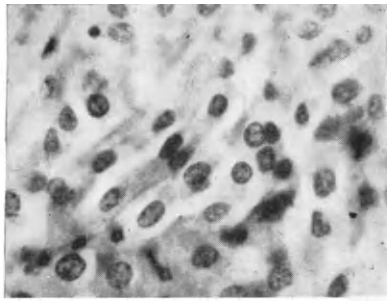

FIG. 58.—Showing pleomorphism of epithelial cells in an area of regenerative epithelial hyperplasia. (× 750.)

remaining lobe was resected. From a comparison of the two lobes it was clear that iodine greatly increased the amount of stored colloid. The acini in the second lobe were often fully distended and the epithelium generally

FIG. 59.—Toxic diffuse goitre showing a remarkably uniform iodine involution (vertical section through the whole of the right lobe). The patient, a woman aged 46, presented with very severe thyrotoxicosis but responded excellently to pre-operative iodine therapy. (× 3.)

was much reduced in height, though isolated sprigs and mounds of tall columnar cells were still constantly present (Fig. 59).

Scattered irregularly throughout the sections were areas of hyperinvolution, colloid microcysts, colloidal "adenomata," (Figs. 60, 61 and 62) and foci of degeneration, the last being indicated by oedema and swelling of

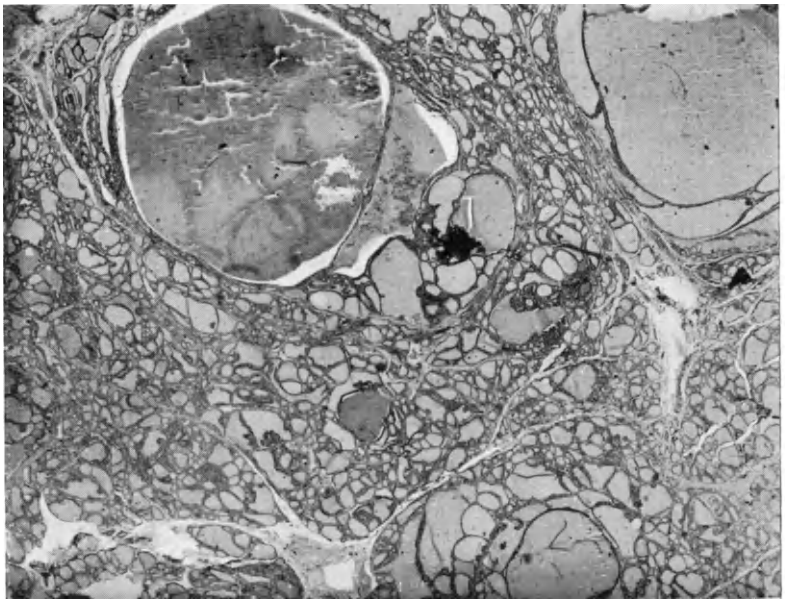

FIG. 60.—Colloid microcysts in a diffuse hyperplastic goitre. Papilliferous hyperplasia can be seen in the gland substance generally. On the left above is a colloid microcyst; in the top right corner the structure is more that of a colloid involution nodule. (× 12.)

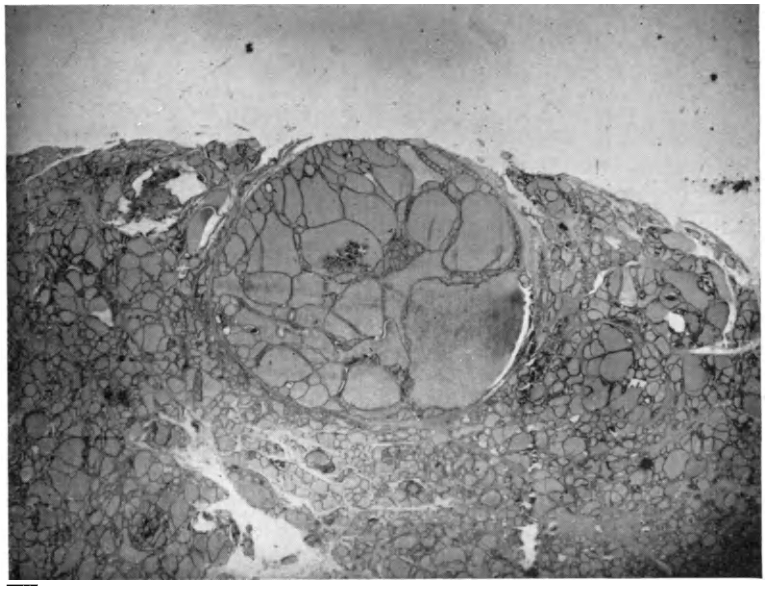

FIG. 61.—Colloidal " adenoma " or hyper-involution nodule. (× 7.)

the stroma, capillary haemorrhage, round cell infiltration, and follicular atrophy and disruption.

(ii) **Thiouracil.** Heavy medication with thiouracil causes marked hyperplasia of the *normal* human thyroid (Doniach and Sharpey-Schafer, 1947). The follicles are small, closely packed, depleted of colloid and lined by high cuboidal epithelium.

Thiouracil blocks the synthesis of hormone and lowers its concentration in the circulating blood. This in turn stimulates the secretion of pituitary

IODINE HYPER-INVOLUTION IN THYROTOXIC GOITRES

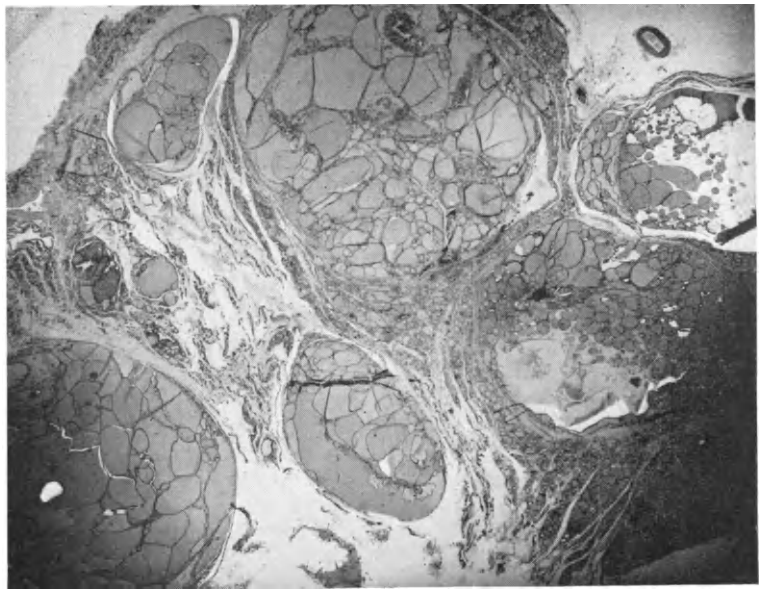

FIG. 62.—The same type of change affecting the gland diffusely. From a patient with chronic mild thyrotoxicosis and auricular fibrillation. (× 7.)

thyrotropic hormone. But the thyroid hyperplasia which results is "frustrated" in the absence of free iodine (*cf.* chapter I).

Thiouracil does not interfere with the release of the existing stores of thyroglobulin, but several days or weeks may elapse before the follicles are completely emptied. The full development of "compensatory" hyperplasia is correspondingly delayed. When this hyperplasia is established the injection of T.S.H. causes no further stimulation indicating that the subject's own anterior pituitary is capable of effecting maximal thyroid activation (Doniach and Sharpey-Schafer, 1947).

In thyrotoxicosis also thiouracil therapy increases the degree of epithelial hyperplasia and colloid is lost from the follicle (Moore *et al.*, 1944; Halpert

et al., 1946). The height of the epithelial cells lining the follicles is increased (Rawson and McArthur, 1947).

It is known that thiouracil and allied compounds increase the potency of thyrotropic extract in the experimental animal (Albert *et al.*, 1947). Their aggravating effect on the thyroid hyperplasia of Graves' disease may thus depend on the potentiation of any T.S.H. impinging on, or already in the gland (Albert *et al.*, 1946).

(iii) **Thiouracil and iodine.** It is remarkable that, in the thyrotoxic gland in which hormone synthesis has been completely blocked by thiouracil, iodine therapy should cause striking involutional changes. The follicles become filled with colloid, the epithelium more flattened and the vascularity much reduced. Surprisingly, the iodine content of such involuted glands is no greater than that of glands treated with thiouracil only (Rawson and McArthur, 1947). These workers conclude that iodine possesses two independent functions: the one is to iodinate the thyroid proteins, the other is to promote follicular storage (the involuting action). After thiouracil, iodine causes involution but the fluid distending the follicles contains only non-iodinated thyroid protein. Thiouracil therapy seems to increase the involuting action of iodine especially if such therapy has shortly been suspended (Buno and Grosso, 1949).

2. **Toxic nodular goitre.** The nodules in multi-nodular toxic goitres derive from:

(a) Foci of excessive hyperplasia and involution in remittent or long-standing thyrotoxicosis.

(b) Hyperplasia-involution foci in a preceding simple goitre, endemic or sporadic (secondary thyrotoxicosis).

(a) The accompanying series of photomicrographs illustrates the development of hyperplasia-involution nodules in the thyrotoxic goitre (Fig. 63a–e). Just as the responsiveness of the thyroid parenchyma varies from subject to subject, so in different areas of the same gland there may be widely differing intensities of hyperplasia. Foci where this is excessive may form the growth centres from which thyroid nodules arise. The intensity of hyperplasia tends, however, to fluctuate as manifested clinically by partial, or temporarily complete, remissions. At such times there is involution in the follicles and where hyperplasia was most intense, colloid micro-cysts tend to form. Thus, during both hyperplasia and remission, there is more enlargement at these foci than in the gland generally.

We agree with Broders (1935) that these hyperplasia-involution nodules in the thyrotoxic gland generally show substantially the same histological changes as the intervening gland tissue, though the two may appear very different to the naked eye. In extensively nodular goitres the intervening tissue may be almost non-existent, being largely or totally replaced by the nodules, or atrophied from compression (Figs. 64, 65 and 66). When present it usually retains the power to respond to the hyperplastic stimulus though its response is usually much less vigorous than is that of the nodules.

GENESIS OF HYPERPLASTIC NODULES

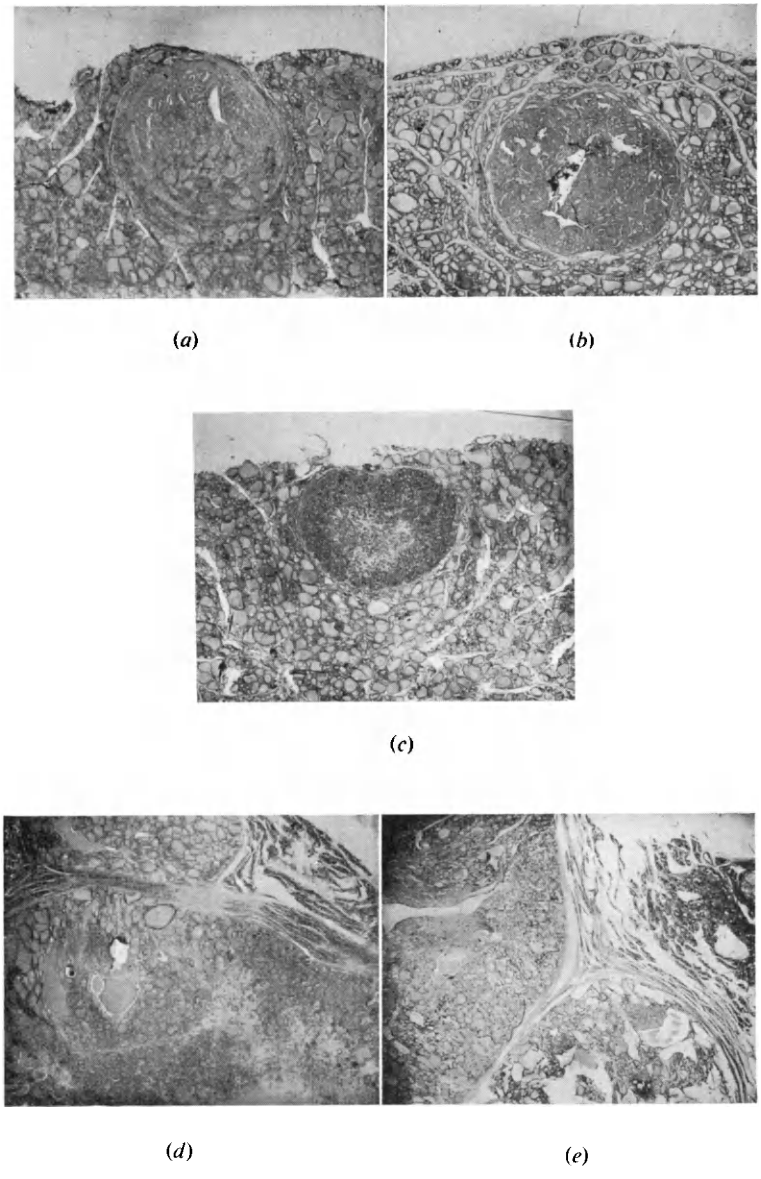

FIG. 63.—Series of hyperplastic nodules from patients with thyrotoxicosis. (*a*) Hyperplasia is rather more active than in the surrounding tissue: in (*b*) and (*c*) there is considerably more activity. (*c*) Shows early central degeneration. (*d*) and (*e*) are from generally nodular goitres, showing compression and atrophy of the remaining internodular tissue. The series, therefore, illustrates the development of nodules in all different stages. (× 7.)

In colloidal nodules and micro-cysts, the epithelium may be clearly quiescent but recurrent waves of hyperplastic activity may result in their partial or complete re-conversion into a territory crowded with hyperactive micro-follicles. We may conclude that when the stimulating agent impinges on the various gland units, they respond according to their several capabilities.

(b) It is characteristic of long-standing simple goitres, turned thyrotoxic, that their nodules show very advanced degenerative changes centrally. Thus the endemic goitre, which has become mildly toxic late in life, may show

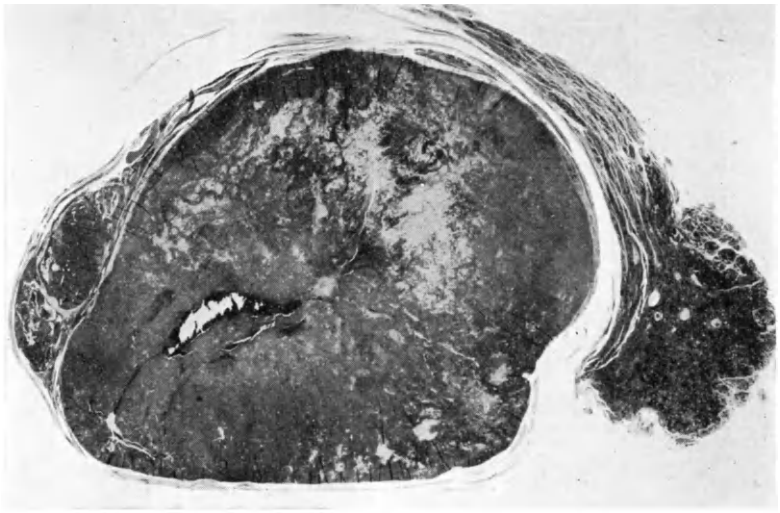

FIG. 64.—Large hyperplastic nodule from a patient aged 34, suffering from severe thyrotoxicosis. The other nodules in her thyroid were small and the intervening gland tissue, though showing some hyperplasia, was mostly compressed and atrophied (cf. Fig. 65). (× 3.)

advanced cystic, mucoid, lipoid, fibrous or even calcific degeneration in the centre of its nodules (Fig. 67).

Autopsy studies (see Table XIV) show that thyroid nodules are often found even when there has been no symptom or visible goitre during life. This morbid background must be taken into account in interpreting the histology of toxic nodular goitre.

There is no clear histological criterion by which the hyperplasia of secondary thyrotoxicosis may be distinguished from that of simple endemic goitre (Graham, 1941) and until the advent of radio-iodine it was often quite impossible to say which hyperplastic changes were responsible for the superadded thyrotoxicosis. Now, techniques of observing the uptake and distribution of radio-iodine enable us to detect precisely the functional activity of any given area or nodule in the gland; in this way the activity of nodular and paranodular tissue can be compared. Autoradiographs of fresh slices

of the excised goitre when compared with the corresponding histological sections provide confirmatory evidence.

TABLE XIV

Author	Date	District	Percentage incidence of Nodules in Autopsy Thyroids
Rice	1932	Minnesota (mildly endemic)	26·3
Nolan	1938	,, ,, ,,	56·95
Rice	1938	,, ,, ,,	Roughly equals the patient's age.
Schlesinger, Gargill and Saxe	1938	Non-goitrous region	8·2 Contained nodules greater than 1 cm. diameter.
Johnson	1949	Minnesota	58·8

Le Blond *et al.* (1946) studied toxic nodular goitres occurring in a goitre belt. Most of the nodules were of the hyperplasia-involution type and were

COMPRESSION-ATROPHY OF INTERNODULAR TISSUE

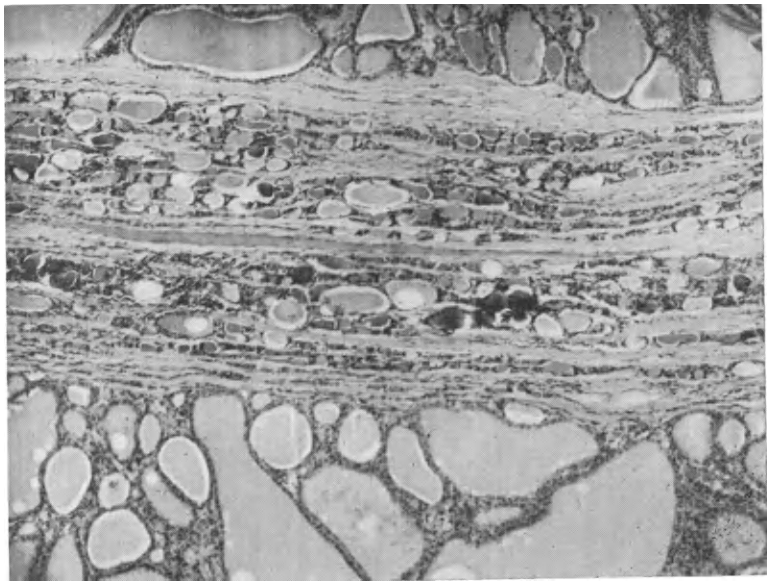

FIG. 65.—Compressed and atrophied gland tissue between adjacent nodules. (× 65.)

found to be functionally less active than the paranodular tissue as indicated by a low-iodine content, a smaller uptake of radio-iodine, and a slower turnover of the iodine into hormone products. Toxic diffuse goitres have,

of course, the greatest avidity for iodine and the greatest ability to convert it into thyroxine and thyroglobulin (Puppel *et al.*, 1946). These workers confirmed that the paranodular tissue of toxic nodular goitres is biochemically similar though not so active as that of the toxic diffuse goitre.

3. **The toxic single nodule (hyperfunctioning adenoma).** The single adenoma is an uncommon cause of hyperthyroidism; it was the pathological finding in only 4 per cent. of Roualle's series (1949). Cope *et al.* (1947), have demonstrated that the truly neoplastic hyperfunctioning nodule can be distinguished by the fact that the uninvolved gland tissue is in a state of

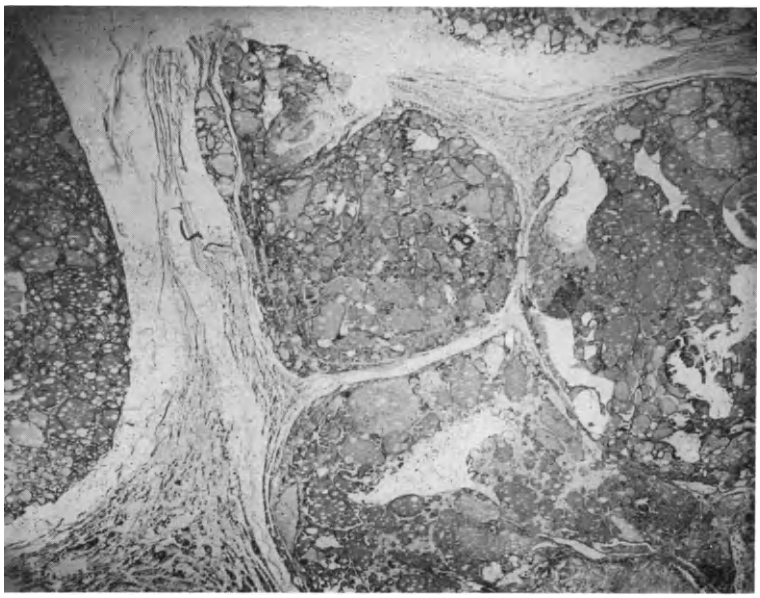

FIG. 66.—Generally nodular gland, showing almost complete atrophy of general gland substance. Chronic mild thyrotoxicosis and auricular fibrillation were present. (× 7.)

physiological rest, or even atrophy. The adenoma like any other new-growth functions autonomously but the rest of the gland is normal and its response is physiological. It is inactive and atrophied because the anterior pituitary is depressed by the excess of thyroid hormone circulating.

The thyrotoxic character of the nodule is conclusively demonstrated by the relief of hyperthyroidism when it is excised. Tissue slices from the nodule have the same abnormal ability to inactive T.S.H. *in vitro* as those from thyrotoxic goitres. The uptake and turnover of radio-iodine by the nodule are also comparable with those of diffusely hyperplastic goitrous tissue (Cope *et al.*, 1947). We thus have the picture of a large single toxic nodule in an otherwise small and involuted gland. The nodule is taking up almost all the

radio-iodine and the rest of the gland none. All gradations exist back to the more usual situation where there is a single nodule in the euthyroid patient; the adenoma is foetal in type and collects and turns over little or none of the iodine, while the result of the gland handles it normally (Fig. 68).

This clear demonstration of the single thyrotoxic adenoma raises interesting considerations in pathogenesis. In classical Graves' disease, the whole gland appears to be swept by some extra-thyroid stimulus, but clearly this

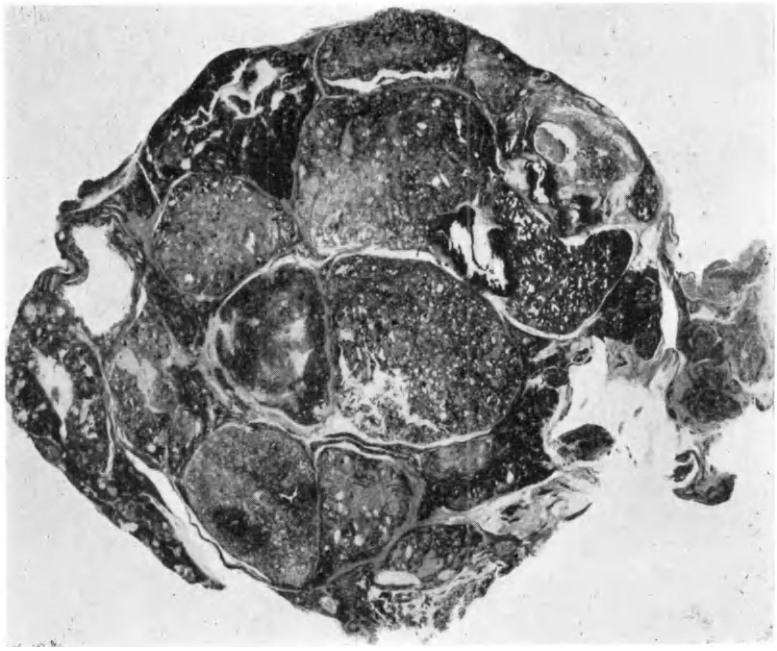

FIG. 67.—Large multinodular goitre from a patient aged 64 who had had a goitre for 35 years. She had lived in an endemic area in South Wales all her life and had suffered no ill effects until the recent onset of palpitations and breathlessness. Slow fibrillation of the auricles was present. (× 3·5.)

cannot occur in the hyperfunctioning adenoma, since the rest of the gland is atrophic. The hyperfunctioning adenoma thus represents a truly thyrogenic form of thyrotoxicosis.

Rawson *et al.* (1948) and Dobyns and Lennon (1948) have shown that the functional activity of single thyroid nodules runs parallel to their degree of cellular differentiation. Hyperfunctioning adenomas show intense microfollicular hyperplasia with uniform increase in cell height. But overt thyrotoxicosis is not always present. It is a question of the size of the adenoma and the degree of inhibition of the uninvolved gland tissue, the decisive factor being the total mass of the hyperfunctioning tissue. A decrease in cell height

and radio-iodine uptake are seen in the uninvolved tissue round hyperfunctioning adenomas. Some non-functioning but hyperplastic adenomas were encountered but in these the microfollicular hyperplasia and increase in cell height were less uniform than in the thyrotoxic adenomas.

Lymphoid Hyperplasia. Lymphorrhages, or aggregations of lymphocytes, may be visible in the gland stroma at any stage of the disease. They may be small and scanty, or large and numerous. They occupy mainly the interstitial tissue, but if large, they spread out among, and obliterate the follicles. Germ centres occur in the largest lymphoid aggregations. Buried in their

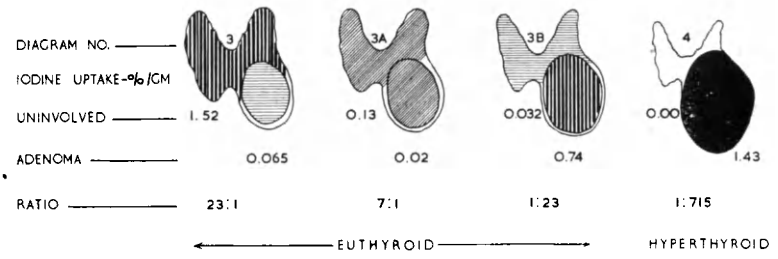

FIG. 68.—Gradations of function of thyroid adenomas indicated by their absorption of a tracer dose of radioactive iodine. The intensity of the shading is proportionate to the avidity of the tissue for the iodine. The measured iodine uptake of each tissue is given below the diagram; the figures represent the per cent. of the dose of iodine found per gram of tissue. The ratio of iodine uptake of uninvolved tissue to adenoma is given in the lowest line of figures. In the first three diagrams (3, 3A, and 3B) the overall thyroid function was normal yet the activities of the adenoma and uninvolved tissues differed. With increasing adenoma function there is a decrease in the function of the uninvolved tissue with overall decrease in size or partial atrophy in diagram 3B as compared with diagram 3. Diagram 4 represents the findings in a hyperfunctioning adenoma; there was no uptake of iodine by the atrophic uninvolved tissue. (Cope, *et al.*, 1947.)

substance can be seen degenerative epithelial cells and follicles. Associated fibrosis may be a prominent feature.

It should be emphasized that these lymphoid accumulations occasionally occur in the normal gland. Nolan found them in 18 per cent. of sundry post-mortem thyroids. But they are considerably better developed as to number and size, in toxic than in non-toxic goitres or normal glands (Simmonds, 1913; Troell, 1923; Rice, 1932). They are also better developed in diffuse than in nodular toxic goitres. There does not however appear to be any strong correlation between the severity of thyrotoxicosis and the degree of lymphatism in the thyroid (Turnbull *et al.*, 1933; Cattell, 1935).

The significance of the lymphoid accumulations is unknown but they may be part of the generalized lymphoid hyperplasia of Graves' disease. It is of interest that even when they are extremely well developed they may not interfere significantly with the secretory powers of the gland (Fig. 69). Nevertheless, as Whitesell and Black (1949) have shown, the greater the

degree of fibrolymphocytic infiltration, the less severe the hyperthyroidism and the greater the incidence of post-operative hypothyroidism.

Clinical features. The thyroid gland is enlarged in thyrotoxicosis, but the degree of enlargement may undoubtedly be almost trivial. Toxic nodular goitres are on average distinctly larger than toxic diffuse goitres. The former frequently weigh 200–400 gm. or more, the latter more usually 75–150 gm.

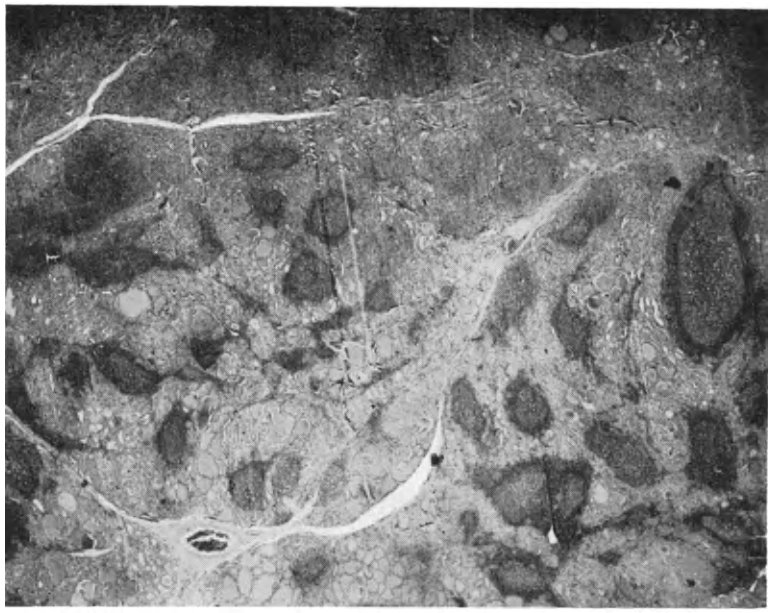

FIG. 69.—Showing generalized lymphadenoid infiltration of intensely hyperplastic thyroid. From a woman aged 27 with thyrotoxicosis of the relapsing type. She had lost one stone in the six months prior to admission. Gland tissue remaining after subtotal thyroidectomy measured $1\frac{1}{2} \times 1 \times \frac{1}{2}$ ins. on the left; on the right a mere fragment. Two years later, the metabolism was normal, though the intensity of the lymphoid infiltration had suggested that myxoedema might supervene.

Errors in estimating the size of the thyroid are due to lack of experience in palpating the smaller goitres, to the tendency for the larger and bulkier lower poles of the gland to lie partly concealed behind the clavicles and the sternum, and to the fact that with powerful muscles, as in men, a goitre which weighs even three or four times as much as a normal gland may be quite inconspicuous.

In toxic diffuse goitre, the gland is typically smooth and firm in consistence but neither of these characteristics is invariable. In early cases the gland is smooth because it is involved uniformly and is free from degenerative changes. It is usually firm because it is more cellular, has less colloid, and is

engorged with blood. It may be softer than normal in those rare cases where the follicles contain a considerable amount of colloid but not enough to cause turgescence in the gland. In the later stages of the disease the gland may be very hard, partly owing to an increase in the supporting connective tissue, a process which may assume great importance, and partly because after prolonged iodine treatment many of the follicles may be filled to bursting-point with firm colloid. The smooth surface is often lost later, owing to the nodular degeneration which may eventually affect the primary toxic no less than the smooth colloid goitre of endemic areas. A cyst, or adenoma, too, may in rare cases be present; there is no reason why an otherwise healthy thyroid gland containing a cyst or adenoma should be more immune to thyrotoxic changes than any other.

Excessive vascularity of the gland, though all too obvious at the time of operation, is not always to be recognized by palpation, though the pulsation of the vessels of the neck may give the impression of extreme vascularity or even of independent expansile pulsation. The bruits and thrills which may usually be felt or heard over the main thyroid vessels and their branches are rarely present also in colloid, nodular or cretin goitres.

The size and character of the goitre change both with the length of time the disease has existed and with the therapeutic agents employed. Rarely fibrosis and myxoedema supervene. When this is the mode of termination Graves' disease has usually been short-lived. Spontaneous fluctuations in the severity of the disease may also be associated with variation in the character of the swelling.

Under thiouracil therapy the gland becomes exceedingly vascular, red, moist and friable. It offers greater technical difficulty to the surgeon than the iodine-prepared gland (Schirer and Cohen, 1945).

Thiouracil may also cause a distinct increase in size of the goitre, especially if the dose be excessive and pushed to the point of hypothyroidism. Occasionally, however, the goitre may decrease in size under anti-thyroid therapy. Therapeutic doses of radio-iodine will also cause fibrosis and decrease the size of the goitre.

The clinical effect of iodine in thyrotoxicosis is to render the gland firmer and its outline more distinct to the palpating fingers. The thrill and bruit may diminish.

The clinical characteristics of the toxic nodular goitre resemble those of the simple nodular goitre in most respects but on average the gland is firmer, indicating greater cellularity, and more vascular. If iodine therapy has been prolonged, the gland contracts fine adhesions to the surrounding fasciae and is therefore less mobile than a comparable, simple, nodular goitre.

As with simple nodular goitre careful clinical palpation of all the nodules and estimation of their size, distribution, and character, are of great importance in toxic nodular goitre. Pressure on, and displacement of, adjacent structures by the goitre, or its descent into the thorax should be determined, as these circumstances will strongly influence therapy.

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CHAPTER XII

THE CARDIOVASCULAR SYSTEM IN THYROTOXICOSIS

Disordered Physiology of the Circulation — Pathological Anatomy and Histology of the Heart — Does Heart Failure occur if Thyrotoxicosis is uncomplicated by organic Disease of the Heart? — Clinical Features of the Heart and Vascular System — Thyrotoxicosis *plus* Hypertensive Heart Disease — Thyrotoxicosis and Arteriosclerosis — Rheumatic Heart Disease and Thyrotoxicosis — Pulmonary Heart Disease and Thyrotoxicosis — Syphilitic Heart Disease and Thyrotoxicosis — Arrhythmias in Thyrotoxicosis — The Electrocardiogram in Thyrotoxicosis — Radiological aspects of the Heart.

Parry (1786) originally described thyrotoxicosis under the heading " Enlargement of the thyroid gland in connection with enlargement or palpitation of the heart." It is clear that he recognized the association between the goitre, rapid, forcible and irregular action of the heart, and congestive failure with oedema.

The effect of thyroxine upon the muscle fibres of the heart is similar to its action upon the tissues generally. Cellular metabolism and energy output are increased; heightened myocardial function expresses itself in an increased rate and vigour of contraction. Thyrotoxicosis drives the circulatory apparatus by whipping up the heart. The related clinical features are amongst the most obvious of the disease. The auricles tend to fibrillate. Congestive failure with oedema is then usually not long delayed. Cardiac exhaustion is one of the commonest causes of death.

Disordered Physiology of the Circulation

Cardiac output and circulation rate. Thyroxine acts *directly* on the myocardium and not via the cardiac nerves. McIntyre's experiments (1931) in which thyroxine caused tachycardia in dogs whose hearts had been previously denervated, have already been referred to (Chapter I). Equally convincing work has been done by other authors. For example, Priestly, Markowitz and Mann (1931) anastomosed the heart of a small dog to the cervical vessels of a large dog. Subsequent injection of thyroxine produced tachycardia in the transplanted heart. Yater (1932) noted the increased force of contraction and tendency to arrhythmia in the perfused hearts of thyroxinized rabbits. After excision of the sino-auricular node the rate was still greatly increased as compared with that in controls. Further, after crushing the bundle of His, the ventricle usually continued to beat at an accelerated rate.

As the result of this direct action of thyroxine upon the myocardium, the cardiac output and circulation rate are both increased. Blalock and Harrison

(1927) showed in the dog that thyroidectomy decreases cardiac output whereas thyroid feeding increases it. Herrick *et al.* (1933) investigated the volume flow of blood through the dog's hind limb. When graduated doses of thyroid extract had produced a 30–40 per cent. increase in the pulse rate, the blood flow in the femoral artery was increased by 200–300 per cent.

Fullerton and Harrop (1930) found the cardiac output to be increased in patients with thyrotoxicosis; the increase was roughly proportional to the elevation of the basal metabolic rate. Boothby and Rynearson (1935) likewise found that the circulation rate was constantly increased in thyrotoxicosis, the increase again running parallel with the intensity of the disease. On the contrary, Stewart *et al.* (1938) showed that in myxoedema the cardiac output per minute and per beat is diminished. The velocity flow of blood is also reduced.

As is well known, physiological increases in tissue metabolism are associated with an increased cardiac output. Thus, Grollman (1931, 1932) has shown that there is an essentially linear relationship between the increase in circulation rate and the increase in oxygen consumption produced by muscular work. Many writers have assumed that the increased cardiac output of thyrotoxicosis is conditioned merely by the increased metabolism of the tissues but in fact all the evidence points to the conclusion that this peripheral factor is of secondary importance. Thus, Davies *et al.* (1924), Means (1925), Liljestrand and Stenström (1925), and Boothby and Rynearson (1935) have all shown that the increase in cardiac output and circulation rate in thyrotoxicosis is out of all proportion to the increase in tissue metabolism.

Entirely different mechanisms operate in exercise and thyrotoxicosis. In exercise the cardiovascular responses are nicely adjusted to the oxidative demands of the skeletal muscles. In thyrotoxicosis the primary factor is overaction of the heart resulting from the direct effect of excessive thyroid hormone on the myocardium; there is a lack of proportion between the increased blood-flow and the oxidative requirements of the tissues.

It is also noteworthy that the increased cardiac output in exercise and thyrotoxicosis are achieved by different mechanisms. In the former, increase in stroke volume is the primary response, increase in cardiac rate is secondary (Liljestrand *et al.*, 1938). On the contrary, in thyrotoxicosis, there is primarily an increase in cardiac rate.

In thyrotoxicosis, the arterio-venous oxygen difference is less than normal, because the cardiac output is increased out of all proportion to the tissue needs. Thus, Gladstone (1936) found that the oxygen-utilization coefficient was decreased on the average by 37 per cent. in a group of thyrotoxics; their average cardiac output was 8·1 litres per minute, compared with the normal 4·2 litres per minute. Böger and Wezler (1937) state that the arterio-venous oxygen difference may be reduced by 50 per cent. in thyrotoxicosis. In myxoedema the opposite obtains; the arterio-venous oxygen difference is increased because the slow transit of blood through the capillaries outweighs the effect of reduced oxygen consumption in the tissues (Stewart *et al.*, 1938).

The diminished arterio-venous oxygen difference and increased circulation rate of thyrotoxicosis can be correlated with the absence of dyspnoea even when the basal metabolic rate is very high. Comparable metabolic levels reached during exercise would be accompanied by definite dyspnoea. In the latter condition, the cardio-respiratory mechanism responds to an increased oxygen utilization and carbon dioxide production in the tissues, whereas in thyrotoxicosis, the primary increase in circulation rate satisfies all the tissue requirements without any rise in pulmonary ventilation.

Other circulatory adjustments. The increased cardiac output depends, of course, on the presence of an increased venous return. In thyrotoxicosis widespread arteriolar and capillary dilatation results in a substantial diminution in peripheral resistance. As the systolic blood pressure is normal or slightly raised this diminished resistance makes for a quick venous return. The increased blood volume and the frequent quick muscular movements of these patients are auxiliary factors.

Frequency curves of the systolic, diastolic and pulse pressures in patients with toxic goitre show their average values to be 140–150 mm. Hg., 70–80 mm. Hg, and 70–80 mm. Hg, respectively (Means, 1937). The systolic and pulse pressures are therefore slightly raised and the diastolic pressure is slightly reduced.

Gibson and Harris (1939) studied changes in the blood volume in thyrotoxicosis and myxoedema. In the former condition, the average value is clearly raised, in the latter it is reduced. The deviation from normal in each group is directly proportional to the metabolic rate. After successful treatment, the values for the blood volume tend to revert to normal.

The capillary circulation. There is evidence from studies of the skin capillaries (Roberts and Griffith, 1937) and those in the cardiac and skeletal muscles (Eriksson and Petren, 1937) that the capillary bed is greatly widened in thyrotoxicosis. Moreover, the rate of filtration through the capillary walls is increased in thyrotoxicosis, but decreased in myxoedema (White and Jones, 1939).

The nutrition of the heart. McDonald, Boyle and De Groat (1938) investigated the effect of thyroid feeding upon the glycogen content of the dog's myocardium. The various chambers, as well as the septal tissue of the heart, were separated and their glycogen contents estimated. Short periods of simple tachycardia were not associated with significant alterations in the heart's store of glycogen. Longer periods of tachycardia caused some reduction, but only in the case of the left ventricle and septum did this ever become substantial in degree. The development of cardiac irregularity or failure in hyperthyroidism was found to be not contingent upon the presence or absence of glycogen.

Pathological Anatomy and Histology of the Heart

Is thyrotoxicosis associated with a specific histological lesion in the myocardium? McEachern and Rake (1931) examined twenty-seven thyrotoxic

hearts, in only six of which was there evidence of coexistent heart disease. They compared the findings with those in 150 control patients dying from post-operative shock and similar causes.

In fourteen of the twenty-seven thyrotoxics, the hearts were normal. In eight there was moderate perivascular and intermuscular fibrosis or small round cell infiltration. Similar changes were encountered in the controls, though less frequently. Conspicuous lesions were found in only five of the twenty-seven cases, and in three of these there was coexistent heart disease.

Cardiac hypertrophy was present in sixteen of the twenty-seven cases and occurred independently of any histological changes. Where auricular fibrillation or prolonged thyrotoxicosis had been present, it left no special mark on the heart. In two cases congestive heart failure had been caused by thyrotoxicosis alone, a possibility which has often been denied but was confirmed by the findings of Weller *et al.* (1932). Similarly, experimentally induced thyrotoxicosis in rabbits is merely associated with the histological changes of cardiac overwork (Nora and Flaxman, 1943). It is thus clear that the cardiac phenomena of thyrotoxicosis cannot be ascribed to structural changes in the myocardium. The disorder is a chemical one.

Where extensive myocardial necrosis occurs, superadded toxic or infective agents are responsible. The experimental findings of Goodpasture (1921 a and b) are of interest in this connexion. The hearts of their thyroxinized rabbits showed relatively insignificant lesions when compared with normal controls. When, however, the thyroxinized rabbits were lightly anaesthetized with chloroform for an hour before being sacrificed, widespread necrosis of the myocardium was demonstrable. No lesions were detectable in control-chloroformed animals. Thyroxinization may thus greatly increase the susceptibility of the myocardium to toxic agents.

Does thyrotoxicosis cause cardiac hypertrophy? As stated above, cardiac hypertrophy was frequently noted in McEachern and Rake's series of thyrotoxic hearts. Kepler (1932) also found hypertrophy to be present. The cardiac hypertrophy is usually mild; if marked, associated organic disease is indicated. The question was studied fully by Friedberg and Sohval (1937) who concluded that cardiac hypertrophy in *uncomplicated* Graves' disease is quite uncommon and of slight degree. Hypertrophy of the heart normally depends on increased diastolic pressure and ventricular filling which are translated into an increased stroke volume. But in Graves' disease the diastolic pressure and stroke volume are not raised, the increased cardiac output being dependent on tachycardia. Thus no significant hypertrophy would be anticipated in uncomplicated cases.

Thyroid therapy in the experimental animal has been found to produce hypertrophy of the heart (Simonds and Brandes, 1930; Sacher and Vesterdal-Jörgensen, 1935). The relative and absolute increase in heart weight depends on true hypertrophy and is not due to oedema (Bodansky and Pilcher, 1935). But, if excessive wasting is produced, the weight of the heart may actually decrease.

Does heart failure occur if thyrotoxicosis is uncomplicated by organic

disease of the heart? It is certain that thyrotoxicosis may be the sole cause of cardiac failure. There was no evidence of other cardiac disease, clinically or at post-mortem, in three of our own cases dying with this complication. This agrees with the observations of Kepler, and of McEachern and Rake shown in Table XV. In 35 per cent. of Hurxthal's series (1928), congestive failure could be explained on no other basis than that of thyrotoxicosis. Rosenblum and Levine (1933) and Maher and Sittler (1936) also accept thyrotoxicosis as a sole cause of cardiac failure. Auricular fibrillation is nearly always the deciding factor. It is, however, generally agreed that associated cardiac disease should always be carefully excluded in thyrotoxics with congestive failure.

There is no evidence that simple, endemic goitre, even if large and of long standing, causes cardiac complications. The presence of the latter signifies some degree of thyrotoxicosis (Hellwig, 1944).

TABLE XV

Author	Number of P.-M. Cases	Congestive Heart Failure in:	Co-existing Organic Disease in:	No cause other than Thyrotoxicosis in:
Kepler	178	27	18	9
McEachern and Rake	27	7	5	2

In summary, the thyrotoxic heart is not a specific pathological entity comparable to the heart in rheumatic fever or cardio-aortic syphilis. There are no specific histological lesions; the disorder is one of function. Because of its greatly increased energy output cardiac hypertrophy occurs, and if thyrotoxicosis be prolonged, exhaustion and failure may supervene in the absence of any other detectable heart disease. The over-activity of the heart results from the direct effect of excessive thyroid hormone on its muscle fibres.

Clinical Features of the Heart and Vascular System in Thyrotoxicosis

Trousseau in 1867 drew attention to a fundamental subdivision of thyrotoxics, with cardiac manifestations:

> " I must add that valvular disease was present in some of Stokes' cases, although he already saw that this was not the rule, and he therefore described separately exophthalmic cachexia complicated by organic disease of the heart, when treating the disease. This clinical division should, I think, be retained because . . . "

In his appraisal of the cardiovascular system the clinician should always consider whether valvular, or other organic heart disease, coexists with

thyrotoxicosis. The association is by no means rare and greatly affects prognosis and treatment. Should the efficiency of the heart be already handicapped by old rheumatic fever, hypertension, or coronary sclerosis, superadded thyrotoxicosis carries with it the risk of severe and rapid decompensation. The concomitant cardiac disease may be slight and have remained latent until the advent of the thyrotoxicosis. Unless ferreted out, it may be overlooked.

The incidence of thyrocardiac complications increases with age. The same is true for nodularity of the thyrotoxic goitre. Hence cardiovascular complications are especially associated with nodular toxic goitres. As we have seen thyrotoxicosis greatly increases the work of the heart and is thus prone to cause exhaustion and failure of the ageing myocardium.

Thyrotoxicosis without associated heart disease. An almost constant complaint is of palpitations. These usually occur in attacks brought on by exertion, excitement or worry. They may cause considerable mental and physical distress. The " throbbing " in the chest or neck is sometimes so intense as to cause difficulty in breathing and speaking. It may also occur at night causing insomnia. Considerable anxiety may then result from an imperfect understanding of their comparatively minor significance. There is a place here for reassurance and it should be explained that the heart's beat is usually forcible while the disease is active.

At other times attacks of palpitations, flushing, difficulty in breathing or speaking under stress, may cause the patient to " go to pieces " in an unaccustomed fashion. Such manifestations bear witness to the hyperexcitability both of the cardiovascular system and of its controlling mechanism. Thus on a ward visit the patient may become flushed and restless. Sometimes she will complain that wherever her limbs and body touch the bed an incessant pulsation can be felt. The bed itself may shake.

Occasionally, an attack of palpitations accompanied by dizziness and faintness may usher in the clinical story. Thus one of our patients, a woman of twenty-one with toxic diffuse goitre, suddenly felt a severe " fluttering of the heart " while out walking. She was seized by a feeling of giddiness and sheer panic. These attacks recurred. They lasted for many hours and were shown subsequently to be paroxysms of sinus tachycardia.

In older patients the sudden onset of such cardiac distress may signify the development of paroxysmal fibrillation of the auricles. Not infrequently thyrotoxic patients become exceedingly heart-conscious. Their perception, sharpened by the disease, enables them to detect and describe the forcible action of the heart and variations in its working with remarkable accuracy.

Though vascular symptoms are so prominent, abnormal physical signs are few. Apart from persistent tachycardia and forcible heart action, the findings are essentially those of a normal heart. As Towers (1933) pointed out the picture is similar to that of a healthy heart after exercise.

Tachycardia is so constant that it has been used as a means of estimating the basal metabolic rate, as with Read's formula (1924):

$$\text{B.M.R.} = 0{\cdot}75\ (\text{P.R.} + 0{\cdot}74\ \text{P.P.}) - 72$$

With this formula Read was able to predict the basal metabolic rate to within 10 per cent. of its actual value in more than 50 per cent. of cases and this has been confirmed by Rabinowitch (1935).

Thyrotoxic tachycardia is distinguishable from most functional tachycardias by the fact that it does not subside during sleep or after a period of rest. Thus Boas, using the cardiotachometer (1932), compared the heart rate in normal, psychoneurotic, and thyrotoxic patients during sleep. In thyrotoxicosis there was little reduction of the rate during sleep. In the psychoneurotics the rate was markedly reduced but did not quite fall to normal. Though it is thus a convenient rule of thumb that thyrotoxic tachycardia persists during sleep, whereas that of functional nervous disease does not, it should be noted that there may be a very marked diurnal variation in the tachycardia of thyrotoxicosis if the patient be hyperexcitable (Fig. 70). Conversely, it must be admitted that there are occasional patients with functional nervous disease whose tachycardia persists even during sleep.

A week or ten days' rest in bed will often reduce the heart rate in thyrotoxicosis, if it has not been very high. The rate may, in fact, return to normal without any other treatment. If mild exercise is then allowed a disproportionate tachycardia will generally result and may not subside for many hours. Such a procedure has been used as a diagnostic test.

The apex beat is peculiarly forcible and " sudden " in thyrotoxicosis. It imparts a vibratory sensation to the fingers, which may be mistaken for a thrill especially as the first mitral sound is accentuated as in early mitral stenosis. In fact mitral stenosis has often been erroneously diagnosed in patients with thyrotoxicosis. Radiological examination in the right oblique position will however exclude the left atrial enlargement characteristic of mitral stenosis (Hill, 1938). Lian and Welti (1938) carefully analysed the first heart sound in thyrotoxicosis and concluded that vibrations in the blood ejected by the atrium and rapid and forcible contraction of the ventricular walls account for its characteristic accentuation.

The first mitral sound is often followed by a short soft systolic murmur. A systolic murmur is even more frequently heard over the base of the heart particularly in the pulmonary area. Such murmurs are almost invariably functional and without significance. Thus in patients who suffer from paroxysms of sinus tachycardia, a pulmonary systolic murmur may be present during the attacks but may disappear in the intervals between them. In five of our patients in whom systolic murmurs of varying intensity and location were present before death, no valvular or pericardial lesion was found post mortem.

Hypertension coexists with thyrotoxicosis. It is established that thyrotoxicosis is frequently associated with cardiovascular hypertension. Hill (1938) charted the blood pressure of 205 patients against the age and superimposed the normal line upon the distribution of points thus obtained. It was clearly shown that the great majority of the systolic pressures lie well above the accepted normal. The diastolic pressures were similarly charted

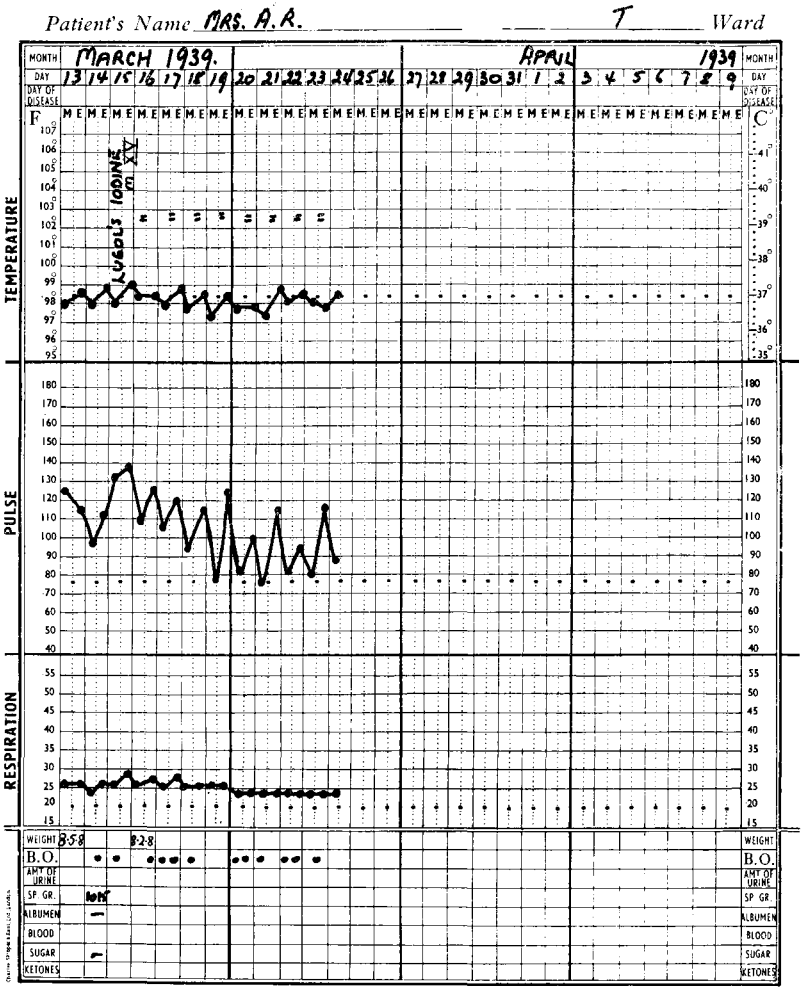


FIG. 70.—The chart is from a woman, aged 34, with severe thyrotoxicosis of short duration. Hyperapprehensiveness was an outstanding feature and is associated with a striking diurnal variation in the pulse rate. The tachycardia late in the day was thus largely " functional ".

and most were low. It has long been recognized that an increase of the pulse pressure is characteristic of thyrotoxicosis (Davis and Eason, 1924).

There is suggestive evidence (Rosenblum and Levine, 1933; Towers, 1933; and Bourne, 1935) that, following control of the thyrotoxic state, the blood pressure may rise further, rather than fall. Hill (1938) found that 50 per cent. of his follow-up patients had a systolic pressure of 150 mm. Hg. or more, and 20 per cent. had a pressure of 170 mm. Hg. or more. In a random series of a hundred out-patients the corresponding percentages were twenty-eight and ten. He concluded that there is a distinctly raised incidence of hypertension in treated thyrotoxics. Hill concluded that the raised pressure present during the active phase of the disease was unaffected by any form of treatment and so persisted afterwards.

Hurxthal (1931) and Fullerton and Harrop (1930) both state that when the blood pressure is taken under basal conditions thyrotoxics show little departure from normal but we have found that even under basal conditions the pressures both systolic and diastolic do not quite revert to normal. It is possible that the raised systolic and lowered diastolic pressures of thyrotoxicosis depend on a fundamental hyperexcitability. This would explain their frequent persistence after thyroidectomy which often leaves untouched the emotional disorder.

Hill (1938) took as his criterion of essential hypertension a diastolic pressure of 95 mm. Hg or more. On this basis some 10 per cent. of his thyrotoxic patients also had essential hypertension. Of these, one-half were less then forty years of age. The corresponding figure in Bisgard's series (1939) was 8 per cent. In a series of 170 patients of our own 24 or 16 per cent. had pre-operative diastolic pressures of 95 mm. Hg or more. However, the average age of our patients was distinctly greater than in the other series mentioned.

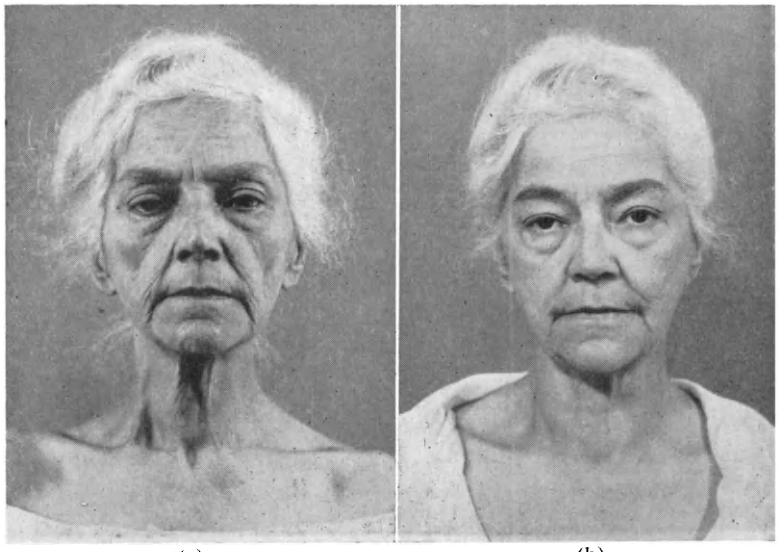
When essential hypertension coexists with thyrotoxicosis, it may be quite latent, contribute a little to the clinical picture, or may dominate it. In the last event the goitre is simple or at most mildly toxic. The combination of essential hypertension with goitre thus presents difficult problems to the clinician. The patient is often menopausal and an effort must be made to assess the relative importance of the hypertension, the goitre and the menopause in her clinical state. An accurate assessment of their relative importance is essential to proper treatment and prognosis. Unless thyrotoxicosis is definite, Maher and Sittler (1936) advise keeping such patients under observation in order that continued observation and repeated measurements of the blood pressure and metabolism may render possible accurate analysis of the symptom-complex.

Thyrotoxicosis and arteriosclerosis co-exist. Arteriosclerosis implies coronary as well as peripheral sclerosis. Because of the special burden placed on the heart in thyrotoxicosis anginal symptoms predominate. Coronary thrombosis and myocardial infarction are occasional complications.

The anginal pain of coronary sclerosis is associated with increased cardiac work (Starr *et al.*, 1938); periods of freedom from pain are associated with

less work. Thus control of the thyrotoxic state, by lowering the energy output of the myocardium, may give dramatic relief. It is evident however that the original coronary sclerosis remains unchanged and the prognosis must be guarded.

Experimental studies have shown that thyroid therapy protects rabbits against the severe generalized atheroma produced by cholesterol feeding (Menne *et al.*, 1937). Atheroma is rarely found at post-mortem in thyrotoxic subjects. Because of its infrequency, complicating arteriosclerosis



(a) (b)

FIG. 71.—Masked hyperthyroidism (*a*). The patient, aged 63, had complained of loss of weight and general malaise and was referred by her practitioner with the request " to exclude malignancy ". On examination there were a small goitre, a suggestion of lid retraction and a slight tremor. Despite a metabolic rate result of + 4 per cent. the clinical diagnosis was thyrotoxicosis and after six months' anti-thyroid therapy (*b*) she was much relieved and said " I am feeling very much better and stronger in myself . . . and am not so nervous or run-down ". (Dr. R. Asher's case.)

tends to be overlooked. One of our patients, a woman aged fifty, had suffered from classical anginal pain for two years and had been attending medical out-patients for most of that period before the thyrotoxic component was recognized. Careful inquiry showed that in addition to the symptoms of angina, she also suffered from palpitations, weakness, loss of weight, profuse sweating and irritability. Her skin was hot and moist and there was a slight " stare ". The thyroid gland was just palpable. The basal metabolic rate was +50 per cent.

Such patients have often been reported as illustrating " masked hyperthyroidism " (Towers, 1933; Hay, 1936). Dunhill (1937), however, affirms

that " it is the practitioners who are masked, eyes and brain too " (!). Yet it cannot be denied that the signs of thyrotoxicosis may be inconspicuous (Fig. 71). Increased awareness of the masked forms of hyperthyroidism will lead to their earlier detection. Similarly when cardiac symptoms are disproportionately prominent in the patient with thyrotoxicosis it is well to search for some added factor increasing the vulnerability of the heart.

The classical " goitre heart " of the older writers occurred in an elderly patient with a large nodular goitre of very long standing. Some degree of venous obstruction and cardiac enlargement with incipient failure were also

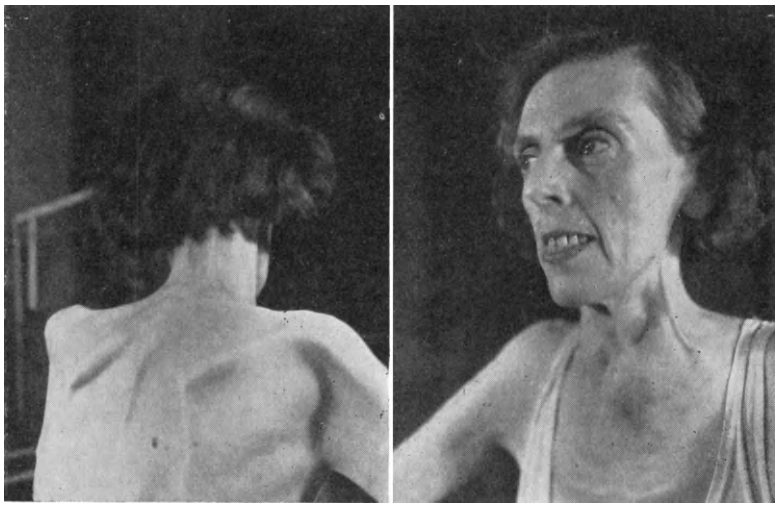


FIG. 72.—Multinodular goitre: thyrotoxicosis of moderate severity: old rheumatic heart disease: auricular fibrillation: severe congestive cardiac failure, with anasarca. Note venous congestion and extreme wasting. The patient, aged 44, had had a goitre for seventeen years. She had suffered from palpitations for many years but cardiac failure was of recent onset.

present. There were often left ventricular hypertrophy and peripheral arteriosclerosis. An X-ray of the thorax might reveal calcification of the aortic arch as well as enlargement of the heart and congestion of the lung roots.

Apart from the cardiac failure, evidence of thyrotoxicosis was lacking and it was widely held that mechanical obstruction of the great veins by the goitre was responsible for the cardiac condition. The concept of the mechanical goitre heart is no longer accepted; it is now believed that low-grade, long continued thyrotoxicosis causes the heart to fail.

Because of the associated arteriosclerosis these patients require careful management if they are to be carried safely through thyroidectomy. The degree of relief which follows is directly related to the relative importance of the thyrotoxic factor. Most patients are much improved but still suffer from

palpitations and minor degrees of dyspnoea, attributable to the arteriosclerosis.

Rheumatic heart disease and thyrotoxicosis. It is well known that rheumatic infection of the endocardium, myocardium and pericardium may remain symptomless and unrecognized for many years. The heart is, however, unlikely to bear the extra burden of thyrotoxicosis without complaint.

The clinician should be on the alert for such patients. A definite history of rheumatic fever and the presence of characteristic signs in the heart may

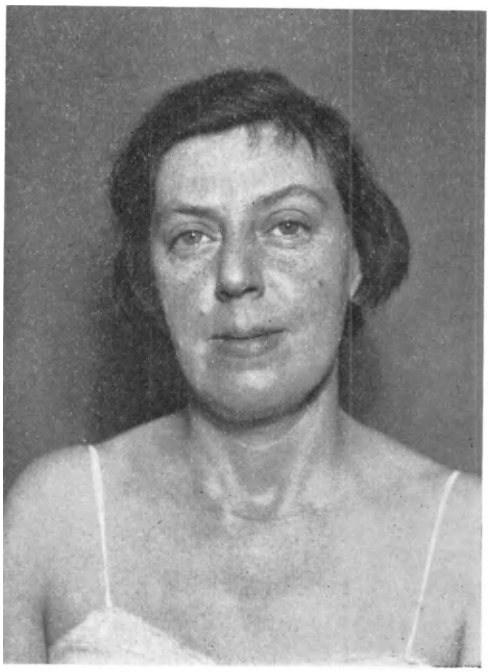


FIG. 73.—Showing a most gratifying result from surgery. Photograph ten months after operation. The scar is at the correct level and is almost invisible. Same patient as in Fig. 72.

render the diagnosis clear. In other cases it will be suspected because of the comparative severity of the cardiac manifestations. Thus auricular fibrillation in a young patient with thyrotoxicosis should always raise the suspicion of coexisting rheumatic heart disease. Recognition of the latter factor is important because it constitutes an additional indication for early and complete control of the thyrotoxic state. Histological studies show that in mitral stenosis the auricular muscle very rarely escapes. Unless thyrotoxicosis is quickly eliminated fibrillation will not be long delayed. Once fibrillation becomes established in such cases the outlook for reversion

to a normal rhythm after thyroidectomy is never so good as in uncomplicated cases.

One of our patients, a woman of forty-three, was admitted with toxic nodular goitre, rapid auricular fibrillation, congestive cardiac failure and anasarca (Figs. 72 and 73). She gave a history of rheumatic fever as a child. The heart was considerably enlarged and a loud systolic bruit was audible at the apex and propagated to the left axilla. A loud aortic systolic murmur was also present. After careful preparation thyroidectomy was successfully carried out and one year afterwards she was much relieved, though still affected slightly by palpitations and shortness of breath. Clinical tests showed her exercise tolerance to be good but the auricular fibrillation, cardiac enlargement, and harsh systolic murmurs were still present.

In an interesting case reported by Bernstein and Simkins (1942) aortic stenosis was associated with " masked hyperthyroidism."

Pulmonary heart disease coexistent with thyrotoxicosis. When a well-marked chronic pulmonary lesion, such as bronchiectasis, or fibroid tuberculosis, exists the clinical recognition of the associated heart disease is easy. More careful search is required in patients with asthma, chronic bronchitis, or other factors predisposing to emphysema and cor pulmonale.

When the changes of cor pulmonale are marked the prognosis is very uncertain. Superadded thyrotoxicosis diminishes the heart's reserves and lowers the general state of health. An intercurrent respiratory infection may then rapidly lead to broncho-pneumonia which in turn precipitates right ventricular failure with a rapidly fatal course (Fig. 74). Early control of the thyrotoxic state and avoidance of respiratory infections are of paramount importance.

Syphilitic heart disease and thyrotoxicosis. This rare combination was present in two of our cases. Syphilis appears not to influence the thyrotoxic state but from the viewpoint of prognosis and treatment the importance of recognizing the dual condition needs no emphasis. Both our patients continued to suffer from cardiac pain after thyroidectomy but it was less severe than previously.

Cardiac arrhythmias in thyrotoxicosis. Though Parry described irregular, as well as forcible and rapid action of the heart, in 1786, it was not until the first decade of this century and the development of electrocardiography that the nature of the arrhythmias associated with thyrotoxicosis could be clearly distinguished. It is now recognized that of these, auricular fibrillation is by far the commonest; auricular flutter, heart block and ectopic beats are comparatively rare.

Auricular fibrillation leads sooner or later to cardiac enlargement and decompensation. Ultimately, the patient may be at death's door with anasarca, yet effective control of thyrotoxicosis rapidly and permanently restores her to good health and a normal working capacity. As Lockwood (1944) remarks in this connexion " the age of miracles is not past! " Thus prompt diagnosis and energetic treatment offer more promise here than in any other form of heart failure. The reason is that fibrillation depends upon

chemical exhaustion of the heart muscle and not upon structural damage (Fig. 75).

On the other hand, as Cowan (1929) affirms, it may well be that prolonged auricular fibrillation leads to degenerative fibroid changes in the walls of the auricles. Such changes may exist in patients who fail to switch to a normal rhythm after thyroidectomy. They may derive from coexistent heart disease or prolonged fibrillation.

Auricular fibrillation. Three distinct clinical types of fibrillation occur: (i) Paroxysmal auricular fibrillation. Thyrotoxicosis is well recognized

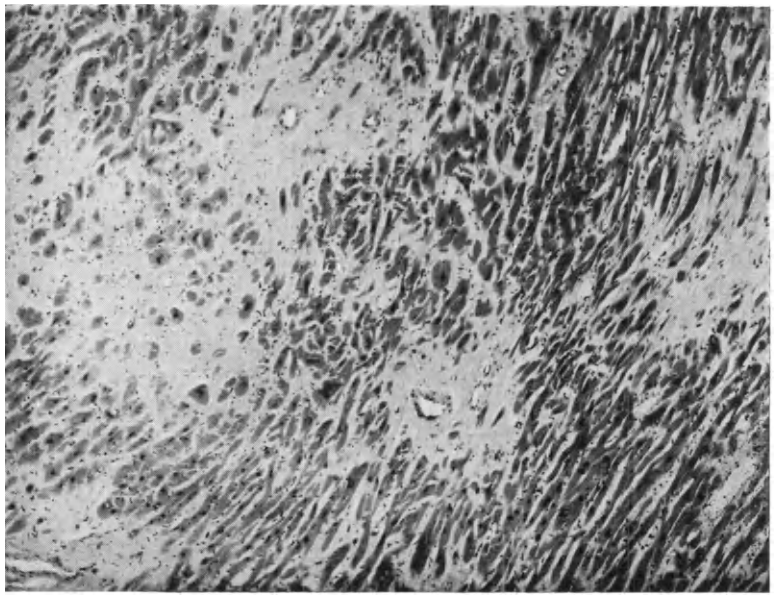


FIG. 74.—Thyrotoxicosis complicated by cor pulmonale. The patient, a woman of 51, had suffered from asthma for many years. Death occurred from intercurrent bronchopneumonia. Section shows extensive perivascular fibrosis in wall of right ventricle. (× 65.)

as a cause of paroxysmal auricular fibrillation. Parkinson and Campbell (1930) in a detailed review of two hundred cases of this disorder, found thyrotoxicosis to be responsible in 14 per cent. Old rheumatic fever, hypertension and coronary artery disease were much commoner causes. The importance of the paroxysms lies in the fact that they tend to become more frequent and prolonged, and to lead eventually to established fibrillation.

This type of irregularity is noticed by the patient because the attacks have an abrupt beginning and a sudden ending, and during them palpitations are unusually severe and rapid. Their duration varies from a few minutes to a few days. They have to be distinguished from simple sinus tachycardia,

paroxysmal tachycardia, and auricular flutter. As a rule, where paroxysmal fibrillation has been present, thyroidectomy is followed by a short period of fibrillation.

(ii) Post-operative auricular fibrillation. In the course of thyroidectomy, or within the first three or four days afterwards, auricular fibrillation makes a transient appearance. It may also occur in a thyrotoxic patient after a non-thyroid operation, for example, tonsillectomy. Usually the paroxysm lasts for from two to five days, persisting during the height of the post-operative reaction and disappearing spontaneously as this subsides. It is rare for more than one bout to occur, or for the paroxysm to give place to established

FIG. 75.—From a woman aged 44 admitted with thyrotoxic heart disease and severe congestive failure. Wall of right auricle, showing structure within normal limits. Auricular fibrillation had been present for many months prior to death. (× 500.)

fibrillation. Where doubt has existed, its occurrence clinches the diagnosis of toxic goitre. One of our patients, a woman aged forty-eight, illustrated well the association between extra-systoles and paroxysmal and post-operative fibrillation. She complained of "jumping of the heart" for five months prior to admission. The attacks commenced suddenly, lasted some five minutes, and then ceased abruptly ". . . as if my heart stops altogether." She was observed in one of the attacks, and the heart was completely irregular. An electrocardiogram between attacks showed frequent auricular extra-systoles. Following thyroidectomy, auricular fibrillation

developed and persisted for thirty-six hours. Thereafter the heart became regular, and the attacks were completely relieved.

(iii) Established auricular fibrillation. Any attack lasting a week or more may be considered to be of this type. The liability to established fibrillation is greater in old age and when other cardiac disease exists. The combination of advanced age, nodular goitre and mild thyrotoxicosis is commonly associated with established fibrillation.

The use of thyroid extract in the treatment of obesity or self-induced hyperthyroidism (thyrotoxicosis factitia) may lead to auricular fibrillation (Hurxthal, 1944; Rogers, 1947).

In a series of 322 consecutive cases, we found fibrillation of one or other type to be present in thirty-four, or 15·6 per cent., as compared with 14·3 per cent. in Hill's series and 20·7 per cent. in Ernstene's (1934). The influence of age is shown by the fact that the average age of our patients with fibrillation was 50·8 years, compared with that of 40·3 years for patients without fibrillation.

There was associated organic disease of the heart in half the fibrillators as compared with 20 per cent. of the non-fibrillators. The thyrotoxic state is more often prolonged and mild in fibrillators, than severe. They have commonly had a goitre and indefinite general symptoms for many years. A history of long-standing goitre with toxic exacerbations is also frequent.

Auricular fibrillation in thyrotoxicosis almost inevitably leads to heart failure. Not all patients have oedema; latent cardiac failure must be regarded as existing whenever there is a rapidly fibrillating heart. Oedema was present in two-thirds of our fibrillators, and was sometimes very gross, involving the peritoneal and pleural cavities. It must not be concluded, however, that this irregularity is always present when failure exists. In our series, there were six examples of failure with oedema despite a regular cardiac rhythm.

Nicholson (1937) remarks on the interesting fact that the ventricular rate in established fibrillation tends to be considerably slower than in the paroxysms. There appears to be no satisfactory explanation for these variations in rate, though Mackenzie (1911) postulated various degrees of organic block in the conducting tissue of the heart as a likely cause. It is noteworthy also that digitalis does not produce its usual reduction in ventricular rate in thyrotoxicosis, unless iodine is given simultaneously.

In Nicholson's series there were twenty-three fibrillators who, for various reasons, were not treated surgically. Fibrillation persisted in every case, and sixteen of the twenty-three patients, or nearly 70 per cent., died. This emphasizes the necessity for complete control of the thyrotoxic state when fibrillation exists.

When thyrotoxicosis is effectively controlled, switch to a normal rhythm occurs in over three-quarters of fibrillators. The clinical results of thyroidectomy are strikingly better when normal rhythm is regained. The heart may fail to revert to a normal rhythm if there is coexistent heart disease, or in old age. With hypertension and arteriosclerosis the prognosis for relief of

fibrillation is even less promising than with rheumatic fever, because the patients are usually older and such cardiac diseases are essentially progressive. Relapse into fibrillation may be produced by intercurrent infections, recurrent thyrotoxicosis and by thyroid therapy for post-operative myxoedema.

The switch to regular rhythm, though desirable from the viewpoint of cardiac function, does involve a risk of cerebral and peripheral embolism, and this risk is greatest when mitral stenosis coexists. In one of our patients fatal cerebral embolism occurred, and in a second, there was bilateral femoral embolism. Two operations for embolectomy were successful and good recovery ensued.

Auricular flutter, heart block and ectopic beats. Phillips and Anderson (1927) found only twenty-one cases of flutter to over three hundred of fibrillation. In Nicholson's 240 cases of thyrotoxic arrhythmia, there were only four with spontaneous flutter and these were only discovered by electrocardiography. Nicholson points out that flutter should be suspected if, in an irregular pulse, there are comparatively long runs of regular rhythm.

The electrocardiogram may show prolongation of the P–R interval in thyrotoxicosis; varying degrees of heart block may occur but complete atrio-ventricular dissociation is rare. Heart block in thyrotoxicosis was fully reviewed by Kremer and Laplace (1936) who found few authentic cases on record. When it does occur thyrotoxicosis is usually complicated by acute rheumatic fever or by some other infection (Maher *et al.*, 1939). Steuer (1936) has reported a patient with thyrotoxicosis and complete heart block. After iodine therapy, the heart reverted to the usual tachycardia. Following thyroidectomy transient auricular fibrillation occurred. Finally the rhythm became normal and the rate slow. This striking case emphasizes the functional character of the cardiac arrhythmias in thyrotoxicosis. Digilio (1938) reported a case of branch-bundle block which was only discovered in the electrocardiograph. The heart was normal to clinical examination. Packard and Graybiel (1950) have reported a similar case; the electrocardiographic disorder disappeared after thyroidectomy. The conductional disturbance gradually disappeared following thyroidectomy. In a patient under methyl thiouracil treatment, pericarditis and complete heart block developed. The tonsils were infected but there was no previous history of rheumatism (Bain, 1945).

Complete heart-block must be suspected in those rare cases of thyrotoxicosis where heart failure occurs despite a normal rhythm and a comparatively slow rate. The rate is not, however, as slow as in other conditions with heart block. Yater showed in the isolated hearts of thyroxinized rabbits that crushing the atrioventricular bundle did not result in the usual marked reduction in ventricular rate. This is explained by the direct action of thyroxine on the ventricular muscle.

Ectopic beats are relatively uncommon in thyrotoxicosis. They are usually of the ventricular type. Auricular ectopic beats are, however, of greater significance, indicating a heightened irritability of the auricular

muscle and a tendency to fibrillation. Early treatment is indicated as the risks are always greater if fibrillation exists.

The Electrocardiogram in Thyrotoxicosis

When irregularity is present or suspected, or when there is coexisting heart disease, electrocardiographic examination provides useful evidence as to the nature and extent of the cardiac affection. The changes in the electrocardiograph due to thyrotoxicosis *per se* are of comparatively minor importance. They are best appreciated by reference to the effect of thyroid therapy on the electrocardiograph in myxoedema. In untreated myxoedema there is a low-voltage curve and some reduction in height, or inversion of the T–wave. With thyroid therapy the voltage increases and the T–wave tends to be restored to normal dimensions, this effect being apparent after two or three weeks' treatment. Vizer (1938) has made the important generalization that the amplitude of the electrocardiographic waves depends upon the work of the heart. The over-acting heart of thyrotoxicosis, therefore, gives a high voltage curve.

In thyrotoxicosis uncomplicated by other heart disease the principal electrocardiographic findings are:

(i) Sinus tachycardia. As is usual, the increased rate is achieved at the expense of a reduction in diastole.

(ii) An increase in the voltage of the curve.

(iii) An increase in the P–R interval. This would indicate some interference with conduction in the bundle of His. However, anything more than minor prolongation of this interval should raise the suspicion of coexisting heart disease.

The series of 168 patients studied by Gordan *et al.* (1944), included at least twenty-eight with organic heart disease. The noteworthy electrocardiographic findings in order of frequency were:

(i) Sinus tachycardia.

(ii) Abnormalities of the T–waves (most commonly low amplitude and notching).

(iii) Auricular fibrillation.

(iv) Partial A–V block.

(v) More rarely auricular flutter.

Radiological Aspects

Recourse to radiological study of the heart is indicated for the same reasons as electrocardiography. The findings in uncomplicated thyrotoxicosis were established by Parkinson and Cookson (1931) and Cookson (1932) as follows:

(i) In some 45 per cent. of cases there is enlargement which is usually slight or moderate and affects mainly the left border of the heart.

(ii) The size and shape of the heart shadow are normal when thyrotoxicosis is mild or of short duration. When it is severe and of long standing, the shadow is often enlarged and modified in shape. The greatest enlargement is seen in patients with auricular fibrillation and heart failure.

(iii) The special characteristic of thyrotoxic enlargement, as contrasted with that of other heart diseases, is its more or less normal symmetry.

(iv) The vascular pedicle exhibits the most characteristic changes, there being undue prominence of the pulmonary arc in about one-third of cases. It forms an added bulge in the left cardiac profile, between the aorta above and the left ventricle below. The radiological picture is easily distinguished from that of mitral stenosis since, in the latter, the left atrium is specially enlarged and there is congestion of the lung roots. Pulmonary congestion is not seen in thyrotoxicosis unless cardiac failure has supervened.

(v) Increase in size of the pulmonary artery and hypertrophy of the left ventricle render the left profile of the heart rather straight and combined with some increase in the prominence of the superior vena cava and right atrium, give the heart a characteristic " ham-shape " in thyrotoxicosis.

(vi) Later, when cardiac failure develops, there are congestion of the lung roots, engorgement of the superior vena cava and pleural effusion, more commonly on the right side. These authors could find no evidence that an enlarged thyroid *per se* ever caused cardiac enlargement.

The findings of Margolies *et al.* (1935) are in agreement with those of Parkinson and Cookson. In follow-up studies the former found that in about three-quarters of the cases the foregoing changes disappeared within one to seven months of thyroidectomy.

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CHAPTER XIII

THE NERVOUS SYSTEM IN THYROTOXICOSIS

Nervous Manifestations produced by Thyrotoxicosis — Hyperexcitability — Changes in Personality — Cycloid and Schizoid Tendencies — Toxic Confusional States — Neurosis and Psychoneurosis associated with Thyrotoxicosis — Organic Reaction-types of Mental Disorder associated with Thyrotoxicosis.

As with the cardiac muscle fibres so with the neurones, exposure to an excess of thyroid hormone produces severe functional derangement rather than structural damage. Nevertheless, minor histological lesions have been reported. Thus Diamond (1938) found degenerative changes in the ganglion cells, oedema of the brain substance, dilatation of the subarachnoid space and infiltration of the pia-arachnoid with lymphocytes, histiocytes, and mesothelial cells. Horanyi-Hechst (1936) found very similar changes in the brains of cats after intensive thyroxine therapy. Rossi and Moruzzi (1946) link the nervous manifestations of hyperthyroidism with a reduced thiamin content of brain tissue, which they have demonstrated in the rabbit following thyroxine therapy.

The excess of circulating thyroid hormone in thyrotoxicosis heightens the characteristic functional activity of nervous tissue. In myxoedema, by contrast, the brain potentials are greatly lowered (Bertrand *et al.*, 1938). Should the hyperactivity of thyrotoxicosis be severe and prolonged a state of toxic exhaustion of the neurone may be produced. Toxic delirium is the clinical expression of such exhaustion affecting the cerebral neurone.

The nervous manifestations of thyrotoxicosis are profoundly influenced by the patient's innate personality. Details of the family history and an interview with the patient's relatives may also give invaluable help.

Nervous manifestations produced by thyrotoxicosis.

(1) **Hyperexcitability.** In thyrotoxicosis excitability is increased and the responses generally are exaggerated. Thus quick, involuntary, purposeless movements are a characteristic feature of patients in whom " nervous " phenomena predominate. These patients are often young and thyrotoxicosis is severe.

Particular stimuli also cause exaggerated responses:

One of our patients said that since being ill startling things had upset her to an extreme degree; for example, one day there was a loud explosion in the exhaust of a car passing in the street and this made her jump so markedly that she almost fell to the ground. On such occasions she felt her whole body " flush up hot " and she would break into a profuse sweat, and shake uncontrollably.

The same hyperexcitability and hyper-responsiveness affect every level of the nervous system. Heightening of the affects expresses itself in undue emotionalism, states of sadness, anxiety, fear and others. Dunlap and Moersch (1935) found apprehension to be the most common mental change. In some patients, the whole consciousness may be dominated by fear. For this reason they postpone seeking medical advice and co-operate poorly in treatment. More often the mood changes rapidly expressing first one exaggerated emotion and then another.

Emotionalism and the tendency to over-react are nowhere better seen than during the history-taking when tearfulness may accompany the evocation and recall of apparently trivial incidents. After melting into tears for no apparent reason, the patient may then become embarrassed and apologetic, saying that she would " never cry in this way before the illness." Such symptoms are quickly relieved by controlling thyrotoxicosis. Thus, one of our patients at the follow-up clinic volunteered the remark, " I seem to have more control over myself now, and don't worry so much." Another said, " I used only to have to be spoken to and I would cry, now I am no longer like that."

Similarly, enteroceptive sensations may obtrude themselves prominently upon the consciousness, and cause unwarranted responses. Thus, one of our patients complained that " palpitations shake the whole of the left side of my body, neck and face." Such bodily sensations often cause acute anxiety and insomnia.

(2) **Changes in Personality.** These are of peculiar interest; the commonest types are illustrated by notes from two of our cases.

One patient complained that she had lost her self-confidence, felt embarrassed and suffered severely from palpitations under stress, as when meeting some important person for the first time. On such occasions she felt " like a fool " yet previously she " could meet anyone without thinking about it."

Another patient stated that at the outset of her illness she had noticed an extraordinary feeling of self-confidence and well-being. She felt " able to do anything and to make friends with anyone "; though usually reserved and quiet she felt herself to be " bursting with life."

Physical freshness and vigour favour a self-assertive frame of mind, whereas fatigue and exhaustion are conducive to self-submission. Thus, initially thyrotoxicosis may stimulate the body's metabolism and conduce to the mental states of euphoria and self-confidence; but these are usually transitory. Physical fatigue, favouring mental depression and inferiority, quickly follows. Thus a normal person may be thrown right off balance by thyrotoxicosis, with predominance of one or other mental reaction.

After control of the thyrotoxic state the patient usually regains her former personality. A common statement in the follow-up clinic is that she has gained control of her " nerves " or " become steadier." One of our patients remarked, " I'll tell you what I have got, and that is more confidence in myself."

(3) **Cycloid and schizoid tendencies.** These represent an exaggeration of the normal character traits. Cycloids are either hypomanic or depressed.

One of our patients, a physician, was normally rather masterful and loud-spoken though full of humour and a typical cyclothyme (Kretschmer, 1936). He related how, while thyrotoxic, he was irritated by the slightest let or hindrance, and yet had at all times a sense of extraordinary well-being. " I became if anything, over confident and was not in the least upset when, on two occasions, fortunately while travelling slowly, the wheel came off my car.

" I felt that I could overcome all opposition by force; for example, I can well remember how I sued a patient, at about that time, for a fee of five guineas, and won the case, though at any other time I would certainly have let the matter drop.

" I was irritable and impatient. In spite of the increase in my mental drive I would become very fatigued, my muscles would ache, and I often had to sit down in the middle of a consultation."

The depressive reaction is illustrated in one of our patients, a woman of forty-six who suffered from severe thyrotoxicosis. She stated that she had felt " out of sorts " and lacking in energy for the past eighteen months. She had lost all her self-confidence, and felt ill at ease in company; she was depressed, felt that life was not worth living, and for the past four months had entertained suicidal thoughts.

The schizoid reaction-type, characterized by emotional coldness, psychic excitability and sudden outbursts, was manifested in another patient, a single woman, aged thirty-six, who had been an assistant matron before becoming ill. She dated her illness from the death of her *fiancé*, three years previously. She became depressed, irritable and nervous. Though previously calm, and, even now, apparently unemotional, she found that she would " snap " at anyone. Sometimes she " boiled inside " and felt " like scratching some nurse or patient's eyes out." At other times, however, she would " be afraid at these thoughts, and would cry."

Depressive and schizoid transformations may pass unnoticed, especially if the patient herself fails to comment on the change in her disposition. They should be deliberately searched for, however, and noted. In this way, potential psychotics will be recognized early, and the catastrophe of a suicide in a depressed thyrotoxic may be averted.

The prognosis for the relief of these cycloid and schizoid states after the control of thyrotoxicosis is excellent. Hypomania or mental depression diminishes *pari passu* with the improvement in the patient's physical condition; eventually she reverts to her pristine personality.

(4) **Toxic confusional states.** Several examples of a toxic confusional state induced solely by excessive consumption of thyroid extract are on record. Thus, a patient described by Karnosh and Williams (1934) had no thyroid disease, and had been taking excessive doses of thyroid extract for obesity. She was admitted to hospital suffering from toxic delirium, quite confused, noisy and talkative. Immediate and steady improvement followed cessation

of thyroid therapy, though in the recovery period there was a tendency towards a manic-depressive reaction. She was normally a somewhat hypomanic person.

Again, in a physician, reported by Thompson (1946) the huge dose of 80–120 gm. of thyroid extract was self-administered daily for over twelve months. He was finally admitted with the physical signs of thyrotoxicosis, including cardiac failure. The psychic accompaniments were those of toxic confusion. Cessation of thyroid therapy relieved the toxic symptomatology but revealed an underlying depression; he had taken the thyroid extract in an attempt to commit suicide.

Some thyrotoxic patients may border on a confusional state, manifesting only short periods of disorientation, often towards the end of the day. Alternatively, a mild delusional state may continue throughout the severe phase of the illness.

A young married woman, aged twenty-four, dated all her symptoms from the birth of her infant two years before. It was premature and weighed only 4 lb. The fear of losing the infant gnawed at her continually. At the same time her husband was unemployed and their financial difficulties were acute. She became depressed, and then began to think that people were scheming behind her back, and that even her husband was " in league " against her.

She was suffering from severe thyrotoxicosis, but improved markedly with the rest and iodine therapy. Concomitantly, she lost all the delusions against her husband and her neighbours.

A significant point in this case was that her mother had died in a mental asylum from " delusional insanity." At least three causes of exhaustion existed, namely, pregnancy and childbirth, financial stress, and thyrotoxicosis.

In other patients there is acute thyrotoxic delirium, which is comparable to the acute confusional state occurring in certain drug poisonings and infective conditions. The attacks of confusion are usually nocturnal at first and associated with extreme motor restlessness.

Illustrative case. The patient, a single woman aged fifty, gave a history suggestive of very severe thyrotoxicosis of eight months' duration.

She was restless, excitable, and much wasted. There was a large symmetrical goitre with a well-marked thrill and bruit.

On the morning of her admission she appeared well orientated but on her first night in hospital she suddenly became acutely confused. She was very restless, tried to get out of bed, and woke all the other patients in the ward with her shouting. She was eventually quieted by large doses of morphia.

Delirium recurred on the second and third nights, and continued through the fourth and subsequent days. She stripped the clothes from her bed and was resistant and quiet by turns. She died in exhaustion on the sixth day after admission.*

* The reader will appreciate that many of the case records quoted in this monograph date from the days before therapy with the anti-thyroid drugs.

Sometimes a toxic exhaustion psychosis develops during the post-operative period. The condition is comparable to the confusional state which follows childbirth. Motor restlessness may not be very marked, but disorientation, hallucinations and delusions all occur. With proper management the prognosis is excellent. Lucid intervals eventually occur and become more frequent and prolonged until finally the patient returns permanently to her normal mental state. As Karnosh and Williams (1934) remark, " experiences with the psychoses associated with thyroid disease are, therefore, raisins in the tasteless dough of psychiatric practice. . . ."

Thyrotoxicosis factitia (alimentary thyrotoxicosis, exogenous thyrotoxicosis). In the cases of Karnosh and Williams and of Thompson, just cited, thyrotoxicosis was of this type. The diagnosis is plain enough if the patient is being treated for obesity with large doses of thyroid extract. But when the condition is self-induced and derives from a psychopathic personality, the history may be unhelpful or positively misleading.

In both spontaneous thyrotoxicosis and thyrotoxicosis factitia the serum protein-bound iodine is high. The systemic effects of exogenous and endogenous thyroid intoxication are, of course, the same. In the former definite eye-signs are lacking unless the patient has suffered from Graves' disease in the past. Further there is no goitre. The patient's own thyroid tends to be atrophic due to pituitary inhibition (Chapter I). Hence radio-iodine collection by the gland is minimal; almost the whole of the administered tracer dose is excreted in the urine (Skanse and Riggs, 1948). Skanse and Riggs consider the combination of a high serum protein-bound iodine and a high urinary excretion of radio-iodine to be characteristic of alimentary thyrotoxicosis. Cessation of the drug and psychiatric treatment are called for.

Thyrotoxicosis factitia should be considered in all patients with clear-cut thyrotoxicosis in whom goitre is lacking. The diagnosis will be confirmed by the absence of radioactivity (other than background) in the neck following a test dose of radio-iodine. A toxic struma ovarii is however a remote possibility under the same conditions. Hyperadrenalinaemia due to phaeochromocytoma may also simulate thyrotoxicosis but the protein-bound iodine and radio-iodine uptake are normal.

Neurosis and psychoneurosis associated with thyrotoxicosis. Functional nervous disease is not as commonly associated with florid states of thyrotoxicosis as with simple goitre; but both hysteria and anxiety neurosis do occasionally co-exist with the former condition. We have known one patient whose history was dominated by such neurotic symptoms as " a feeling that the heart has been turned round," that her " toes, feet, legs, and, in fact, the whole body," were " icy cold at times." At other times she felt flushed and hot; she was sleepless, depressed and tearful, and complained that her stomach would often " work as if full of electric wires." Yet, on physical examination, the presence of severe thyrotoxicosis was unquestionable. Disturbances of sensation in thyrotoxicosis will, on close inquiry, usually be found to depend on associated hysteria. In such patients psychic

trauma is often a prominent feature in the history. The personality is also psychopathic.

In some patients, there is a mélange of thyrotoxicosis, functional nervous disease, hypertension, and menopausal symptoms. It is then difficult or impossible to estimate the relative importance of each factor in the clinical state. Accordingly, each should be treated as well as may be, for if attention be confined solely to the goitre, the end result will often be unsatisfactory.

It is to the follow-up clinic or to those patients in whom the goitre is simple, or, at most, slightly toxic, that we must turn to find the best examples of neurosis or psychoneurosis associated with thyroid disease. The combination of simple goitre and functional nervous disease may simulate the thyrotoxic state.

To the surgeon, nervousness plus goitre too often mean unquestioned thyrotoxicosis. To the psychiatrist, however, nervousness can and does mean a symptom secondary to physical ailment or to any one of the neuroses or psychoses. As Bateman (1943) points out, nervous tension, sweating, palpitation, tachycardia and even increased metabolism are not always indicative of hyperthyroidism. A rapid pulse is sometimes found in effort syndrome, functional nervous disease or in the schizophrenic reaction-type. Should simple goitre co-exist, as often happens in an endemic area, a part of the thyroid will generally be removed, but afterwards the pulse remains rapid and the patient eventually drifts into the hands of a psychiatrist. Bateman analysed 380 such cases, collected from among the thyroidectomized patients attending the Ohio State Mental Hygiene Institutions.

The surgeon's task here is to see beyond the goitre to the psycho-physical constitution of the patient. A careful history and physical examination will usually reveal a psychopathic personality, or the physical inadequacy of effort syndrome. Consultation with a physician or psychiatrist should be sought in doubtful cases. As Ficarra (1946) remarks, the care of the borderline hyperthyroid patient is a problem in psychosomatic medicine.

A period of rest in hospital, away from the patient's usual environment, will often render clear the differential diagnosis between thyrotoxicosis on the one hand and simple goitre plus anxiety neurosis on the other. Valuable confirmatory evidence may be obtained from biochemical investigations (see Chap. XVI). The differentiation is important because thyroidectomy often gives exceedingly poor results in neurotic patients, and leads to chronic invalidism.

Organic reaction-types of mental disorder associated with thyrotoxicosis. Where thyrotoxicosis occurs with the manic-depressive psychosis, schizophrenia, epilepsy, paranoia or the paranoid states, a previous psychopathic personality may be assumed. This will often be ascertained by inquiring into the family or personal history. A history of paranoid tendencies or " a nervous breakdown with delusions " may be elicited.

In the extroverted cyclothymic type the psychophysical response to thyrotoxicosis is generally predictable, prompt and complete. The hypomanic cycloid becomes manic. In introverted schizoids, however, there is a lack

of uniformity in the response, and a lack of harmony between the mental and physical states. Thus, though hypermetabolism may be marked, there is a complete absence of emotional or physical reaction. Lahey (1931) describes these patients as manifesting " apathetic thyroidism " as opposed to " the activation type." Of course, it is not a question of different types of thyrotoxicosis, but of the different types of personality on which it has developed.

Ostenfeld (1944) claims that thyroid disorders are abnormally frequent in psychopathic subjects, especially those with depression or the manic-depressive state. Man and Kahn (1945), however, were unable to find any special tendency to thyroid dysfunction in manic-depressive psychotics, on the basis of serum-iodine studies. In fact, the development of thyrotoxicosis in long-standing psychotics is merely fortuitous.

Some of the important factors in assessing the relationship of thyrotoxicosis to the psychotic state are the following:

(i) The chronological relationship of the two disorders.

(ii) The severity of the thyrotoxic state. Other things being equal, the more severe the thyrotoxicosis, the more urgent is the need for its effective control, and the greater the benefit afterwards.

(iii) The character and time of onset of the mental disease. Provided insanity has not clearly ante-dated thyrotoxicosis, the prognosis is never hopeless. Intervals of lucidity are a favourable sign. In the management of these patients the surgeon should clearly work in the closest association with the physician and psychiatrist.

(iv) When the psychosis develops at a time remote from thyroidectomy, it is unlikely to be benefited by other than psychiatric treatment unless hypothyroidism or myxoedema exists.

It is established (Karnosh and Williams, 1934) that there is a much higher incidence of psychotic disorder in myxoedema than in thyrotoxicosis. It is usually a depressive state, often mild in character, accompanied by inactivity, apathy, or moderate paranoia (Bieringer, 1944). Untreated, it leads to premature dementia, but with reasonably early treatment the prognosis is good. Thyroid therapy must be persisted in, however, for otherwise there is a very strong tendency to relapse.

It may be repeated also that functional nervous disorder is more often seen after thyroidectomy than during the florid state of the disease. Such disorder appears more prone to develop where the scar is imperfect or where injury to the recurrent nerves has caused persistent laryngeal symptoms. There are many complaints, of the scar, of difficulty in swallowing and speaking, and of a general state of ill-health and lack of strength.

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CHAPTER XIV

OTHER SYSTEMS IN THYROTOXICOSIS

The Skeletal Muscles in Graves' Disease — The Skeletal Changes in Thyrotoxicosis — Ovarian, Adrenal, and Pancreatic Changes — The Thymus and Lymph Glands — The Pathology of the Liver — Changes in the Blood Picture — Cutaneous Manifestations of Thyrotoxicosis.

1. The Skeletal Muscles in Graves' Disease

A sense of utter physical exhaustion is common in severe thyrotoxicosis and even in the mild degrees the skeletal muscles suffer. The basic chemistry of muscular contraction is deranged. The following disorders may be differentiated:

1. Thyrotoxic myopathy.
2. Non-hyperthyroid myopathy of Graves' disease.
3. Thyrotoxicosis and myasthenia gravis.
4. Thyrotoxicosis and periodic paralysis.

The expression, *thyrotoxic myopathy*, is used here to signify the generalized muscular weakness and wasting commonly occurring in thyrotoxicosis and associated with creatinuria; it is quickly relieved by thyroidectomy. The expression, *chronic thyrotoxic myopathy*, has generally been employed to describe patients in whom muscular weakness was either very severe or out of proportion to the degree of thyrotoxicosis. Its application has thus been purely arbitrary and, since in any case some degree of myopathy is an inevitable consequence of hyperthyroidism, we prefer to use the inclusive term, thyrotoxic myopathy, and to distinguish mild, moderate or severe degrees of the process.

A second disorder of the skeletal muscles also occurs; it may be termed the *non-hyperthyroid myopathy of Graves' disease*. It manifests itself clinically in ophthalmoplegia. It is not relieved by thyroidectomy and appears to be directly related to the basic hormonal disturbance of Graves' disease.

Thyrotoxic myopathy; clinical aspects. Weakness and a sense of fatigue amounting sometimes to sheer exhaustion, are common complaints in thyrotoxicosis. The contrast with myasthenia gravis is of some interest. In thyrotoxicosis the weakness is continual and not benefited by a period of rest. Patients will say that they feel tired even on rising in the morning. In myasthenia gravis, of course, rest causes marked, if temporary, improvement.

Weakness of the arms, " shakiness," or " giving way " of the knees, is the usual complaint. Various degrees of invalidism result. But it is remarkable how some patients with severe thyrotoxicosis continue working and even

maintain that they feel quite well. This is a consequence of euphoria and demonstrates the power of mind over matter. In continued severe thyrotoxicosis, however, the working capacity usually dwindles and the patient is ultimately unable to continue her occupation because of weakness. Wasting, tremor, and generalized loss of muscular power are a very constant triad of physical signs. Wasting is detectable in the quadriceps extensors at an early date and later spreads to all muscle groups but, like the weakness, it remains most marked in the muscles of the trunk, shoulder and hip girdles. Coarse fasciculation is rare except when the myopathy is severe (Ayer *et al.*, 1934). It is peripheral in origin since it persists after anaesthetizing the corresponding motor nerve (McEachern and Ross, 1942).

Tremor is probably indicative of neuro-muscular fatigue. The classical type is a fine tremor, best seen when the patient raises the upper limbs from the sides to the horizontal with the fingers outstretched. If she realizes that the tremor is being examined, a coarse component may be superadded and the picture obscured. The tremor is also greatly exaggerated under stress, or after muscular effort. In one of our patients, a mechanic, shakiness of the hands became uncontrollable when people stood by watching him repair a machine; he would have to make some excuse to stop his work and come back to it later when they had gone.

According to Chavát and Silink (1934) muscular weakness is the earliest physical sign in thyrotoxicosis and is as constantly seen as an elevation in the basal metabolic rate. Systematic testing of the grip and the thigh muscles (Lahey, 1926) demonstrates the frequency of weakness in thyrotoxicosis.

In the thigh test the patient sits on a chair and holds the leg up horizontally. A normal subject can hold the limb up steadily in this way for about a minute, but in thyrotoxicosis gross tremor develops in about twenty seconds and the limb is soon afterwards lowered to the floor. Sometimes it cannot even be raised to the horizontal. Thyrotoxic myopathy is a direct thyroxine-muscle effect; it is promptly relieved by thyroidectomy.

In experiments on rats, Diaz-Guerrero *et al.* (1947) showed that thyroxine therapy weakens the response of the gastrocnemius-soleus muscles to faradic stimulation of the tibial nerve. The muscles also fatigue rapidly, probably due to changes in neuro-muscular transmission. Confirmatory experimental results have been obtained by Cox (1948).

Total muscular efficiency in thyrotoxicosis. The cost of work is high. Boothby and Sandiford (1923) found that thyrotoxic subjects use about twice the normal number of calories to do a given amount of work; in other words the mechanical efficiency of the human " machine " was reduced from the normal 25 per cent. to about half this figure in thyrotoxicosis. There is some evidence to support Thaddea's suggestion (1929) that the faulty muscle economy is due to deficient reconversion of lactic acid to glycogen in the muscles after contraction. At all events, it is not a simple consequence of the raised metabolism since patients with leukaemia in whom the basal metabolic rate may be quite high do not manifest it (Briard *et al.*, 1935).

The biochemistry of thyrotoxic myopathy. The weakness and muscular wasting of thyrotoxicosis are believed to be related to a defect in the metabolism of creatine. This substance is known to be intimately concerned with the contraction of skeletal muscle (Fig. 76).

Normal male adults do not excrete creatine in the urine and though

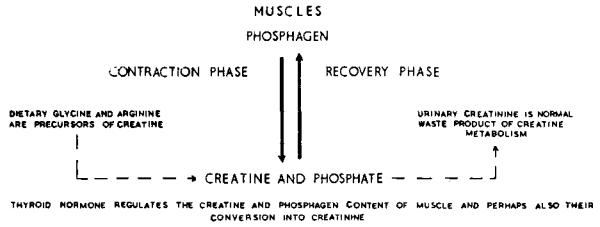

FIG. 76.

females do excrete it intermittently the amount is so small, save during the puerperium, as to be insignificant. In thyrotoxicosis creatinuria occurs very regularly. It also occurs in a wide range of other diseases associated with muscular wasting, and in heart failure.

The typical findings in thyrotoxicosis are illustrated in the histogram (Fig. 77). The creatinine excretion for a normal male adult is about 1·2 gm.

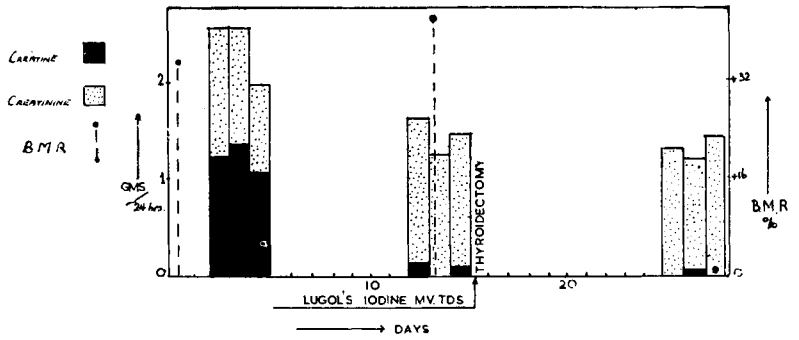

FIG. 77.—Creatinuria—male, aged 41. Diagnosis: severe thyrotoxicosis. Iodine therapy controls creatinuria in thyrotoxicosis as do thiouracil and thyroidectomy.

daily and this is seen to be unaffected. The excretion of creatine on three successive days prior to commencing iodine was 1·2, 1·3 and 1·0 gm. but on the eighth, ninth and tenth days of iodine therapy, the values had fallen to a negligible level, namely 0·1, 0·0 and 0·06 gm. respectively. Palmer, Carson and Sloane (1929) noted the marked diminution in urinary creatine which follows the administration of iodine. On the eleventh, twelfth and thirteenth days after sub-total thyroidectomy there was still no definite creatinuria though

iodine had been suspended during the post-operative period. Clearly, thyroidectomy was also effective in controlling creatinuria.

Precisely how an excess of thyroid hormone causes myasthenia and creatinuria is not known. The creatine evidently comes from the skeletal muscle, and Wang (1939) found that both their creatine and phosphagen contents were reduced by thyroxine therapy in the rabbit. Thyroidectomy increased the muscle stores of both substances. The synthesis of creatine itself is not affected by thyroxine therapy (Wilkins and Fleischmann, 1946). The high blood creatine and creatinuria may derive from both breakdown of the muscle protoplasm and interference with the enzyme normally promoting phosphagen synthesis in the recovery phase of muscular contraction. Steroid hormone deficiency may be a contributory factor when myopathy is very severe (Thorne and Eder, 1946).

HISTOLOGY OF STRIATED MUSCLES IN THYROTOXICOSIS

Author	Year	Number of observations	Findings
Askanazy	1898	4	Severe atrophy and degeneration of fibres; proliferation of muscle nuclei.
Dudgeon and Urquhart	1926	9	Muscle atrophy. Lymphorrhages in 8 out of 9 cases. Changes most marked in ocular muscles.
Eppinger	1937	15	Some fibre degeneration, capillary thickening and pericapillary oedema.
Liechti	1938	13	Changes neither marked nor specific. Lymphorrhages only in three cases.

In addition to creatinuria there is usually diminished creatine tolerance in thyrotoxicosis. Both the presence of creatinuria and the diminished tolerance have been claimed to be of diagnostic value (see Chap. XVI). Creatinuria, of course, occurs in a variety of other conditions but the fact that it is completely controlled by thiouracil distinguishes that due to thyrotoxicosis (Schrire, 1948).

Histology of the Muscles. As long ago as 1898 Askanazy described fatty degeneration and fatty infiltration together with atrophy of the muscle substance in thyrotoxic subjects coming to post-mortem. Atrophy of the muscle fibres is associated with proliferation of the sarcolemma nuclei.

It should be emphasized, however, that the histological findings may be scanty and disappointing even when severe thyrotoxic myopathy has been present before death. Further, the changes noted as occurring in thyrotoxicosis are non-specific, being the usual manifestations of degeneration in skeletal muscle (Tower, 1939).

The table summarizes the histological findings reported in thyrotoxicosis.

It will be noted that the occurrence of lymphorrhages has often been described. It is true that well-defined lymphorrhages are regularly found in the extra-ocular muscles in thyrotoxicosis even when eye-signs have been lacking before death. But they are much less common in the skeleton muscles generally.

Illustrative case of severe thyrotoxic myopathy. The patient, a woman aged thirty-nine, had had symptoms of thyrotoxicosis for just over a year, and had noticed a " paralysed feeling " in the legs for the past four months. This had become steadily worse. She could not rise from the floor or a chair unaided and constantly needed support when walking because on several occasions her knees had given way under her completely. One week prior to admission she had suddenly lost all power in the right hand.

Examination showed profound generalized wasting most evident in the shoulder and hip girdle regions but also extreme in the extensors of the elbows and knees, and in the hands.

Both eyes could be shut but were easily forced open. The jaw and neck muscles appeared fairly strong. Shoulder movements could not be made against slight resistance. All active movements of the more distal segments of the limbs were much more easily overcome than normal Active dorsiflexion of the right wrist was lost and there was no real " grip " in either hand.

Both triceps and the left supinator jerks were indeterminate. The knee jerks were hard to elicit. Other reflexes appeared slightly exaggerated.

Coarse fasciculation was present in the deltoid and pectoral regions on both sides and in the buttocks. There was some tenderness in the muscles of the thighs and calves, but no spontaneous pain.

The thyroid gland was diffusely and considerably enlarged and over it a well-marked thrill and bruit were present. Eye-signs were negative apart from very slight lagging of the upper lids. Rapid auricular fibrillation was present without appreciable congestive failure. The other signs indicated a severe degree of hyperthyroidism. She became restless and confused mentally and in spite of a good response to iodine died from intercurrent bronchopneumonia.

A total of twenty-two sections was taken from the muscles of the orbit, neck, trunk and limbs. The most marked degenerative changes were found in the levator palpebrae superioris. Elsewhere the changes were those of simple fibre degeneration, nuclear proliferation and slight fatty degeneration.

Non-hyperthyroid myopathy of Graves' disease. This includes the ophthalmoplegia which is described in detail with the other ocular manifestations in Chapter XV. It is usually associated with exophthalmos. Like exophthalmos, ophthalmoplegia may be most severe when hyperthyroidism is slight or absent (Rundle and Wilson, 1944). It is possible that the agent responsible for ophthalmoplegia also affects the other skeletal muscles though the upset in them is insufficient to produce clear physical signs.

It is interesting that in the published cases of severe thyrotoxic myopathy, exophthalmos and other eye-signs have usually been absent. Alternatively, ophthalmoplegia and exophthalmos have developed only after thyroidectomy has completely relieved the thyrotoxic myopathy, as in McEachern and Ross's highly significant case.

Thyrotoxicosis and myasthenia gravis. Myasthenia gravis and thyrotoxicosis have thymic enlargement, as well as myasthenia, in common. Excision of the enlarged thymus is said to relieve myasthenia gravis (Blalock, 1944). Clearly the myasthenic defect may be related to thymic hyperplasia and it is thus not surprising that thyrotoxicosis should sometimes be associated with a myopathy having myasthenic characteristics. Thus McEachern and Ross (1942) report two thyrotoxic patients in whom myopathy was

TABLE XVI

MYOPATHIES IN GRAVES' DISEASE

	Thyrotoxic Myopathy	Non-Hyperthyroid myopathy of Graves' disease	Myasthenia Gravis
Effect of thyroidectomy	Relieves	Unchanged	Unchanged
Maximal impact on	Muscles of trunk and proximal muscles of limbs	Extrinsic eye-muscles	Muscles innervated by cranial nerves
Prostigmine	No effect	No effect	Temporary striking benefit.

It should be emphasized that considerable overlapping of these three myopathies may occur.

severe and was partially relieved by prostigmine. The patients did not actually have myasthenia gravis because they showed no weakness or fatiguability of the muscles innervated by the cranial nerves. Moreover, thyroidectomy relieved the myopathy.

In patients with palatal weakness and other signs suggestive of cranial nerve involvement, as in Sanderson's case (1948), the possibility of co-existing myasthenia gravis should always be considered and a diagnostic test made with prostigmine. There are some twenty-five cases reported in which thyrotoxicosis has been combined with myasthenia. Then thyroidectomy only relieves the hyperthyroid component of the myopathy. In one of Thorn and Eder's cases the prostigmine requirement was still 15 mg. per day six-and-a-half years after thyroidectomy, though it had dropped steadily. But the myasthenia gravis may become worse after control of thyrotoxicosis as in the cases reported by Thorner (1939) and Cohen (1946). Fortunately a therapeutic trial with thiouracil may now be made and the advisability of permanent control of thyrotoxicosis may thus be determined.

Finally there are cases like that of Sheldon and Walker (1946) where thyrotoxicosis appears to bring out a myasthenic anlage; thyroidectomy greatly relieves the myasthenia but prostigmine can only be discontinued several months afterwards.

Thyrotoxicosis and periodic paralysis. Periodic paralysis is a rare affliction characterized by attacks of flaccid paralysis associated with a reduction of the serum potassium. Shinosaki (1926) first drew attention to the frequent association of thyrotoxicosis with periodic paralysis. Seven of his twenty-four patients had Graves' disease. He also confirmed Mitchell's earlier

observation (1899) that thyroid feeding will precipitate attacks in susceptible persons.

The mechanism of periodic paralysis has been carefully investigated by Aitken *et al.* (1937), and Allott and McArdle (1938). It seems clear that the serum potassium level is abnormally low during the paralytic attack and that this lowering can be produced by the administration of large amounts of glucose by mouth or by the injection of insulin or adrenaline. It is possible that in these patients there is a defect in the metabolism of hexose-phosphate within the muscles, and that an excess of thyroid hormone aggravates this defect. In Seed's case (1947) the paralytic attacks were controlled by the administration of propylthiouracil but re-appeared, together with thyrotoxicosis, when the drug was discontinued, only to disappear again on its resumption.

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2. The Skeletal Changes in Thyrotoxicosis

Clinical aspects. As early as 1891, von Recklinghausen reported the case of a young woman of twenty-two who, in addition to severe thyrotoxicosis, suffered from pain in the back and in both arms. At post-mortem extreme rarefaction of many of the bones was noted. The cortices of the

long bones were everywhere marked by vascular striae. All the bones could be sawn like rotten wood and the sternum and calvaria were readily cut with a knife.

Puppel *et al.* (1945) and de Brux and Curie-Seimbres (1946) both mention muscle, joint and bone pains as occurring in thyrotoxicosis but, in general, osseous rarefaction is silent clinically. Without any warning in extreme cases, spontaneous fracture occurs. The patient is usually past middle age and thyrotoxicosis is of long standing. A noteworthy feature is that the fractures are often multiple, and most commonly affect the long bones, the ribs and vertebrae. " Crush " fractures of vertebrae occurred in two cases reported by Bartels and Haggart (1938). In both cases fractures were multiple. In Gottlieb and Schachter's case (1937) there were also multiple fractures.

It is of interest that in children with thyrotoxicosis the bones may show accelerated growth with premature ossification (Parker, 1949). These changes occurred in a six-year-old girl studied by Lederer (1946). There were also premature dentition and the usual negative calcium balance and signs of osteoporosis.

Radiological aspects. Kummer (1917) was apparently the first to note decalcification of the bones radiologically. Dunlap and Moore (1929) confirmed that osteoporosis affects all the bones, but is most readily discerned in the skull and ribs and in the bones of the extremities. In the long bones it is most marked in the epiphyses and towards the ends of the diaphyses. The loss of calcium varies. When it is pronounced the bony shadow is faint, the trabeculae are ill-defined, and the normal architecture of the bone is lost. In some places the cortex of the bone may have disappeared (de Brux and Curie-Seimbres, 1946). In the generality of cases, however, osseous decalcification is slight and only demonstrable in controlled radiograms (Golden and Abbott, 1933).

Calcium and phosphorus metabolism in thyrotoxicosis. Aub (1929) showed that the calcium excretion in thyrotoxicosis is as much as 231 per cent. greater than normal. There is a proportionate increase in the excretion of phosphorus, which agrees with the radiological evidence that tertiary calcium phosphate is lost from the bones. Aub's view was that the thyroid hormone acts directly on the bones, mobilizing their calcium and phosphorus.

Other workers, however, have suggested that the progressive demineralization of the skeleton depends on an associated hyperparathyroidism (Hansman and Fraser, 1938). Thus Hansman found that small doses of X-rays to the neck converted the usual negative calcium balance of these patients, to a positive balance. The therapeutic irradiation was insufficient to lower the metabolic rate, and presumably therefore had not affected the output of thyroid hormone. The most likely explanation seemed that it had controlled a mild associated hyperparathyroidism.

Robertson (1942) has produced strong evidence that the excess of thyroid hormone present in thyrotoxicosis acts directly on the kidney, lowering the renal threshold for calcium. The raised excretion of phosphorus is secondary to the change in calcium excretion. Robertson bases his theory on the fact

that in untreated thyrotoxicosis the serum calcium is lower than normal and the urinary excretion of calcium is greatly increased, while the output in the faeces remains sensibly normal. The mechanism of the osseous decalcification is thus a *vis a fronte*, the rapid urinary loss of calcium, lowering the serum calcium, and this, in turn, causing calcium to be mobilized from the bones in an attempt to restore the normal level.

Thyroidectomy causes a significant rise in the serum calcium and inorganic phosphorus levels, associated with sharp decreases in the urinary excretion of calcium and phosphorus, and their negative balances before treatment. On the other hand, thyroid therapy in myxoedema produces a distinct rise in the urinary output of calcium, a fall in the serum calcium level, and, if therapy is pushed, a negative calcium balance.

In view of the markedly negative calcium and phosphorus balances in untreated thyrotoxicosis, Robertson (1941) advocated, as part of the treat-

TABLE XVII

BLOOD-SERUM STUDIES IN THYROPARATHYROID DISEASES
(*From Robertson*, 1942)

	No. of Cases	Serum Calcium		Serum inorganic phosphorus		Calcium X Phosphorus Product
		Mean	Range	Mean	Range	
		(Mg. per 100 c.cm.)				
Normal controls	60	10·39	9·9–11·1	3·83	3·1–4·8	39·8
Untreated thyrotoxicosis	14	9·71	9·1–10·8	3·17	2 –3·5	30·8
Thyrotoxicosis after subtotal thyroidectomy.	14	10·52	9·8–11·2	3·74	3·2–4·7	39·3
Untreated Myxoedema	9	10·51	9·8–11·2	3·93	3·5–4·5	41·3
Treated Myxoedema	9	9·85	9 –10·6	4·22	3·8–4·7	41·6
Parathyroid Tetany	10	6·83	3·4– 8·7	5·64	4·4–8·4	38·5
Hyperparathyroidism	8	12·35	13·3–16·7	1·87	1 –2·6	26·8

ment of this disease, the administration of calcium in sufficient doses to raise the intake well above the normal optimum of 1 gm. daily, and even further in thyrotoxic women who are pregnant. Puppel *et al.* (1945) maintain that 3 gm. of calcium should be given daily if the depleted calcium stores are to be restored. The phosphorus requirements are similarly increased and vitamin D should be added to promote calcium absorption by the bowel. Of course, speedy and effective control of hyperthyroidism is highly desirable, and is a necessary preliminary to the treatment of any fracture or deformity that may have occurred.

Morbid anatomy and histology of the bones. The normal homogeneous, ivory-like cut surface of the cortex is lacking in thyrotoxicosis. Instead, the compact bone is interrupted by narrow, red striae and rows of dots, which indicate abnormal vascularity and resorption of bone. The spongy, vascular medullary bone appears to encroach on the compact cortex. The macerated and dried long bone in thyrotoxicosis is surprisingly light compared with

the corresponding normal bone. The corticalis is seen to be greatly thinned and porous, the medullary cavity is enlarged, and its bony trabeculae are markedly slender and lace-like.

Histologically the compact lamellar structure of the cortex and its mosaic arrangement of Haversian systems are almost entirely lost; instead, the cortex resembles a spongework not sharply distinct from the marrow. Its interstices are rich in blood vessels and filled by haemopoietic marrow (Fig. 78). The trabeculae themselves are narrow and irregularly arranged. Osseous resorption is perivascular in distribution. Osteoclasts are seen in large numbers in suitably prepared sections.

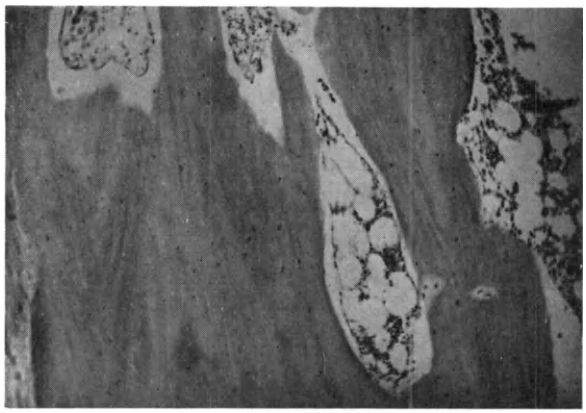

FIG. 78.—Section of sternum from a patient dying of severe thyrotoxicosis which was of more than eighteen months' duration. (× 3.)

Martos (1938) was able to reproduce this bony decalcification in rabbits and guinea pigs by prolonged thyroxine therapy. The inner aspect of the cortex was most attacked and here the osteoclasts occurred in rows within the lacunae; the Haversian canals were six to eight times wider than normal. Sponginess was most marked at the site of the tendinous insertions, but was sometimes seen throughout the femur and tibia.

Martos correctly emphasizes that the bone changes are not in any way specific to thyrotoxicosis, but are those normally found in hyperaemic decalcification, which may derive from a multitude of causes.

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3. Ovarian, Adrenal and Pancreatic Function in Thyrotoxicosis

Pregnancy and the thyroid gland. The thyroid gland undergoes hyperplasia during pregnancy and, during the later months, there is a gradual rise in the basal metabolic rate (Sandiford and Wheeler, 1924). Peters, Man and Heinemann (1948) have obtained some rather exciting data from their studies of the precipitable serum iodine during pregnancy. The precipitable iodine rises sharply at the onset of pregnancy from the normal 4–8 gamma per cent. to 6–10 gamma per cent., and remains at these levels until delivery, after which it rapidly returns to normal. Failure of the precipitable iodine to rise leads to early miscarriage and, though such patients present none of the clinical signs of hypothyroidism, such miscarriage can be prevented by administration of thyroid extract.

There is little doubt that the increased precipitable iodine in pregnancy is circulating thyroid hormone, though its increase in the blood is not associated with any of the other manifestations of thyrotoxicosis. It is even doubtful whether it is responsible for the rise in metabolism, since this occurs only late in pregnancy.

In the experimental animal, complete thyroidectomy has frequently been shown to cause sterility but once pregnancy has been established thyroidectomy usually does not interrupt it (Krichesky, 1939; Pawik, 1948). In man miscarriages and a tendency to habitual abortion are frequent accompaniments of dysthyroidism.

Thyrotoxicosis occurring in the pregnant woman presents no special feature, but its intensity may be affected variously; fortunately, in most cases its degree remains static or lessens slightly. Indeed, patients with mild or moderate thyrotoxicosis tolerate pregnancy remarkably well, but occasionally in toxic diffuse goitre there is a progressive intensification of hyperthyroidism and crisis ultimately supervenes.

The toxaemias of pregnancy occur more frequently in patients suffering from thyrotoxicosis (McLaughlin and McGoogan, 1943). Close supervision is therefore necessary throughout the pregnancy and should be continued into the puerperium, since, following childbirth, the clinical course of the thyrotoxicosis may be modified sharply in the direction of improvement or exacerbation.

The pregnant woman with thyrotoxicosis thus presents an individual problem. Where thyrotoxicosis is mild, medical management may be used to carry her through the pregnancy and childbirth. If it is more intense, thyroidectomy should be performed. It is a sound general rule that it is the

thyrotoxicosis and not the pregnancy which should be interrupted. Mussey, Haines and Ward (1948) affirm that the standard treatment of hyperthyroidism by iodine and thyroidectomy can be carried out safely in the great majority of cases. We agree that there is no particular contra-indication to thyroidectomy in the pregnant woman. Anti-thyroid drugs may also be used with advantage in preparing the patient for operation.

Lactation and the thyroid gland. Robinson (1947b) has shown that failure to establish lactation normally during the puerperium is often due to a deficient production of thyroid hormone. In women whose daily output of milk was very low, thyroid extract or thyroxine often more than doubled it. Further, the rate of increase in output was most rapid in subjects given large doses of the dried extract (9–12 gr. daily). While thyroid therapy was continued, the output of milk remained high but it decreased sharply after cessation of treatment.

These subjects showing deficient lactation manifested no clinical signs of hypothyroidism and further studies suggested that the deficient lactation was due, not to an under-active thyroid gland, but to an inadequate iodine intake (Robinson, 1947a). It is possible that lactation increases the demand for the hormone and that this can only be met if the iodine intake is abundant.

Libido. The libido which might be expected to increase with the rise of metabolism in thyrotoxicosis generally does not do so. Indeed, in men, actual impotence may develop. The effect of thyrotoxicosis on the gonads is not well understood but it is clear that thyrotoxic women are less fertile than normal. The same has not been shown for thyrotoxic men.

Menstrual function. Menstruation is often unaffected in mild and moderate thyrotoxicosis, but this is rarely so in severe thyrotoxicosis, which is characterized by scanty and irregular periods (Russell and Dean, 1942; Riisfeldt, 1948).

Indeed, nearly 60 per cent. of Russell and Dean's severe cases had amenorrhoea. We agree with Hoet and Lederer (1946) that menorrhagia also may occur in severe cases, though this is admittedly rare. Menstrual function is more likely to become deranged in patients over thirty years of age. Occasionally the menstrual anomaly is the first symptom of thyrotoxicosis (Riisfeldt, 1948).

Laurent-Gerard and Welti (1939) found that the urinary oestrin was subnormal in six thyrotoxics, four of whom had amenorrhoea. Following thyroidectomy the menses returned and the oestrin excretion was increased. The preceding menstrual habit had been normal in a very high proportion of thyrotoxics studied by Gardiner-Hill (1929) which suggests that as far as the pituitary-gonad axis is concerned, there is no indication of an abnormal endocrine background for the disease.

Following thyroidectomy, the great majority of women in whom there has been menstrual irregularity return to a normal habit. Oddly enough, the habit occasionally becomes abnormal for the first time after thyroidectomy; this is, of course, more likely to occur when the operation is followed

by hypothyroidism. On the other hand post-operative myxoedema is ofte 1 associated with an increased flow which at times is so great as to simulate an incomplete abortion and produce secondary anaemia (Thompson *et al.*, 1947). Regardless of the type of menstrual disturbance in hypothyroidism, the giving of thyroid extract fortunately tends to correct it. Amenorrhoea, however, may not be relieved by thyroid therapy, even though the patient is below the age of the menopause.

Thyroid-adrenal interrelations. Since the classical experimental work of Marine and his colleagues over twenty-five years ago which suggested a functional relationship between the thyroid gland, the adrenal, and the gonads, this difficult problem has been persistently attacked by endocrinologists, but their results have been confusing and without much bearing on clinical work.

Certain clinical data may, however, be taken as established even if their significance is ill-understood. It appears that there is a decreased excretion of 17–ketosteroids in the urine in thyrotoxicosis (Fraser *et al.*, 1941). Williams (1947) noted in the course of examining thyrotoxic patients that their axillary hair was scanty. Of 102 consecutive patients, fifty had little or no axillary hair at all. The amount of axillary hair is known to be largely govered by the androgenic function of the adrenals (Albright *et al.*, 1942; Kepler *et al.*, 1943). Williams found that the axillary hypotrichosis had nearly always ante-dated thyrotoxicosis. It is possible that the decreased axillary hair is associated with some endocrine imbalance predisposing to the development of thyrotoxicosis. Conversely, hirsuties is occasionally a feature of myxoedema and may disappear with thyroid therapy (Hurxthal and Musulin, 1945).

In other patients, thyrotoxicosis is combined with the clinical and blood electrolytic changes characteristic of adrenal cortical insufficiency (Anderson and Lyall, 1937; Gitman *et al.*, 1943). Control of thyrotoxicosis may relieve all the manifestations of cortical insufficiency. A possible interpretation is that hyperthyroidism increases the demands on adrenal cortical function, so that where an insufficiency anlage exists, exhaustion soon follows.

Carbohydrate metabolism and diabetes in thyrotoxicosis. In thyrotoxicosis the fasting blood sugar level is often somewhat raised. Thus, John (1932) found that 6·88 per cent. of a series of 9,000 thyrotoxics had a high fasting blood sugar. A correspondingly diminished sugar tolerance exists in the majority of cases, and this affects all three of the monosaccharides. John (1930) found an abnormally high curve in 63·5 per cent. of 239 patients submitted to a glucose tolerance test. According to Chiba (1934) the height reached by the curve is proportional to the severity of the thyrotoxicosis. Thyroidectomy results in a return to the normal curve. In simple goitre there is no deviation from the normal.

Similarly, glycosuria is common. It depends on the impaired sugar tolerance and frequently also on a lowering of the renal threshold. According to John the threshold is reduced in about 80 per cent. of cases.

It is often difficult to distinguish between the lowered sugar tolerance and its associated hyperglycaemia and glycosuria, all of which may result from defective hepatic glycogenesis, and true diabetes associated with thyrotoxicosis.

Uncomplicated diabetes can usually be diagnosed when glycosuria is associated with a fasting blood sugar of 130 mg. per cent. or more, or with a non-fasting blood sugar of greater than 170 mg. per cent. But if thyrotoxicosis is present the special criteria proposed by Joslin (1934) should be observed, namely that unless the fasting blood sugar is 150 mg. per cent. or more, or the non-fasting blood sugar is greater than 200 mg. per cent., diabetes should not be diagnosed.

However, a single blood sugar test below 150 mg. per cent. does not exclude diabetes. To avoid error Allan *et al.* (1947) advise that normal or borderline blood sugar tests be repeated, if the urine contains more than 0·5 per cent. of glucose, or if it contains any glucose before breakfast. They also recommend that the blood sugar test be done after a liberal meal, since the fasting test may not reveal the pancreatic weakness. A glucose tolerance test provides further valuable information. Borderline cases should be kept under observation, and if thyroidectomy be performed, very close supervision is advisable during the period immediately following operation.

Incidence of diabetes in thyrotoxics. Allan *et al.* (1947) state that diabetes is about twice as common in patients with thyrotoxicosis (2–4 per cent.) as in the general population (1–2 per cent.). Regan and Wilder (1940) found an over-all incidence of 3·2 per cent. of diabetes among 5,353 patients with thyrotoxicosis. In toxic diffuse goitre the incidence (1·7 per cent.) was no higher than in the general population, but it was three times as high (5·6 per cent.) in cases of toxic nodular goitre.

Allan *et al.* (1947) produce interesting data to show that diabetes in patients with thyrotoxicosis is likely to be either unusually severe or unusually mild. In the former the insulin requirement is high, the disease progresses rapidly and stabilization is difficult. In the latter, only slight dietetic restrictions are needed to control hyperglycaemia and glycosuria. It is possible that true pancreatic deficiency exists in the former, whereas in the latter the defect is predominantly one of hepatic glycogenesis.

John found that the carbohydrate upset disappeared in about 70 per cent. of patients soon after thyroidectomy. The remaining 30 per cent. needed continued treatment for diabetes, and about one-third of these required insulin. Follow-up studies (Regan and Wilder, 1940) also show that if hyperthyroidism is satisfactorily controlled the expectation of life of these truly diabetic patients is about the same as that in the general run of diabetics. But those in whom hyperthyroidism is not controlled fare badly.

Reveno (1946) suggests that the prognosis for relief of, or improvement in, the diabetic state following control of thyrotoxicosis is distinctly more favourable in toxic nodular goitre than in toxic diffuse goitre. In the former thyroidectomy and thiouracil therapy are equally effective, in the latter,

though thyrotoxicosis is controlled, the associated diabetes seems to be little benefited.

When diabetic coma threatens or supervenes in the patient with thyrotoxicosis, the prognosis is serious. The onset of coma may be rapid and heroic doses of insulin may have relatively little effect. Allan *et al.* (1947) found it necessary to give one of their patients 2,600 units in twenty-four hours. After thyroidectomy, however, the patient's diabetes became mild and was later controlled by diet alone. Scriver (1948) also reports a remarkable example of insulin resistance in diabetes complicated by thyrotoxicosis. The patient was a woman of forty-one whose metabolic rate fell to +8 with pre-operative iodine, but whose fasting blood sugar level remained at 250 mg. per cent. in spite of 112 units of insulin daily. Following thyroidectomy, the blood sugar rose progressively and despite 100 units of insulin hourly, she gradually passed into coma and eventually died. There seems little doubt that thyroidectomy is occasionally followed by an exacerbation of the diabetic state and Regan and Wilder (1940) emphasize that this may occur even after thyroidectomy for coincidental non-toxic nodular goitre.

The mechanism of these disorders of carbohydrate metabolism has been the subject of much study. A diabetic state may be reproduced experimentally by subtotal pancreatectomy. Subsequent thyroid feeding produces different effects in the dog and rat (Houssay, 1944; 1946). In the pancreatectomized rat in which diabetes is already incipient, prolonged thyroid feeding may cause its complete disappearance; Houssay considers that this may be due to stimulation of the existing islets or to their new formation in the fragment of pancreas remaining. It is possible that in patients such as Scriver's (1948) the thyroid-pancreatic relationship is similar to that in the thyroid-fed pancreatectomized rat of Houssay, eradication of the hyperthyroidism aggravating the diabetic state.

On the other hand, in the pancreatectomized dog (Houssay, 1944) thyroid feeding, if continued for more than short periods, results in permanent damage to the islet cells, with resulting glycosuria, hyperglycaemia, ketonuria and fatty liver. Thyroid therapy also reduces the capacity of the pancreas to produce insulin in the intact dog.

Clearly, the effects in the dog agree, in the main, with the responses in man. Thyrotoxicosis may precipitate diabetes mellitus, where a diabetic anlage already exists, or may greatly aggravate existing diabetes. The raised level of tissue metabolism in thyrotoxicosis depends for its proper maintenance upon a proportionate increase in carbohydrate oxidation. It thus greatly increases the functional demands made upon the islet cells of the pancreas. Carbohydrate metabolism acts by " sparing " protein and by facilitating the oxidation of fats. Thus, if thyrotoxic subjects are given a carbohydrate-free diet for forty-eight hours, there is a marked increase in the blood ketone bodies (John, 1932).

Griffiths (1939) presents data suggesting that the thyroid hormone excites resistance to the action of insulin both in the liver and the muscles. This insulin resistance may exist in patients who manifest very severe diabetes

during the active stage of thyrotoxicosis but who show no sign of it subsequently. The possibility that hyperadrenalinaemia and sympatheticotonia raise the blood glucose level in thyrotoxicosis must also be mentioned.

John (1932) concluded that a big factor is the increased appetite and overeating in thyrotoxicosis. This imposes a great strain on the insulogenic apparatus which, if normal, can stand it well. But if lacking in reserve, it quickly becomes exhausted and diabetes results. Insulin resistance is doubtless an important factor in many cases. Houssay's experimental data also suggest that the thyroid hormone exerts an important though variable effect directly on the beta cells of the pancreatic islets.

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4. The Thymus and Lymph Nodes in Thyrotoxicosis

The occurrence of a relative lymphocytosis and a relative and absolute monocytosis in the blood of thyrotoxic patients is referred to elsewhere (see p. 234). Two independent investigations (Hammar, 1929; Young and Turnbull, 1931) have also established that the thymus is enlarged and hyperplastic in Graves' disease. The weight of the thymus in the various age

groups, and the proportion of it constituted by glandular tissue as opposed to fat, have been carefully measured, and the results are given in the tables.

TABLE XVIII

MEAN WEIGHT OF THYMUS IN THYROTOXICOSIS, COMPARED WITH NORMAL

Age-Groups in Years	Committee's Data. Mean weight of Thymus (gm.)		Hammar's Data. Mean weight of Thymus (gm.)	
	Graves' disease	Normal series	Graves' disease	Normal series
16–21	36·1 (3)	21·3 (35)	30·0 (4)	24·9 (18)
21–26	36·0 (7)	18·4 (29)	32·8 (2)	20·3 (24)
26–36	30·3 (7)	14·8 (39)	41·7 (19)	18·7 (30)
36–46	35·3 (6)	14·2 (25)	32·1 (10)	18·9 (12)
16–46	34·1 (23)	17·3 (128)	37·1 (35)	20·5 (84)

Numbers in brackets are the numbers of observations.

TABLE XIX

THE MEAN PROPORTION OF THE THYMUS, ESTIMATED TO BE GLANDULAR BY THE MICROSCOPE, IN THYROTOXICOSIS, COMPARED WITH NORMAL.

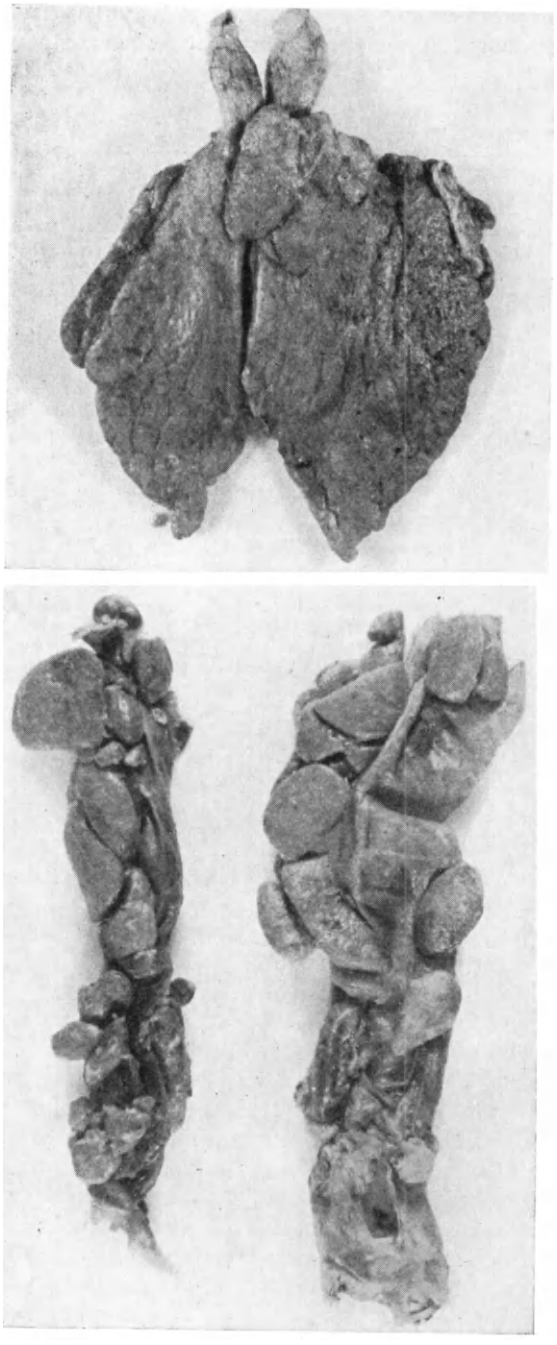
Age-Groups in Years.	Committee's Data. Mean Percentage of Thymus Glandular.		Hammar's Data. Mean Percentage of Thymus Glandular.	
	Graves' disease	Normal series	Graves' disease	Normal series
16–21	62 (2)	80 (3)	69 (4)	54 (18)
21–26	78 (5)	62 (5)	71 (2)	49 (24)
26–36	79 (4)	51 (4)	65 (19)	30 (30)
36–46	58 (1)	31 (5)	57 (10)	22 (12)
16–46	74 (12)	53 (17)	64 (35)	39 (84)

Numbers in brackets are the numbers of observations.

It is clear from these tables that in any thyrotoxic subject taken at random the thymus will be approximately twice the normal weight (Figs. 79 and 80), and will show an abnormal cellularity in stained sections.

Other lymphoid tissues, including the faucial tonsils, the cervical, axillary and inguinal lymph nodes, often appear to be enlarged (Fig. 79). The spleen is also occasionally palpable especially in young subjects with full-blown Graves' disease. Regression of tonsillar enlargement may be anticipated after thyroidectomy. For other reasons also control of thyrotoxicosis takes precedence over tonsillectomy when there is co-existing tonsillitis.

There is experimental evidence that the anterior pituitary governs thymic development and activity; the injection of T.S.H. in chicks produces thymic hyperplasia (Grégoire, 1941). Rawson *et al.* (1942) also found that the thymus and lymph glands, like the thyroid, inactivate T.S.H. *in vitro*. It is admitted however that the significance of thymic enlargement and hyperplasia in Graves' disease is quite obscure. There is no adequate evidence



FIGS. 79.—Thymus (74 gms.) and cervical lymph nodes in a female patient aged thirty-nine, dying from Graves' disease. She showed marked thyrotoxic myopathy. The cervical axillary and inguinal lymph nodes were palpably enlarged.

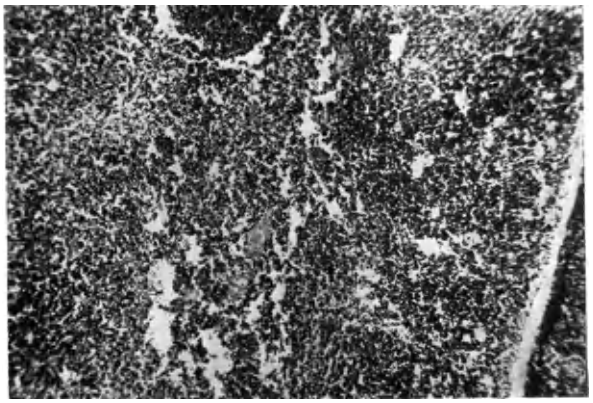


FIG. 80.—Section of thymus shown in Fig. 79. Both cortex and medulla show glandular hyperplasia. (× 3.)

either that a lymphatic constitution is characteristic of thyrotoxic patients or that the status thymo-lymphaticus is in fact a clinico-pathological entity.

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5. The Liver in Thyrotoxicosis

Jaundice has long been recognized as an occasional complication in severe thyrotoxicosis and Cameron and Karunaratne (1935) claim that about two out of three cases show post-mortem liver damage apart from chronic passive venous congestion which is, of course, common in the fibrillators. The characteristic lesion is a chemical hepatitis comparable to that produced

TABLE OF LIVER CHANGES IN EXOPHTHALMIC GOITRE.

(*Enlarged from Cameron and Karunaratne*, 1935)

Author	Date	No. of Cases	Clinical Jaundice and Pathology of Liver
PAUL . . .	1865	1	Cirrhosis.
TROUSSEAU . .	1868	2	Cirrhosis ("hypertrophic").
HABERSHON .	1874	1	Jaundice; fatty; "A bright yellow colour, anæmic, and in no way nutmegged"; weight, 74 oz.
EGER . . .	1880	1	Jaundice; liver markedly fatty; atrophy of left lobe.
HALE WHITE .	1886	1	Cirrhosis.
CLARKE (quoted by Buschan).	1887	1	Atrophy.

Author	Date	No. of Cases	Clinical Jaundice and Pathology of Liver
JACCOUD	1890	1	Jaundice; fatty.
BOETEAU	1892	1	Fatty.
BUSCHAN	1894	1	Fatty.
FARNER	1896	2	Atrophic cirrhosis.
ASKANAZY	1898	3	Cirrhosis; atrophy, with nutmeg liver; fatty change.
KOCHER	1902	1	Fatty.
GEBELE	1910	1	Cirrhosis.
LANDAU	1911	1	Cirrhosis, distinct from nutmeg change.
MARINE and LENHART.	1911	6	Thickening of Glisson's capsule; atrophic cirrhosis in 4.
MATTI	1912	5	Fatty in all, stasis in 1.
PETTEVAL	1912	4	Fatty; atrophy; cirrhosis. (Tuberculosis in 1 case.)
KERR and RUSK	1922	1	Jaundice; cellular necrosis and cirrhosis; weight, 1290 g.
RAAB and TERPLAN.	1923	1	Jaundice plus; genuine red atrophy; marked fatty change; weight, 1160 g.
YOUMANS AND WARFIELD.	1926	2	Chronic passive venous congestion and fatty change.
BARKER	1930	1	Small; areas of necrosis and stasis.
ASSMANN	1931	1	Jaundice plus; marked fatty change and atrophy; slight bile duct proliferation; marked stasis.
LEWIS	1931	12	Minor changes; in 1, cirrhosis.
ZIMMERMANN	1932	3	Fibrosis and atrophy.
HABÁN	1933–34	26	Passive venous congestion in 8; fatty change in 6; acute red and yellow atrophy in 2; cirrhosis in 10.
WELLER	1933	48	Eight had jaundice or icterus; slight chronic hepatitis in 16; well-marked chronic hepatitis in 26; no chronic hepatitis in 6.
RÖSSLE	1933	30	Average weight, 1225 g. (1) Acute changes—necrosis, fatty change, serous hepatitis. (2) Chronic changes—surface fibrosis, local atrophy and fibrosis, cirrhosis.
BEAVER and PEMBERTON.	1933	107	(1) Acute degeneration—fatty, focal and central necrosis. (2) Surface atrophy. (3) Subacute toxic atrophy and toxic cirrhosis.
MAHORNER	1934	3	"Severe liver damage." In one case, it weighed only 892 g.
CAMERON and KARUNARATNE.	1935	30	Average weight, 1157 g. (1) Passive venous congestion alone in 10. (2) No stasis, or stasis secondary in 20. Fatty change, atrophy and nodule formation, cirrhosis.
WEGELIN	1936	19	(1) Fatty changes. (2) Circulatory stasis.
ZELDENRUST and VAN BEEK.	1939	14	Chronic liver atrophy and cirrhosis; acute yellow atrophy; circulatory stasis.
SHAFFER	1940	24	Severe fatty change in 7; "Chronic localized interstitial hepatitis" in 20. Average liver weight reduced.
HILL	1943	1	Weight of liver was 900 gm. Severe centri-lobular fatty degeneration.
GUYE and RUTISHAUSER.	1947	*28	Cellular necrosis, fatty change and cirrhosis.

(*Includes data previously published by others.)

by a wide variety of toxic agents. The liver is often conspicuously reduced in size and weight at necropsy. It shows no deformity or nodule formation such as occurs in certain other types of cirrhosis. But its surface is often slightly adherent and rather granular. Its cut section shows thickening of the capsule with increased prominence of the portal canals and a fibrous tissue "striation." Fatty change may be exceedingly prominent.

When death has occurred after a prolonged period of cardiac failure the liver may be typically "nutmeg." In this case it will be increased in both

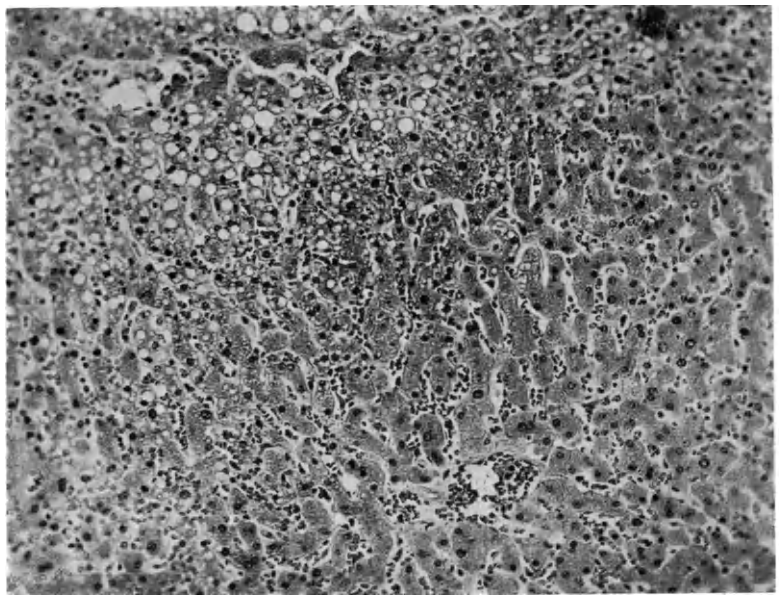

FIG. 81.—Fatty degeneration at the periphery of the lobule. Note central vein below. From a woman aged 36 who had suffered from severe thyrotoxicosis for many months and who died in crisis, after developing acute streptococcal tonsillitis. (× 150.)

size and weight and will be tough to the knife due to cardiac and thyrotoxic cirrhosis.

If large sections of the liver are prepared and studied histologically a remarkable variety of lesions may be seen in different areas. Acute changes include cellular necrosis and fatty degeneration. Necrosis may occur in small and scattered foci or involve considerable areas of the liver substance. In some livers the changes are equal in severity to those in acute yellow atrophy. Necrosis is most often demonstrable in relation to the larger portal canals. At the periphery of the foci of necrosis there is a variable degree of infiltration with endothelioid and immature connective tissue cells; foreign-body giant cells are sometimes seen. In some foci the protoplasmic debris

and giant cells have disappeared and all that is left is an aggregation of connective tissue cells. Atrophy of the liver columns towards the centre of the lobule is often marked.

Fatty degeneration of the hepatic cells may have a peri- or centrilobular distribution (Fig. 81). In the latter event it is usually associated with the other changes characteristic of chronic passive venous congestion.

Subacute or chronic changes are however much more often found in the thyrotoxic liver than the foregoing acute lesions. There are degeneration and

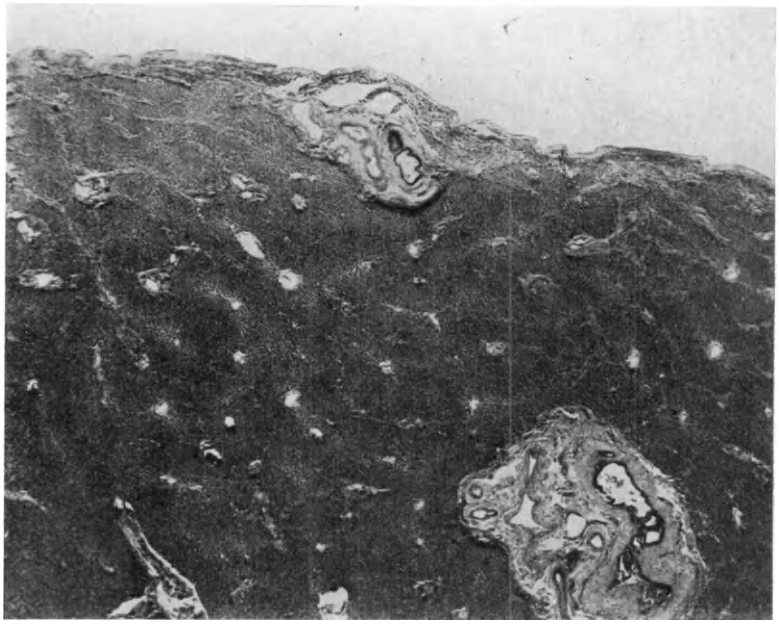

FIG. 82.—Surface atrophy and liver cirrhosis in thyrotoxicosis. Note the enlarged portal canals, one of which is " stranded " on the liver surface. From a patient aged forty-two who was admitted in a state verging on thyroid crisis and died shortly afterwards. (× 12.)

atrophy of the hepatic cells with replacement by fine connective tissue (thyrotoxic cirrhosis). This process is best observed immediately beneath the capsule and around the larger portal canals. The capsule is thickened and wrinkled and the portal canals are widened; general atrophy of the liver columns results in diminution in size of the lobule as a whole (Fig. 82). Consequently an unusually large number of liver units can be seen in the one field. The portal canals become linked by strands of fine connective tissue and these may surround many of the individual lobules. In fact the inter-insular and annular stages by which monolobular cirrhosis classically develops are well illustrated in some thyrotoxic livers (Fig. 83).

Thyrotoxic cirrhosis, however, differs from other monolobular cirrhoses in that parenchymal regeneration is inconspicuous; nodular masses of regenerating liver cells are not found post mortem. Beaver and Pemberton (1933) and Cameron and Karunaratne (1935) have emphasized this. It is perhaps relevant that thyroid feeding inhibits hepatic regeneration in the experimental animal (Davis and Whipple, 1919).

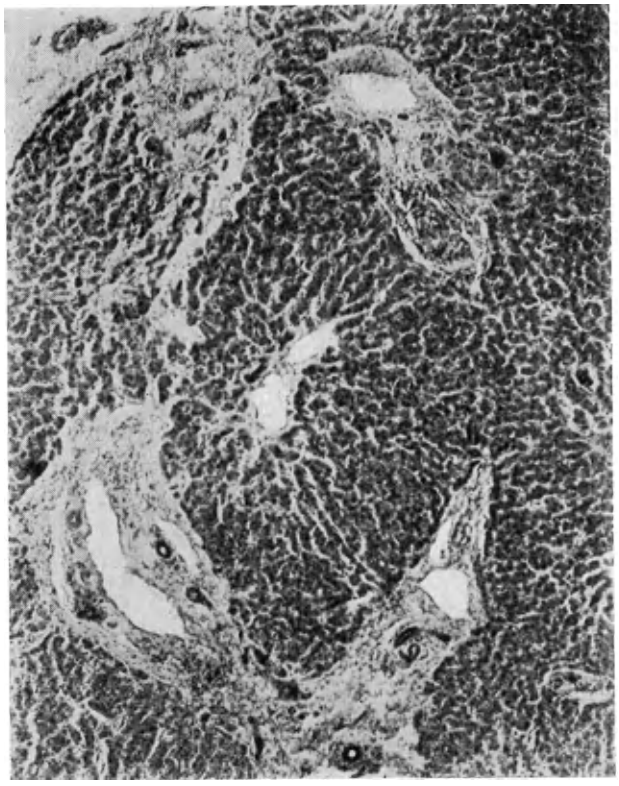

FIG. 83.—The inter-insular stage of thyrotoxic cirrhosis. (× 65.)

Farrant (1913) was one of the first to study the hepatic lesions produced by thyroid feeding in the experimental animal. Numerous workers have since confirmed that parenchymal lesions similar to those in thyrotoxicosis can thus be produced. When the dosage is heavy severe necrotic lesions are rapidly produced in the liver. Associated toxic inflammatory lesions increase the susceptibility of hyperthyroid guinea pigs to liver necrosis (Sealy and Lyons, 1949). When thyroxine therapy is light and long-continued, lesions corresponding to thyrotoxic cirrhosis in man are observed (Gerlei, 1937).

Fatty degeneration of any considerable degree rarely follows thyroxine therapy. It is readily produced, however, by injecting thyrotropic hormone in the guinea pig or chick. Its degree may be remarkable, the liver being the colour of yolk of egg. The lesions are acute and are seen in animals injected for only a few days. Indeed, a marked fatty infiltration of the rabbit's liver has been produced within twenty-four hours by the injection of a single large dose of anterior pituitary extract (Mukerji and Guha, 1938). This was confirmed in guinea pigs by Dobyns (1946).

Disorders of liver function in thyrotoxicosis. The thyroid hormone exerts a powerful inhibitory action upon hepatic glycogenesis from the circulating blood lactate and monosaccharides (Buell and Strauss, 1934). Hence characteristically there is an increase in blood lactate and a diminished sugar tolerance in thyrotoxicosis. Further, the raised metabolism of the tissues increases the demands upon the liver glycogen. Frazier and Frieman (1935) observed that even the addition of glucose to the standard diet of thyroid-fed guinea pigs fails to prevent depletion of liver glycogen. The skeletal muscle stores of glycogen are much less affected.

The diminished tolerance for glucose, laevulose, and galactose in thyrotoxicosis depends on interference with hepatic glycogenesis. Glucose and laevulose tolerance are lowered in some 60 per cent. of cases (John, 1930; Chiba, 1934). But to some extent these sugars are also handled by the muscles. Galactose on the other hand is converted into glycogen only by the liver (Mann, 1934), therefore a defective galactose tolerance occurs in a much higher percentage of cases, namely in about 85 per cent. (Maclagan and Rundle, 1940).

The excretory function of the liver as measured by the icterus index, the bromsulphthalein and other tests, is unimpaired in thyrotoxicosis. Thus the functional upset in thyrotoxicosis is quite different from that in many other types of toxic hepatitis.

The detoxicating function of the liver is, however, deranged as shown by a generally abnormal hippuric acid test (Boyce and McFetridge, 1938; Mills, 1942).

Decomposition and excretion of thyroid hormone. As stated in Chapter I, the thyroid hormone after undergoing a variable degree of decomposition in the liver cells is excreted in the bile. Thus, in thyrotoxicosis the liver plays a role of peculiar importance, any interference with which might greatly modify the severity of the disease. It is possible that in some severe cases a vicious circle becomes established, excess thyroid hormone damaging the liver cells, this damage in turn interfering with hormone elimination.

Clinical aspects of hepatic damage. Though post-mortem sections and tests of liver function, such as the galactose tolerance, indicate that the organ may be severely damaged in thyrotoxicosis, clinical evidence of this is usually lacking. Jaundice is very rare.

Clinical latency does not imply unimportance. Lahey (1935) expresses the view that in patients dying from hyper-acute thyrotoxicosis the decisive terminal factors are liver necrosis and failure. He draws attention to the

high temperature (105°–106° F.) and toxic jaundice which often precede death. Many authors, including Boyce and McFetridge (1938), consider that thyroid crisis is due to hepatic failure. It is possible that the vicious circle mentioned above operates in these cases. In other cases the sudden flooding of the system with increased amounts of hormone may precipitate fatal liver injury and failure.

The alimentary canal in thyrotoxicosis.—Gastro-intestinal secretion. The volume of saliva is diminished in thyrotoxicosis but its concentrations of sodium chloride and diastase are increased (Fabian and Lorentz, 1939).

Both the volume and acidity of the gastric juice are also decreased. In fact, thyrotoxicosis is one of the most important endocrine causes of achlorhydria and hypochlorhydria. Thus, of Louis and Wills' eighteen cases (1937), eight showed complete achlorhydria and seven hypochlorhydria. Eight to ten days after thyroidectomy, twelve of these fifteen cases showed a return to normal or an increase in the free acid in the specimens. There was a clear correlation between the basal metabolic rate, the gastric acidity and the blood bicarbonate and chloride. The volume and acidity of the gastric juice are also reduced by thyroid feeding in the experimental animal (Chang and Sloan, 1927; Moll and Flint, 1928).

By contrast, thyroxine therapy augments the rate and volume of jejunal secretion in the dog (Fink, 1944). The increase involves both the mucoprotein and the enzymes. The effect persists for a long time after cessation of thyroxine therapy.

The rate of absorption of monosaccharides from the small intestine remains normal in thyrotoxicosis (Moseley and Chornock, 1947). The same applies to the products of fat and protein digestion.

Gastro-intestinal hypermotility. There is general agreement that the rate of emptying of the stomach and the downward passage of intestinal contents are accelerated in thyrotoxicosis (Fabian and Lorentz, 1939; Fink, 1944). Thus, though the intestinal secretions and the mucosa are able to digest and absorb the food normally, its onward passage may be so hurried that much fluid and fat are lost in the faeces. In thyrotoxic diarrhoea, for example, the fat content of the stools is often doubled, though there are normal proportions of split and partially saponified fats. The findings are those of defective absorption and result from the abnormally rapid passage of the food through the intestines.

Shirer (1933) studied the gastro-intestinal motility in thyrotoxics by observing the passage of an opaque meal fluoroscopically. There was a general hypermotility of the whole gastro-intestinal tract, and though this could not be closely correlated with the severity of the disease, it was greatly decreased after thyroidectomy in three-quarters of the cases studied.

In some nervous patients, however, diarrhoea tends to recur, even though the thyrotoxic state has been fully controlled, being relatively more common in the pre-menstrual period.

Clinical manifestations. In some patients thyrotoxicosis may simulate gastro-duodenal disease. There are loss of weight, dyspepsia and even

vomiting. The more usual manifestations of thyrotoxicosis are latent. How far the dyspeptic symptoms are related to the defective gastric secretion is unknown. In other patients the symptoms are plainly those of " nervous " dyspepsia.

Vomiting and diarrhoea may occur and are ominous features in patients verging on thyroid crisis. In other patients diarrhoea with excess of mucus and fat in the stools is of longer standing. Such cases have been misdiagnosed, " ulcerative colitis with thyrotoxicosis."

The occurrence of upwards of five or six copious fluid motions daily is however not rare in patients with thyrotoxicosis. It is a feature which should never be taken lightly, since it is often associated with rapid loss of weight. The diarrhoea tends to occur in the mornings or after meals. It fortunately responds gratifyingly to control of the thyrotoxic state.

Some change in bowel habit is a regular feature of thyrotoxicosis; the stools tend to be looser. The usually costive patient will change to a regular daily habit or, where the latter has existed previously, two or three stools may be passed daily. The bowel habit tends to revert to normal after thyroidectomy.

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6. Haematology in Thyrotoxicosis[7]

Changes in the red blood cells and haemoglobin, as observed in blood films, merely reflect alterations in activity of the marrow tissue. The marrow findings in thyrotoxic patients have been investigated by sternal puncture (Jones, 1940; Bistrom, 1946). There is an increase in the percentage of nucleated cells to more than twice the normal number and this increase disappears after thyroidectomy. Jones (1940) claimed that the nucleated cells are immature granular cells, but according to Bistrom (1946), there is a percentage increase in the precursors of both erythrocytes and leucocytes. It is remarkable that this hyperplasia of the bone marrow in thyrotoxicosis is not reflected in the peripheral blood.

Gordon *et al.* (1946) observed the return of the blood picture to normal after bleeding rats. Thyroidectomy greatly delayed recovery of the blood picture but with thyroxine therapy the rate of return was normal, though thyroxine had little effect unless the animal had been thyroidectomized. Whether thyroid hormone acts directly on the blood forming tissue or indirectly through its effect on the general level of metabolism, is still an open question.

It has been found both in man (Hoskins and Jellinek, 1932) and in the experimental animal (Power, 1934; Latta and Benner, 1934) that thyroid therapy causes at first an increase and then a decrease in the total red cell count and haemoglobin percentage. This suggests that there is first hypertrophy and then a variable degree of toxic degeneration of the erythron. Thus Power, in his study of thyroxinized rabbits, found that the erythropoietic marrow was at first hyperplastic, but after prolonged thyroxine therapy, there were a poverty and degeneration of the erythropoietic cells.

At this stage the blood picture showed definite anaemia, characterized by a low colour index and reduced diameter of the red cells.

Different authors have reported the occurrence of erythrocytosis, a normal red cell count, and a mild or moderate anaemia in thyrotoxicosis. These apparently contradictory reports may merely coincide with different stages in the response of the bone marrow.

In a statistical analysis of 1,200 routine blood counts, in consecutive cases of thyrotoxicosis (McCullagh and Dunlap, 1932) the average results were as follows:

Red blood cells: 4,555,154 per cu. mm.
Haemoglobin: 82·5 per cent.
Colour index: 0·9.

The deficiency in the red cells and haemoglobin is therefore generally slight. However thyrotoxicosis may be complicated by one of the severe anaemias, e.g. Addisonian anaemia (Boenheim *et al.*, 1945). Such an association is probably fortuitous and if a satisfactory response is to be obtained specific treatment must be directed towards both conditions. However, Mulder and Mulder (1947) have recorded two such cases in which lasting cure of the pernicious anaemia followed thyroidectomy alone.

The white blood cells. The supravital staining technique used by Hertz and Lerman (1932) renders possible a clear differentiation of the large lymphocyte, the monocyte, and the transitional polymorphonuclear cell, a distinction which cannot always be made in ordinary fixed smears. They found that 80 per cent. of normals have counts below this level, indicating a definite tendency to leucopenia in thyrotoxicosis.

The total number of lymphocytes was about normal in thyrotoxicosis, but because the neutrophil count is lowered by about 12 per cent., there is a relative lymphocytosis. The eosinophils and basophils are unchanged in thyrotoxicosis. In fact, apart from neutropenia, no striking change has been reported in the granular leucocytes, though Gottlieb (1933) observed a shift to the right of the Arneth index.

Nearly all patients with thyrotoxicosis have high monocyte counts, the average figure being raised to about three times the normal value. The raised monocyte count is lowered by iodine therapy. If the view that the monocyte is part of the reticulo-endothelial apparatus be correct, then Hertz and Lerman's counts suggest that this system is activated in thyrotoxicosis.

Potentially important disorders occur in the bleeding and coagulation times in thyrotoxicosis. Bechgaard (1946) investigated the coagulability of the blood in fifty patients with thyrotoxicosis, and showed that there are a significant decrease in the prothrombin level and an increase in the coagulation time. He suggests that the decrease in the blood prothrombin is due to liver damage. The increase in coagulation time is not, however, closely correlated with the lowering of the blood prothrombin; some other factor must play a part. Nor could any relationship be determined between the amount of bleeding at thyroidectomy and the previous laboratory findings.

Ziffren *et al.* (1942) also found the blood prothrombin level reduced in two patients with thyroid crisis. In fact, in one, which was fatal, the prothrombin level was only 16 per cent. of normal, and this author too ascribed the decrease to liver damage in thyrotoxicosis.

Woodruff (1940) has reported an interesting case in which thrombocytopenic purpura co-existed with thyrotoxicosis. All the classical features of the former condition were present, namely, spontaneous haemorrhages, a greatly prolonged bleeding time and low blood platelet count; the coagulation time was only very slightly prolonged. From the history, thyrotoxicosis appeared to have preceded the purpura and thyroidectomy fully relieved both conditions. Thrombocytopenic purpura is known to develop in severe toxaemias, and it may well be that an excess of thyroid hormone can be a sufficient cause.

Woodruff went on to examine the blood platelets in a series of unselected thyrotoxics, and found that their average number was considerably lower than in his normal control group. Their variance was also considerably greater. He concludes that the excess of thyroid hormone in thyrotoxicosis produces a toxic depression of the thrombocyte forming tissues, which, when exaggerated, may result in thrombocytopenic purpura. Conklin and Shank's case (1944) provides supporting evidence.

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7. Cutaneous Manifestations in Thyrotoxicosis

The thyroid gland is intimately concerned in heat regulation and thyrotoxicosis is constantly associated with excessive heat production. In the normal subject about three-quarters of the total heat produced by the body is lost in the skin by radiation and conduction. The remaining quarter is lost by the evaporation of water from the skin and lungs. Laroche, Saidman and de Zuloaga (1936) showed that in thyrotoxicosis the skin temperature is clearly greater than normal being roughly correlated with the basal metabolic rate. The skin temperature was raised in all localities tested but the greatest elevations were found on the trunk and lower limbs. Roberts and

Griffith (1937) from counts of the cutaneous capillaries also found that their number is significantly increased in thyrotoxicosis. Further, Inui (1938) showed that the skin capillaries do not contract as vigorously as those of normal subjects on the direct application of cold stimuli. Such observations would explain the pathological sense of heat often experienced by thyrotoxics when the environmental temperature is unpleasantly cold to normal subjects.

The warm skin of thyrotoxicosis and the cold skin of myxoedema are too well known clinically to need emphasis. The skin is also moist in thyrotoxicosis, both the sensible and insensible perspiration being increased. The proportion of the total body heat lost by the evaporation of water from the skin and lungs is increased to nearly 50 per cent. in thyrotoxicosis (Coller and Maddock, 1933). Normal subjects of course behave similarly when the metabolic rate is raised; an approximately linear relationship exists between the basal metabolic rate and the insensible perspiration (Benedict and Root, 1926).

Abelin (1940) has shown that the administration of thyroid extract to rats diminishes the fat content of the skin. As a poor conductor of heat, fat normally protects the organism against undue heat loss, and this decrease in hyperthyroidism may facilitate such loss and thus render possible the maintenance of a normal body temperature despite hypermetabolism. In Abelin's hyperthyroid rats also an increased cholesterol content could be demonstrated in the skin. This increased cholesterol enables the skin to imbibe more water and then to secrete it as sweat, the increased water content of the skin being associated with a corresponding increase in its chloride content.

Myxoedema circumscriptum thyrotoxicum. This name has been recommended by Cohen (1946) for the myxoedematous thickening to be found in the pretibial skin and less often in that of the posterior aspect of the calf of some patients with Graves' disease. This remarkable complication is rather rare. Both Dunhill (1935) and Trotter and Eden (1942) estimate its incidence at 3 per cent. They suggest that it may be produced by the same factor as is responsible for exophthalmos. It develops equally, before or after thyroidectomy. In some patients in whom the lesion first appears after thyroidectomy the metabolic rate is normal or lowered. Thus, it cannot be directly related to excessive secretion of thyroid hormone. On the other hand, it does not occur apart from present or past thyrotoxicosis. In one of our patients it developed five years after the onset of thyrotoxicosis and concomitantly with severe postoperative exophthalmos. Three thyroidectomies had been done previously, two for re-growth of the gland fragments. Such a case which agrees with others in the literature suggests a connexion with the basic hormonal disturbance of Graves' disease.

The pathology and clinical features of the condition have been admirably reviewed by Trotter and Eden (1942). Histologically the connective tissue fibres of the cutis are widely separated by a homogeneous material which has been identified as mucin (Carol, 1932). A glairy fluid can be seen exuding from the cut surfaces when the biopsy is performed and sections stained with

thionin-blue show that the substance separating the fibres stains pink, a reaction specific for mucin. Chemical analysis shows it to be rich in the mucopolysaccharides, hyaluronic acid and chondroitin sulphuric acid (Watson, 1946).

Pretibial myxoedema may be associated with a slight aching or tingling of the affected area, but its development is insidious, the lesion being usually well established by the time it is noticed clinically. It occurs usually as an extensive cutaneous thickening on the antero-lateral aspect of the lower half of the leg. It is bilateral from the beginning or becomes so eventually. The skin and subcutaneous tissues are swollen, the swelling being uniform and leathery, or irregular and lumpy (Fig. 84). Occasionally there are three or four

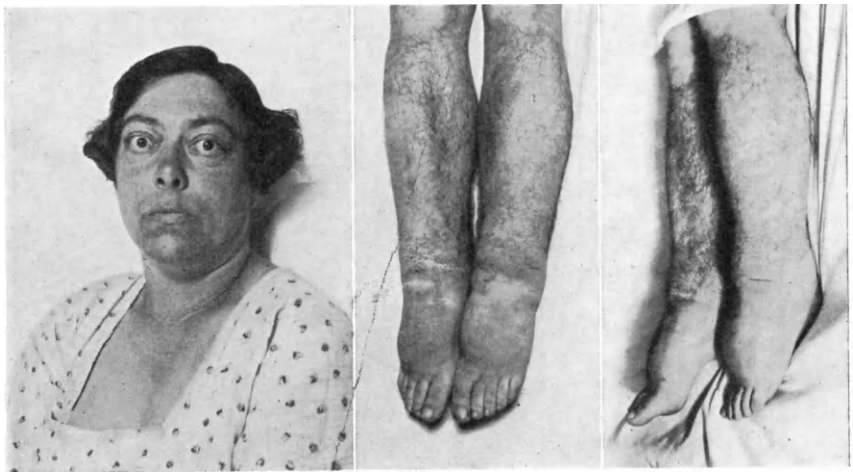

FIG. 84.—Localized pretibial myxoedema. The patient, aged forty-one, was operated on for severe thyrotoxicosis in October 1935. One year later she reported that both legs had become swollen and hairy.

smooth, painless lumps the size of hen's eggs (Schrire, 1948). The area affected may be markedly hairy, or have a characteristic "pig-skin" appearance and convey a leathery impression to the touch. It is a pinkish, brownish or waxen colour. Temperature and sweating are unaffected.

No effective treatment for these lesions is known. They cause little disability, however, and seem to disappear spontaneously, or at all events to diminish in size over a period of years (Linnell and Piercy, 1949). Dunhill claims that in many of his patients in which the condition was associated with active thyrotoxicosis, thyroidectomy benefited it, but other observers have found no apparent effect from thyroidectomy. Cohen (1946) has reported a case in which thiouracil therapy was without effect on the lesion, though it controlled coexisting hyperthyroidism.

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CHAPTER XV

THE OCULAR MANIFESTATIONS OF GRAVES' DISEASE

Historical Sketch — Definitions and Anatomy of Exophthalmos — Bulging of the Lids — Diagnosis and Varieties of Exophthalmos — Retraction of the Lids in Graves' Disease — Ophthalmoplegia — Morbid Anatomy and Histology of the Retro-Bulbar Tissues — Ophthalmic forms of Graves' Disease — Natural History of the Ocular Changes — Effect of Thyroidectomy on the Ocular Changes — Pathogenesis of the Eye Changes — Treatment of Malignant Exophthalmos.

The ocular manifestations comprise one of the most fascinating aspects of Graves' disease. Together they pose a challenging problem in aetiology. They are also of the greatest significance in diagnosis. Finally, the " malignant " degrees of exophthalmos call for considerable skill and judgment in treatment.

Historical sketch. Parry (1825), who first described thyrotoxicosis, noticed that " the eyes were protruded from their sockets." Basedow (1840) paid much attention to the ocular phenomena, noting that one of his patients " slept with the eyes open, and by no effort could they be closed." In another, " both eyes were lost as the result of corneal ulceration." Naumann (1853) reported the association of ophthalmoplegia with exophthalmic goitre.

In 1858 and 1859 H. Müller described the retrobulbar and palpebral plain musculature found in man and other mammals. Wagner (1859) and H. Müller (1860, 1861) stimulated the cervical sympathetic trunk in human heads after execution. Mydriasis and widening of the palpebral fissure occurred in both cases. Wagner reported no exophthalmos and Müller also said that no definite exophthalmos followed. Unverricht (1925) proved by stimulating the cervical sympathetic trunk in the living human subject, with an exophthalmometer *in situ*, that no exophthalmos occurs in man. Bristowe (1885) examined the orbits in a patient dying from exophthalmic goitre; " there was a good deal of fat in the orbits, the ocular muscles were unusually pale and seemed stretched."

Claude Bernard (1852) first described the exophthalmos that follows stimulation of the cervical sympathetic trunk in the experimental animal. Broddaert (1894) studied experimentally the effect of cervical sympathectomy, and ligation of the external and internal jugular veins, and the common carotid artery. McCallum and Cornell (1904) confirmed Broddaert's work and showed graphically that venous obstruction or sympathetic stimulation caused measurable protrusion of the eyeball in the experimental animal.

Burch (1929), Zimmermann (1929), Naffziger (1931, 1933, 1938, 1948), and Thomas and Woods (1936) have given prominence to a severe form of exophthalmos often occurring in euthyroid or hypothyroid patients and

termed by Ruedemann (1936), " malignant exophthalmos." Naffziger has devised an orbital decompression operation to prevent loss of vision and sloughing of the eye in this condition.

Loeb and Friedman (1932) produced exophthalmos in the guinea pig by the injection of extracts of the anterior pituitary lobe of cattle. Smelser (1936, 1939) showed that anterior pituitary exophthalmos in the guinea pig is due to a measurable increase in the bulk of the retrobulbar contents of the orbit. Pochin (1944) demonstrated that this type of exophthalmos is equal in normal and thyroidectomized animals and is quantitatively accounted for by oedematous swelling of the orbital tissues.

Pochin (1938, 1939b) has also contributed a detailed account of the clinical aspects and mechanism of lid retraction in Graves' disease. Ophthalmoplegia in Graves' disease and the bulging of the eyelids occurring with exophthalmos have been similarly described by Rundle and Wilson (1944a, 1944b). Data on the natural history of exophthalmos and ophthalmoplegia were collected by Rundle (1945b).

TABLE XVIII

TABLE OF EYE SIGNS AND ORBITAL TISSUE CHANGES

Eye Sign	Orbital Tissue Changes
1. Lid retraction (retraction of the upper lid)	Spasm of the striated levator palpebrae superioris.
2. Protrusion of the eyeball (exophthalmos) and lids	Enlargement of the orbital tissues due to deposition of fat in classic Graves', ? oedema in " malignant exophthalmos ".
3. Ophthalmoplegia	Fatty and round cell degeneration in extrinsic eye muscles.

Rundle and Pochin (1944) made a detailed quantitative analysis of the orbital contents in a series of seventeen thyrotoxic patients coming to post-mortem. They were able to relate exophthalmos to a bulk increase of the orbital contents which could be accounted for by deposition of fat in the orbital fibro-fatty tissue and eye muscles. Interest now centres chiefly on the local mechanism of " malignant " exophthalmos; and, of course, little is known concerning the factors ultimately responsible for these orbital changes in both the classic and " malignant " forms of Graves' disease.

Definitions. The term *exophthalmos* is used here synonymously with *proptosis* to mean abnormal protrusion of the eyeball relative to its usual position in the subject concerned. It can hardly be over-emphasized that the prominence of the normal eye varies over a wide range the apex of the cornea normally lying in a plane from 10–23 mm. beyond the lateral orbital margin, so that a patient with a reading, in health, of 14 mm. may develop 4–5 mm. of exophthalmos and still have a measurement well within

the normal range. It is often wrongly assumed that exophthalmos can be diagnosed or excluded by comparing a single reading from some patient with the general average value, 17 mm., but clearly, because of the wide normal range, this is not so, except in extreme cases.

The Hertel exophthalmometer is best used for measuring ocular prominence. When it rests in position on the lateral orbital margins, the eye is seen in profile against a millimetre scale. As the eye protrudes the reading increases, and conversely. An actual reading of ocular prominence constitutes the best record of the patient's status on any particular visit. Serial readings, if plotted, give the level and trend of the exophthalmos.

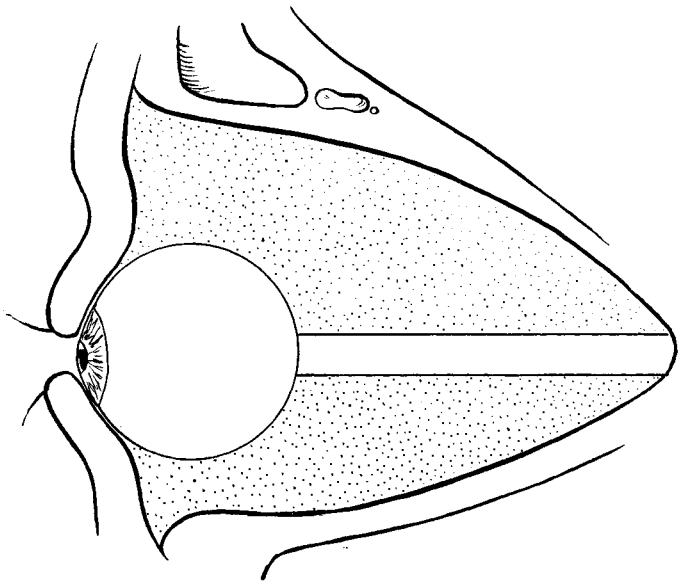


FIG. 85.—Orbit in section. The bony cavity is closed posteriorly and enlargement of the orbital contents results in displacement of the globe and lids forward. (Rundle, 1947).

The readings should be made with a standardized technique and preferably by the same observer.

It is clear that the term *exophthalmos* as used in patients with Graves' disease has rarely been employed in an exact sense and it is probably true to say that the diagnosis of exophthalmic goitre has generally depended on the presence of any one of the many eye signs rather than strictly on exophthalmos itself and toxic goitre. The multitudinous eponymous eye signs mainly relate to one or other aspect of three basic changes:

(i) Lid retraction, or more precisely, retraction of the upper lid relative to the cornea.

(ii) Protrusion of the globe and lids due to enlargement of the orbital tissues.

(iii) Ophthalmoplegia resulting from degeneration of one or more of the extrinsic eye muscles (Table XVIII).

The anatomy of exophthalmos. In a sense, the eyeball and lids are just parts of a mobile anterior diaphragm for the orbit (Fig. 85). Behind this diaphragm the cavity is filled by the fibro-fatty tissues, the extrinsic muscles, the lacrimal gland and the small blood vessels and nerves. The orbit is a

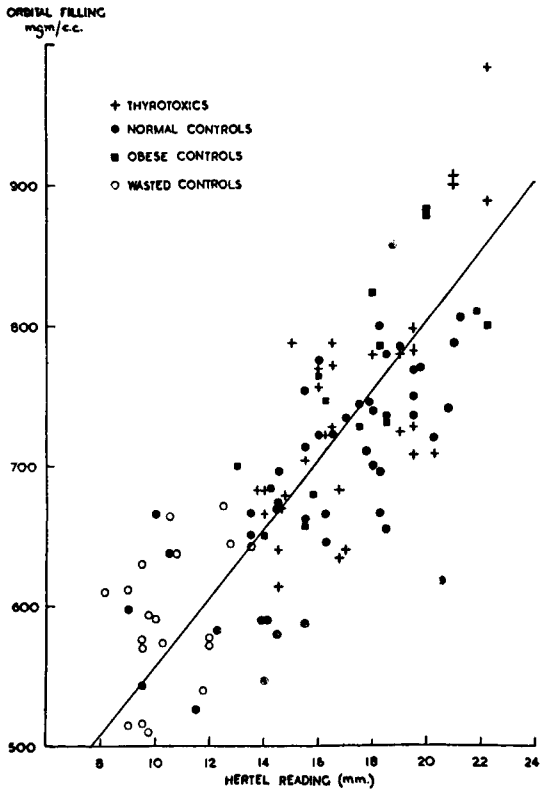


FIG. 86.—Hertel exophthalmometer reading in millimetres plotted against degree of orbital filling, in mg. orbital tissue per c.c. of orbital volume, for thyrotoxic and control cases. Each point represents one orbit. (Rundle and Pochin, 1944.)

closed cavity posteriorly; only this anterior diaphragm is mobile and distensible.

In control subjects, measurements before and after death show that the eye recedes by about 2·5 mm. with the onset of rigor mortis. In thyrotoxics with exophthalmos, recession also occurs but is no greater than the 2·5 mm. occurring in controls. In effect, therefore, thyrotoxic exophthalmos persists post mortem which shows that it cannot be due to a locally raised vascular pressure or to muscular spasm.

Fig. 86 shows the relationship between ocular prominence and the degree of orbital filling, in different types of subjects. The degree of orbital filling (mg./c.c.) was taken as the ratio of the bulk of the retro-bulbar tissues to the volume of the orbital cavity. It is clear that the greater the degree of orbital filling the greater the prominence of the eye and conversely. Compared with normal subjects, wasted patients have a sunken eye and decreased

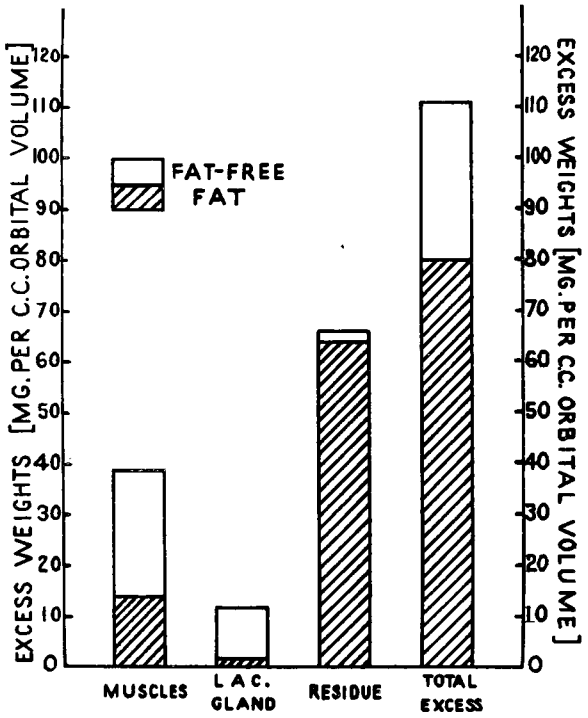


FIG. 87.—Distribution and analysis of excess bulk of the orbital tissues in exophthalmic thyrotoxics. (Rundle, 1947.)

orbital filling whereas in obese subjects the eye is a little more prominent than normal due to slight enlargement of the orbital tissues. In thyrotoxics with exophthalmos the highest readings were obtained for both exophthalmos and orbital filling. The points from all the orbits analysed lie roughly on the same line and it seems clear that the position of the eye depends simply on the degree of orbital filling, and that exophthalmos is caused by an increase in this filling. This in turn depends on enlargement of the contents, not contraction of the volume of the orbit.

The water and fat contents of the different orbital structures have been determined in thyrotoxicosis by chemical analysis (Rundle and Pochin, 1944). The results in patients with exophthalmos are summarized in the histogram

(Fig. 87). Seventy per cent. of the increase in bulk of the orbital tissues in exophthalmic thyrotoxics was found to be due to fat. Roughly three-quarters of this fat comes from the fibro-fatty residue. The rest is from the muscles. There is some non-fatty enlargement (fat-free component) of the eye muscles and lacrimal gland and this accounts for the remaining 30 per cent. of the total excess.

It is remarkable that deposition of fat occurs in the orbit in view of the fact that thyrotoxics, especially those coming to post-mortem, are in general wasted. Similar chemical analysis of the orbital tissues in other forms of wasting shows that the sunken eye and decreased orbital filling are associated with a marked *loss* of fat from the fibro-fatty tissues and eye muscles.

Examination of the water content of the orbital structures showed no evidence of orbital oedema in thyrotoxic exophthalmos (Rundle and Pochin, 1944). But this must not be taken to imply that oedema of the orbital tissues does not occur in " malignant " exophthalmos. As far back as 1920, Moore reported finding oedema of the orbital fat and extrinsic eye muscles in a patient with very severe proptosis. Naffziger and others, in the course of decompression operations on the orbit, have since repeatedly observed that the contents were greatly swollen and seemed oedematous. Quantitative evidence of the oedema has recently been obtained by chemical analysis of snippets from the orbit in a case of malignant exophthalmics (Rundle, unpublished data).

The bulk increase in orbital contents corresponding to different degrees of proptosis has been determined precisely by observing the results of injecting wax into the retrobulbar space post mortem (Rundle and Wilson, 1944b). In the early stages of the resulting curve of exophthalmos, 1 mm. of proptosis results from a bulk increase of 0·75 c.c. So, even a considerable exophthalmos of some 6 mm. would be caused by as little as a 4·5 c.c. bulk increase. Since the average exophthalmos in a group of unselected thyrotoxics is only about 2 mm. the bulk increase of the orbital tissues is only about 1·5 c.c. Compare this 1·5 c.c., or rather the 70 per cent. of it which is fat, with the 12 gm. of recognizable fat in the normal orbit and it is clear that the increased fat content in the general run of thyrotoxics could not be demonstrable without recourse to careful quantitative analysis.

Bulging of the lids in Graves' disease. When wax is injected into the retrobulbar space post mortem there is concomitant protrusion of the globe and lids. In a wasted subject, the lids from being sunken become normal and then bulged. Ultimately the bulging is extreme. Concomitantly with the gradual overfilling of the orbit, changes are seen identical with those in progressive degrees of clinical ophthalmopathy.

There is a simple anatomical explanation for this concomitant protrusion of the globe and lids associated with overfilling of the orbit in Graves' disease. The shape of the orbit is generally likened to that of a pyramid with rounded angles or to a cone. Towards its apex it is conical, but towards its base or outlet it fills like a cylinder; in other words the area of the protruding " face " of the orbital tissues is constant.

The tissues exclusive of the eye-ball normally fill the orbit to about 70 per cent. of its capacity. When orbital filling increases to 90 or 100 per cent., as it often does in Graves' disease, the whole anterior " face " of the orbital tissue moves forwards, so causing protrusion of both the lids and eye-ball.

The eye-ball and lids should, in fact, be regarded as interdependent parts of a mobile anterior diaphragm for the orbital contents. Thus, if the lids are lightly closed the eye-ball can easily be pressed back 2–3 mm. with the finger-tip. As the eye-ball goes back, the lids bulge forward. Since the orbit is a closed cavity posteriorly, when the eye-ball goes back the incompressible fatty tissue comes forward round it and bulges the lids. The eye-ball itself occupies less than one-half of the orbital opening, the major part being filled by the peribulbar tissues lying directly deep to the lids.

Similarly, when the orbital contents are enlarged fat herniates forwards and bulges the lids. The bulging is lumpy, since the herniation occurs through certain well-defined anatomical hiatuses. These are four in number: (i) between the superior orbital margin and the levator palpebrae expansion (ii) deep to the medial part of the upper lid around the terminal ophthalmic vessels (iii) deep to the lateral part of the lower lid, above the infero-lateral margin of the orbit and (iv) deep to the medial part of the lower lid above and medial to the inferior oblique muscle.

The degree of protrusion of the lids runs closely parallel to that of exophthalmos (cf. Fig. 89).

The plane of the eyelids. A general survey of the plane of the lids gives valuable diagnostic help in thyrotoxicosis. The upper lid is best observed with the eye lightly closed, the lower lid with the eye open and the gaze directed forwards. It can hardly be over-emphasized that the impression of a prominent eye or exophthalmos is often illusory. Sympathetic stimulation, though it does not cause exophthalmos, does retract the upper and lower lids, thus exposing an abnormal extent of the eye-ball's surface. Hence, in states of stress, anxiety or unusual animation the eye looks as if it is starting out of its socket, even though its position is unchanged. If the patient is then examined with the eyes lightly closed the plane of the lids is seen to be obviously normal. Thus orbital overfilling and exophthalmos can be excluded at once.

Protrusion of the lids associated with orbital overfilling and exophthalmos has often been confused with palpebral oedema. The latter is, of course, common, and occurs in the lax layer between the skin and the orbicularis oculi. It is, however, readily distinguishable from lid protrusion due to orbital overfilling. The oedematous lid pits on pressure but the protruded lid does not. Instead, in the case of the lower lid, the prolapsed orbital fat can be felt by the observer's finger-tip slipping back over the inferior orbital margin into the orbit. Again, oedema tends to affect the lid diffusely, whereas fatty protrusion may be localized. Even when it is generalized, it tends to be lumpy and most evident towards the orbital margins (Fig. 88).

In some patients with " malignant " exophthalmos protrusion may be

combined with oedema and pitting of the lids on pressure. Retraction of the lids in Graves' disease will be dealt with in a separate sub-section.

Diagnosis and varieties of exophthalmos. The diagnosis of unilateral exophthalmos presents little difficulty but it is admittedly a rare event in classical Graves' disease (Rundle and Wilson, 1945). The normal range of asymmetry extends up to about 3 mm. and beyond this the probability of exophthalmos on the more prominent side is very great. Unilateral retraction of the upper lid in Graves' disease which is not so rare is often misdiagnosed, " unilateral exophthalmos," because the lid retraction results in the exposure of an abnormal extent of the eyeball's surface, and this

FIG. 88.—Protrusion of the lower lid by prolapsing orbital fibro-fatty tissue. Note the peripheral distribution and lumpy character of the palpebral swelling. (Rundle and Wilson, 1944.)

creates the illusion of exophthalmos. Such an error may be avoided by routine examination of the plane of the lids with the eyes lightly closed. In simple unilateral lid retraction, no significant asymmetry exists.

If on the other hand, overfilling of the orbit is bilateral, the consequent exophthalmos may be difficult or impossible to diagnose because of the wide range in the normal prominence of the eye. Slight and moderate degrees of exophthalmos can only be established with certainty by reference to previous exophthalmometer readings, which will hardly ever have been made in health. Of course, when the reading is clearly outside the normal range, as with values of 25–30 mm., exophthalmos and orbital overfilling can be diagnosed, but then, too, they are abundantly obvious without recourse to exophthalmometry.

Due regard should be had to bulging of the lids. The bulging has well-defined characteristics and with a little practice, lids with slight, moderate, and severe degrees of bulging can be differentiated from those in a normal or sunken plane. The existence of moderate or considerable protrusion of the

lids is strong circumstantial evidence in favour of orbital overfilling, and of course this overfilling is likely to be pathological in a thyrotoxic patient who is otherwise wasted.

The chief varieties of exophthalmos and their mechanism are summarized in Table XIX.

It will be noted that, in contrast with its lack of effect in man, stimulation of the sympathetic trunk in the anaesthetized dog causes 4–5 mm. of proptosis (Essex and Corwin, 1937). This results from contraction of the muscular

TABLE XIX

VARIETIES AND MECHANISMS OF EXOPHTHALMOS

(*Modified from Rundle*, 1947)

Condition	Average extent of Exophthalmos	Causal Mechanism	
		General	Particular
Thyrotoxicosis	2 mm.	Orbital overfilling	Deposition of fat.
Ophthalmic type of Graves' disease	5 mm.	Orbital overfilling	? Deposition of fat + orbital oedema.
Anterior Pituitary Exophthalmos in Guinea Pigs	1–2 mm.	Orbital overfilling	Oedema of orbital tissues.
Carotico-cavernous fistula	14 mm.	Orbital overfilling	Oedema of orbital tissues.
Sympathetic stimulation in man	Nil	—	—
In cat and dog	1–5 mm.	Reduction in orbital capacity	Contraction of muscular orbital wall.
Orbital varix	18 mm.	Orbital overfilling	Distension of varix.
Orbital tumour	4–14 mm.	Orbital overfilling	Space-occupying lesion.

lateral orbital wall. This exophthalmos is thus due, not to an increase in tissue bulk, but to a reduction in orbital capacity. The stimulation is carried out under full anaesthesia which is associated with flaccidity of this muscular wall, and consequent recession of the eye. Sympathetic stimulation only serves to restore muscular tone, orbital capacity and ocular prominence to normal.

Retraction of the lids in Graves' Disease

Retraction of the lids is not a simple phenomenon. At least four varieties are distinguishable. Two or more may co-exist. (i) Retraction of the *upper* lid, due to spasm of the striated levator palpebrae superioris. This is referred to hereafter as *the spastic type of lid retraction.*

(ii) Retraction of the upper lid associated with paralysis of elevation also occurs, and is referred to as *the paralytic type of lid retraction.*

(iii) Retraction of both upper and lower lids occurs in sympatheticotonia, which may be associated with Graves' disease.

(iv) Finally, the effect of orbital overfilling *per se* on the level of the lid margins must be considered; it may lead to retraction of the lower lid.

(i) The clinical features and pathology of the spastic type of lid retraction have been accurately described by Pochin (1938, 1939b). They are most clearly seen in unilateral cases, for then the eyes and lids on the normal and abnormal sides can be compared in the same subject. The findings are shown diagrammatically in Fig. 89.

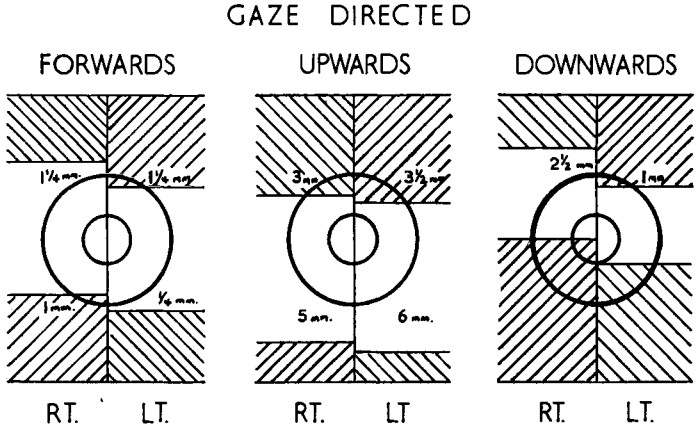


FIG. 89.—Clinical record of the position of the lid margins in a patient with unilateral (right-sided) lid retraction. Note relative elevation of right lower lid.

The upper lid is retracted so that its free border is raised and with the gaze directed forward a band of sclera may be exposed above the cornea. The difference in levels of the lids is greatest in full depression of the gaze.

The lower lid is slightly raised, relative to the cornea, when the eyes are directed forward. According to Pochin, this is probably due, not only to a slight actual elevation of the lower lid, but also to downward displacement of the globe.

When the eyes are lightly closed, the level of apposition of the lids is higher on the affected side and there is a conspicuous crease in the skin of the upper lid about 6–10 mm. above its free border. This is due to indrawing of the cutaneous insertion of the spastic levator palpebrae. Spastic lid retraction is of course usually bilateral.

(ii) In states of stress, anxiety, or unusual animation sympatheticotonic retraction of the lids may exist. Sympathetic lid retraction differs from the characteristic lid retraction of Graves' disease in that both upper and lower

lids are retracted. It has been produced in man by instilling sympathetico-mimetic drugs into the conjunctival sac and by stimulating the cervical sympathetic trunk at operation. The upper lid is seen to be raised from 1–2 mm. and the lower lid depressed by about $\frac{1}{2}$ mm. Clinically, this type of lid retraction is variable and fluctuates with the patient's mental state. When she is calm and relaxed, it usually passes off completely, unlike either the spastic or paralytic types. It is not confined to patients with Graves' disease but occurs in sympatheticotonic states generally.

(iii) The paralytic type of retraction is seen in association with paralysis of elevation of the eyes. Paralysis more often affects elevation than any other movement of the eye in Graves' disease and consequently, the paralytic type of lid retraction is not uncommon. It is, however, found in a wide variety of other conditions characterized by deficient elevation of the eye. Unlike the spastic type of lid retraction, it is more marked when the patient strains to look up and passes off completely when the gaze is depressed.

Paralytic lid retraction perhaps derives from the fact that the levator palpebrae superioris and the superior rectus are associated muscles with a common nerve supply. So, over-innervation of the rectus in the effort to look up results in over-contraction of the intact levator palpebrae and, consequently, in lid retraction.

Lid lag. The patient's head is held in the normal anatomical position with Reid's baseline horizontal while the eyes are made to follow the observer's finger through a full range of vertical movement in both directions. In normal subjects the eye and the upper lid work smoothly together, so that with but very few exceptions the sclera above the iris is covered throughout the range. In the spastic type of lid-retraction, sclera becomes evident as the eye follows the finger down below the horizontal, and is most marked in the lower part of the range. In the paralytic type, on the contrary, no lagging is apparent in depression, but as the eye turns up the lid shoots ahead near the horizontal, and retraction is most evident in the upper part of the range. It is useful to record the precise relationship of the lids to the cornea in the standard central, fully elevated, and fully depressed positions of the gaze as in Fig. 89.

Effect of overfilling " per se " on the lids. The effect of orbital overfilling on the level of the lid margins has been studied in a patient with an orbital varix in whom inflation of a pneumatic cuff placed round the neck enabled the phenomenon to be produced at will (Rundle, 1945a). The findings are shown in Fig. 90. It will be seen that overfilling of the orbit tends to cause ptosis of the upper lid and retraction of the lower lid. Marked ptosis is usual in carotico-cavernous fistula and slight ptosis is common in orbital tumour. It is evident that active contraction or spasm of the levator palpebrae in Graves' disease greatly modifies the changes dependent on purely mechanical factors.

Exposure of a band of sclera between the margin of the lower lid and limbus occurs in exophthalmos, and is often held to be a valuable diagnostic

sign, but with Reid's baseline horizontal and the gaze directed forwards, up to 2 mm. may be so exposed in normal subjects, and in the patient with varix this width was not exceeded until over 14 mm. of exophthalmos had developed. We do not believe that this sign is of any special value in the diagnosis of Graves' disease.

Ophthalmoplegia in Graves' disease. Ophthalmoplegia is an interesting and important sign and has provided a tool for the investigation of the relationship between classic Graves' disease and the rare ophthalmic types. The pattern of ophthalmoplegia is identical in both forms but in the ophthal-

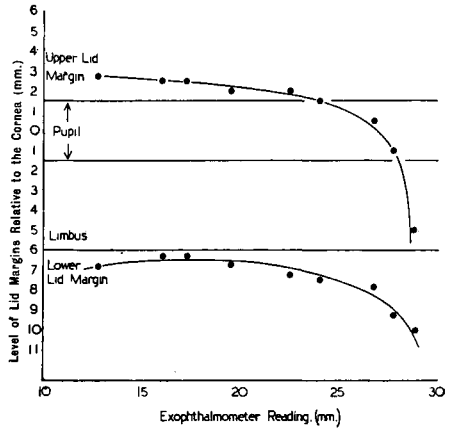


FIG. 90.—Changes in level of lid margins as the eye protrudes. Measurements are made in the standard central position in which the eye looks directly forwards, Reid's base line being horizontal. Observed changes relative to the cornea represent true changes in level since the horizontal plane of the globe remains constant throughout. (Rundle, 1945.)

mic types its frequency and severity are clearly greater (Rundle and Wilson, 1944a).

Ophthalmoplegia in Graves' disease has a well-defined pattern. Paralysis of elevation is of outstanding frequency and severity. It tends to be bilateral and symmetrical, so conjugate vision is retained. It is compensated for by torticollis in extension. Thus, the eyes look forwards though the visual axes are depressed relative to Reid's baseline. Paralysis of elevation depends mainly on weakness of the superior rectus muscle and is most evident when the patient looks upwards and outwards.

Paralysis of elevation is more frequent than that of all the other movements combined. Next in importance is paralysis of abduction, then adduction. Depression of the eye is least and most rarely affected.

This pattern of paralysis is also observed in individual patients, and is strikingly exemplified in Fig. 91. In this patient elevation of both eyes became completely paralysed and remained so. Paralysis of horizontal movements was never more than moderate, and recovery was complete

except for abduction on the right. Depression was only slightly affected and returned fully to normal.

Asymmetry of muscle power commonly leads to squint. Hypophoric and convergent squints are the most usual, corresponding to the greatest incidence of paralysis of elevation and abduction of the eye.

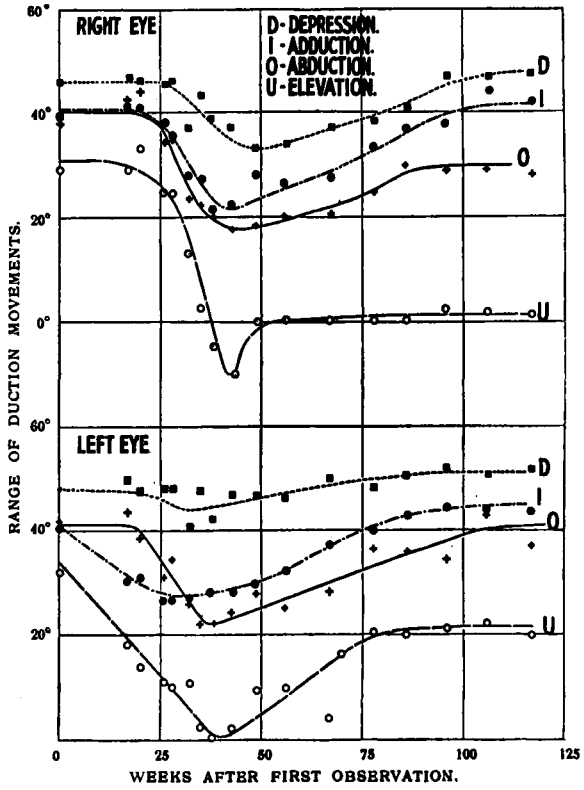


FIG. 91.—Development and remission of ophthalmoplegia in a patient with severe ocular changes occurring after thyroidectomy. The first set of readings was taken a few days before the operation. The order of vulnerability of the ductions (elevation, abduction, adduction and depression) is well shown. (Rundle and Wilson, 1944a.)

Morbid anatomy and histology of the retrobulbar tissues of the orbit. In classical Graves' disease the extrinsic eye muscles regularly appear rather pale and fatty. Microscopically, in severe cases, there are advanced fibre degeneration and proliferation of the sarcolemma nuclei. There is pronounced fatty degeneration. Strands of fat cells normally lie between the fibre bundles of the skeletal eye muscles and in thyrotoxicosis the amount of this adipose tissue is increased by about 85 per cent. (Fig. 92). On

average, the diameter of the individual fat globules is decreased but there is a greatly increased total number of adipose tissue cells (Pochin and Rundle, 1949). Aggregations of round cells (lymphorrhages) are also regularly found. All the foregoing changes may be demonstrable even in thyrotoxic patients who have manifested no eye-signs before death.

Lymphorrhages may also be found in the lacrimal gland. The fibro-fatty tissue of the orbit, however, shows nothing abnormal either to the naked eye or microscopically

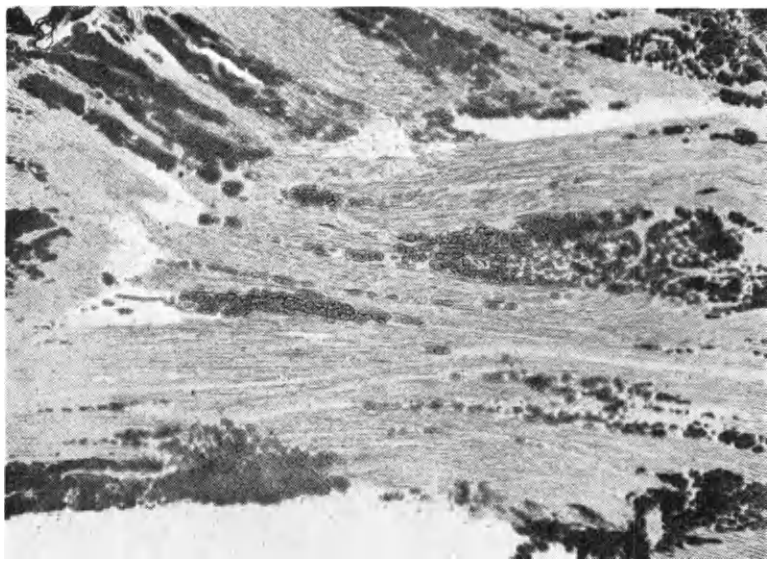


FIG. 92.—Section of levator palpebrae superioris muscle from a case of thyrotoxicosis, stained with Sudan III, and showing numerous strands of adipose tissue between the muscle bundles. (× 16.) (From Pochin and Rundle, 1949.)

In " malignant " exophthalmos the eye muscles and indeed all the tissues of the orbit appear tremendously swollen by oedema. Dissection of the eye muscles intact may thereby be rendered difficult. Histological examination reveals advanced degeneration and disorganization of the muscle substance. The individual fibres are shrunken, fragmented, and spaced out widely by oedema. Cellular infiltration and fibrosis are regular features.

Ophthalmic forms of Graves' disease. Patients are occasionally encountered who present one or more of the eye changes characteristic of Graves' disease without goitre or hyperthyroidism. Indeed, in recent years it has become established that the ocular manifestations of Graves' disease may be associated with any level of thyroid activity. The eye changes may develop

for the first time after thyroidectomy. They are then usually severe and associated with post-operative hypothyroidism. Similar severe changes may follow control of hyperthyroidism with thiouracil (Williams and Bissell, 1943; Haines and Keating, 1947). In other patients the ophthalmopathy comes on spontaneously and, though supervision be maintained for many years, goitre and hyperthyroidism are never observed to develop.

The commonest clinical types are the following:

(i) Severe exophthalmos and ophthalmoplegia are associated with lid retraction of the paralytic type. The general state is usually one of euthyroidism in the spontaneous types and hypothyroidism in the post-operative cases.

(ii) Exophthalmos and lid retraction without ophthalmoplegia develop spontaneously. The patient is euthyroid. This type developed during adolescence in the patient illustrated in Fig. 93.

(iii) The only eye-sign is spastic lid retraction which may be unilateral. The patient is euthyroid but may later develop classical Graves' disease. First lid retraction becomes bilateral and then goitre and hyperthyroidism develop.

Nomenclature presents a difficulty in these patients. No single descriptive term is satisfactory. The following are some of the expressions which have been used:

" Malignant " exophthalmos	(Ruedemann, 1936)
Graves' disease without raised metabolic rate	(Bram, 1936)
Exophthalmic ophthalmoplegia	(Brain and Turnbull, 1938)
Thyrotropic exophthalmos	(Mulvany, 1944)
Ophthalmic forms of Graves' disease	(Rundle and Wilson, 1944a)
Hyperophthalmopathic Graves' disease	(Means, 1948)

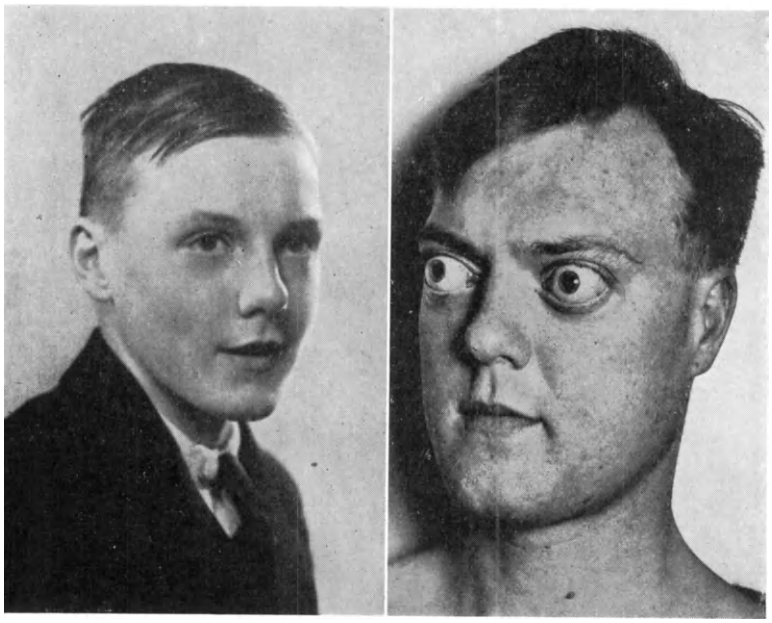
Because of our ignorance it is better to avoid aetiological descriptions; the last two expressions are perhaps open to least objection. Certain authors (Mulvany, 1944; Martens, 1947; Beierwaltes, 1948) claim that in patients with thyrotoxicosis two types of exophthalmos can be distinguished *ab initio*, the " thyrotropic " and " thyrotoxic", or " malignant " and " non-malignant " exophthalmos. We ourselves are unable to forecast which patients will go on to develop the severe degrees of exophthalmos conventionally described as malignant.

We believe that the ocular changes in the ophthalmic types are similar in kind though generally more severe than those in classical Graves' disease.

Occurring spontaneously, these cases may be regarded as abortive forms of Graves' disease in which the thyroid gland has failed to respond to the causal stimulus usually exciting both ocular and hyperthyroid changes. In other words they lie at one extreme of the disease spectrum. At the other is the patient with marked hyperthyroidism but no eye-signs. At the centre of the spectrum lie patients with classical Graves' disease.

However, two reservations must be made. The one is that even in the patients without eye-signs, well-marked chemical and histological changes

may be found in the orbit after death. The other is that in the most severe ophthalmic types the pathological changes in the orbit differ from those in classical Graves' disease. Thus in the former there is severe oedema of the orbital tissues whereas in the latter the enlargement is due solely to the deposition of fat. It is tempting to accept the unifying concept that fatty enlargement of the orbital tissues is the initial change in all cases and that when overfilling of the orbit progresses beyond a certain limit, the efferent veins become obstructed, with resulting generalized oedema and further



Aged 16 Aged 24

FIG. 93.—Ophthalmic type of Graves' disease. Severe exophthalmos and lid retraction developed at the age of nineteen. Eye movements were unusually free in all directions. There were no symptoms or signs of hyperthyroidism whatever.

swelling of the contents of the orbit. These ophthalmic types present an intriguing problem, and firm evidence as to the nature of their local and general pathology is still awaited.

The natural history of the ocular changes. Lid retraction with its consequent widening of the palpebral fissure creates the illusion of exophthalmos and variations in lid retraction, which may be rapid and conspicuous, that of corresponding fluctuations in prominence of the eyes. Thus, it has often been asserted that exophthalmos may develop abruptly, even over-night, and that its extent may vary greatly from day to day. But evidence from measurements fails to support such claims.

To obtain an adequate record of the development and course of exophthalmos and ophthalmoplegia in Graves' disease, measurements must be continued for months or years and clearly this is not practicable when full-blown Graves' disease is present; but the relevant observations have been made on patients suffering from the ophthalmic forms (Rundle, 1945*b*).

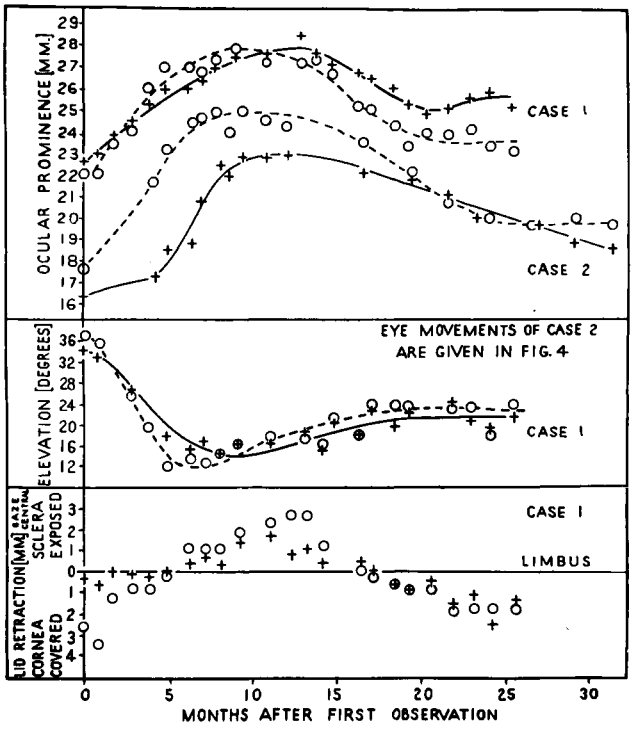


FIG. 94.—Dynamic phase of exophthalmos, ophthalmoplegia and paralytic lid retraction. In Case 1, ocular changes developed spontaneously, in Case 2, they were slight before thyroidectomy for thyrotoxicosis (cf. first readings) but progressed rapidly afterwards. (Rundle, 1945*b*.)

Patients with Graves' disease do not usually come under close observation while the eye is protruding, most present later when exophthalmos is established and stationary. Thus a dynamic phase of the ocular changes precedes the static phase, which may endure for years. Illustrative curves obtained during the dynamic phase are shown in Fig. 94. In both patients the cycle of protrusion and recession of the eyes approaches completeness. Recession is usually incomplete. Thus the dynamic phase gives place to a static phase. Recognition of these stages in the natural history of exophthalmos facilitates interpretation of incomplete data from individual cases.

During ingravescence, the eye may protrude up to 8 mm. or more and a figure of 3–4 mm. is quite usual. Exophthalmos may become static at its

maximum level but this does not seem to be common. The extent of recession is, however, systematically less than that of protrusion, so the eyes do not return to their pristine state. However, recession may be sufficient to restore the patient's appearance to normal and of course this also depends on the state of the lids and the width of the palpebral fissure.

The rates of protrusion and recession are slow. Progress was relatively rapid in the cases shown (Fig. 94), yet the cycle occupied over two years.

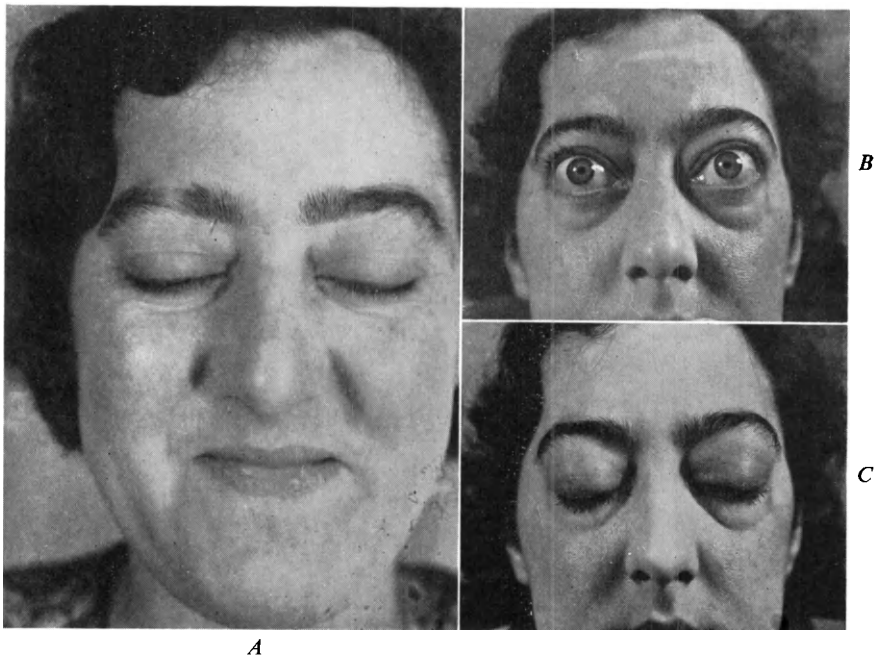


FIG. 95.—Ophthalmic type of Graves' disease. Severe orbital overfilling (as indicated by the lid protrusion and exophthalmos seen in *B* and *C*), ophthalmoplegia and lid retraction developed while she was under observation. There was no goitre or hyperthyroidism. (Rundle and Wilson, 1944*b*.) Photograph *A* was taken early in the course of the disease, photographs *B* and *C* at its peak.

The most rapid rate of protrusion observed was approximately 1 mm. per month. An average figure is approximately 0·5 mm. monthly. Recession is even slower and in general proceeds at about half this rate.

A close symmetry of the ocular changes as illustrated in Case 1 (Figs. 94 and 95) is usual, but the onset of clinical signs on one side may be delayed for months or years. It will be seen that in case 8 protrusion of the right eye was delayed for four months but then occurred rapidly. We have known a patient in whom an interval of five years elapsed between the protrusion of the two eyes.

Paralysis of elevation of the eye usually develops *pari passu* with exophthalmos. However, maximum recovery from ophthalmoplegia often precedes that from proptosis.

At the peak of the curve of ingravescence various other ocular changes may appear. The conjunctiva of the lateral and lower fornices may become heaped up and prolapse through the palpebral fissure. At first a grey, glistening translucent fold, it later becomes opaque, reddish and firm, and prevents apposition of the lids (Fig. 96.).

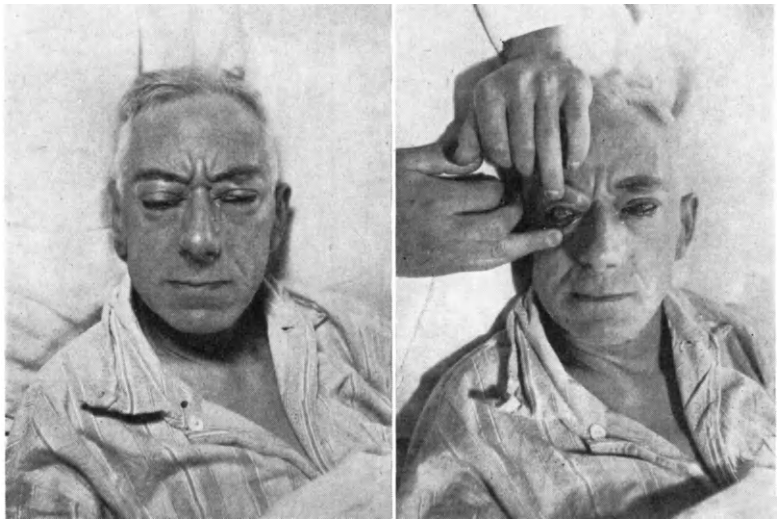


FIG. 96.—The patient, aged forty-eight, had a small goitre and the general symptoms and signs of hyperthyroidism. Exophthalmos had progressed rapidly during the five months prior to admission and, at the time of thyroidectomy, was extreme. Note the corneal ulcer on the right side, the chemosis, epiphora and the marked tenseness of the lids. Improvement was delayed and then very slow but three years later his appearance was almost normal.

In the extreme phase of overfilling of the orbit the normal ready fluctuation of the globe with light digital pressure on the closed lid is lost; instead the eyeball is conspicuously firm and unyielding. The lids in these cases are usually exceedingly full and tightly stretched. Epiphora may be a marked feature at this stage and ophthalmoplegia usually approaches completeness.

Should the condition progress further, or persist unrelieved, exposure keratitis, corneal ulceration, hypopyon and ophthalmitis follow.

Effect of thyroidectomy on the ocular changes. Careful measurements before and at regular intervals after thyroidectomy show that on the average the eye protrudes by about 1 mm. during the year following operation (Fig. 97). This slight protrusion is a consistent finding and the average

result does not depend on the occasional case with obvious post-operative ingravescence. Slight protrusion of the lid is associated with this increased prominence of the eye. Nevertheless the patient nearly always believes that the eyes have receded and, in fact, their general appearance is usually distinctly improved after control of the thyrotoxic state. It is now established (Bothman 1934; Soley 1942; Eden and Trotter, 1942) that this improvement in appearance depends on diminution of lid retraction. The paradox thus

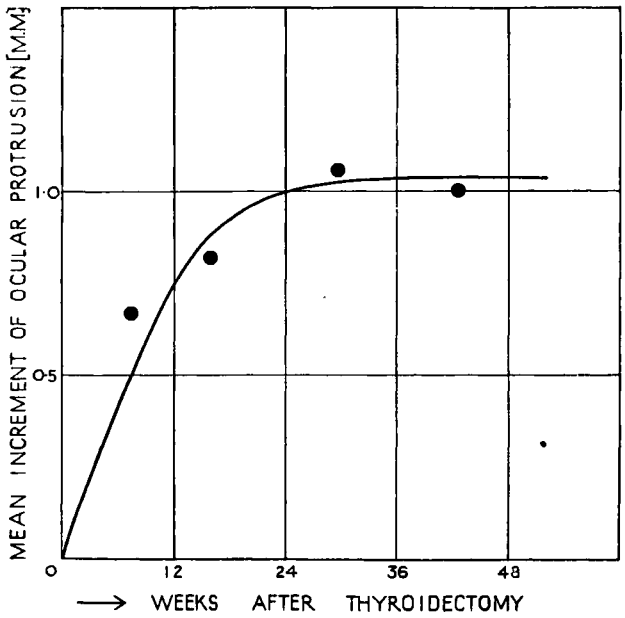


FIG. 97.—Average ocular protrusion following thyroidectomy in thirty-nine consecutive thyrotoxics. Pre-operative exophthalmometer readings were subtracted from post-operative and results averaged. (From Rundle's 1945b data.)

obtains that there is cosmetic and subjective improvement in spite of slight further filling of the orbit with consequent protrusion of the globe and lids. Similarly any ophthalmoplegia present is usually not benefited by thyroidectomy. It seems probable that the post-operative increment in orbital filling depends on recovery from wasting with concomitant slight enlargement of the orbital tissues.

Pathogenesis of the ocular phenomena. The occurrence of the ophthalmic forms of Graves' disease and the negligible effect of thyroidectomy upon exophthalmos and ophthalmoplegia strongly suggest that these phenomena are not produced or even potentiated by an excess of thyroid hormone. Lid retraction, on the contrary, is frequently benefited by control of the thyrotoxic state, but even here there may be no *direct* causal relationship. Lid

retraction is a complex phenomenon and the characteristic spastic type frequently persists after adequate thyroidectomy (Fig. 98).

Increase in the bulk of the orbital tissues and exophthalmos are of course usually associated with loss of body weight in thyrotoxicosis. The reverse phenomenon, recession of the eye and decrease in the bulk of the orbital tissue associated with a gain in body weight, occurred in Case 2 (Fig. 94). Again, in Case 1 (Fig. 94), the bulk of the orbital tissues must have increased by some 20 per cent. while the body weight remained practically stationary.

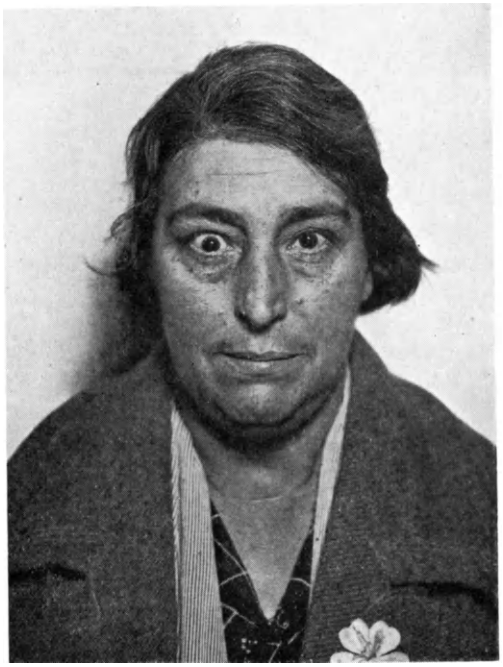


FIG. 98.—Persistent right-sided lid retraction six months after an otherwise completely satisfactory thyroidectomy for thyrotoxicosis. Note the typical elevation of the right *lower* lid relative to the cornea.

We may conclude that in Graves' disease some non-thyroid hormone exerts a disproportionate influence on the bulk of the orbital tissues and that this can far outweigh the local nutritional effect of hyperthyroidism or its elimination.

The production of exophthalmos in the guinea-pig by injecting pituitary extract was first reported by Loeb and Friedman in 1932 and numerous workers have since confirmed their observations. Pochin (1944) has made a detailed study of this phenomenon and the following brief account is largely based on his work.

It has been established that anterior pituitary exophthalmos is most easily produced in young growing guinea-pigs of about 200 gm. weight. It is not certain that the exophthalmos is caused by the thyrotropic hormone itself. In fact, recent experimental data (Jefferies, 1949a) suggest that the exophthalmic and thyrotropic effects of pituitary extracts can be dissociated by previous iodination of the extracts at a suitable *p*H. Pituitary exophthalmos may thus depend on an entirely separate principle or on the combined action of two or more of the recognized principles. It does not depend on adrenocorticotropic hormone (Jefferies, 1949b).

This anterior pituitary exophthalmos can usually be detected at twenty-four hours after the first injection and is constantly present after forty-eight hours. The degree of exophthalmos increases rapidly for one to three days, then slowly until about the seventh day, after which it decreases, even though injections are continued until, at fourteen days, the exophthalmos has declined to about 70 per cent. of its maximum value. Measurements show that the maximum extent of anterior pituitary exophthalmos is 3–4 mm. (total for both eyes).

If, during the second week, the injections are discontinued, the eyes recede little or no more rapidly than if the injections are continued. But if the injections are interrupted during the first week, recession is rapid and exophthalmos may be halved within twenty-four hours of the missed dose.

By contrast, thyroxine therapy caused sinking of the eyes which is proportional to the loss of body weight. It has been stated that the degree of exophthalmos produced by anterior pituitary extract is much greater in thyroidectomized than in intact guinea pigs. However, Pochin has shown that the difference depends merely upon the decrease in body weight following injections in the intact pig, such decrease resulting from activation of the thyroid. If allowance be made for this loss of body weight the amount of exophthalmos is equal in the two conditions.

The mechanism upon which this anterior pituitary exophthalmos depends is oedematous swelling of the orbital tissues, which displaces the eyeball forwards. By far the most important factor is enlargement of the dorsal lacrimal gland and its sheath but the water content of all the orbital tissues increases.

Examination of two well-demarcated fat depots, in the axilla and on the psoas muscle within the abdomen, showed that both were wasted. Their loss of fat was associated with a rise in percentage water, but not absolute water content. The odd conclusion emerges, therefore, that in young growing guinea pigs injected with anterior pituitary extract, there is a remarkable increase in the absolute water content of the tissues in the orbit but not elsewhere. This occurs irrespective of the presence or absence of the thyroid gland. In intact guinea pigs, the injections are associated with a loss of body weight and a decrease in the fat content of the adipose tissues. This is associated with a lipaemic " tide " in the blood, and the appearance of stainable fat droplets in the liver, skeletal muscles, thyroid gland, and other tissues (Dobyns, 1946). Injections of thyrotropic pituitary extract have also

been shown to produce gross exophthalmos in a small fish, the Fundulus (Albert, 1945). Fluid rapidly accumulates in the retrobulbar space, and, remarkably enough, this fluid contains the injected material.

The pituitary theory of origin of exophthalmos in man is an attractive one in view of the foregoing experimental findings but arguing directly from animal experiments to disease states in man is apt to be fallacious. It must be emphasized that pituitary exophthalmos in guinea pigs is an acute phenomenon, coming on in a matter of hours after the first injection, and resulting from oedema. In classical Graves' disease, by contrast, exophthalmos comes on gradually over a period of many months, and results from the deposition of fat in the orbit.

In recent experiments Pochin (1949b) has introduced a perspex frame into the subcutaneous tissue of the rabbit's back. The artificial cavity within this frame at first fills with protein-rich fluid but later this is largely replaced by ordinary adipose tissue. The application of these observations to exophthalmos in man is however not yet clear.

Treatment of " malignant " exophthalmos. This necessitates the close collaboration of the ophthalmologist and the thyroid and neuro-surgeons. As we have seen from studies of the natural history, some recession of the eyes will eventually occur spontaneously, and treatment during the stage of maximal overfilling of the orbit is aimed essentially at preserving the visual media intact during the phase of maximal protrusion. The thyroid status must never be overlooked. Any hyper- or hypothyroidism present must be corrected. If vision is acutely threatened, interim control of hyperthyroidism by anti-thyroid drugs will be preferable to thyroidectomy.

The advice and help of the ophthalmologist are valuable in preventing or minimizing conjunctival infection and corneal desiccation and ulceration. A temporary tarsorrhaphy is often of value. Apposing the lateral third of the free margins of the lids will suffice in many cases. This limited tarsorrhaphy also has the advantage of allowing unimpeded vision and giving considerable cosmetic improvement.

Since the basic disorder is overfilling of the bony orbit, Naffziger's orbital decompression operation (1948) has a sound rationale. It is indicated when there is threat of visual impairment from corneal desiccation and ulceration or from choking of the disc (Naffziger, 1948b). Severe chemosis is an ominous sign for it may interfere with apposition of the lids. Corneal ulceration, if untreated, rapidly leads to hypopyon and ophthalmitis with the loss of an eye (Fig. 99). In this day and age, patients are still thus losing both eyes (Spanyol, 1947), though there can be little doubt that timely decompression will prevent such a disaster. In certain rare instances the operation may be justified on cosmetic grounds, for example in the young actress with severe static exophthalmos.

Decompression should be wide and adequate. In severe cases the whole roof and lateral wall of the orbit are resected but care is taken not to open into the ethmoid, frontal, or maxillary sinuses. Naffziger (1947) has found that it is not necessary to unroof the optic foramen or to divide the zonule

of Zinn. After removal of the bone, the orbital fascia is divided longitudinally and transversely, allowing the orbital tissues to bulge freely. Naffziger uses a coronal scalp incision and trans-frontal approach.

Quite narrow triangular bone flaps are turned down, the broad portion of the flap being under the temporal muscle as far anteriorly as possible.

In lesser cases it may suffice to remove the temporal wall of the orbit, as practised recently by Dr. Alan Woods of Baltimore. A curved incision

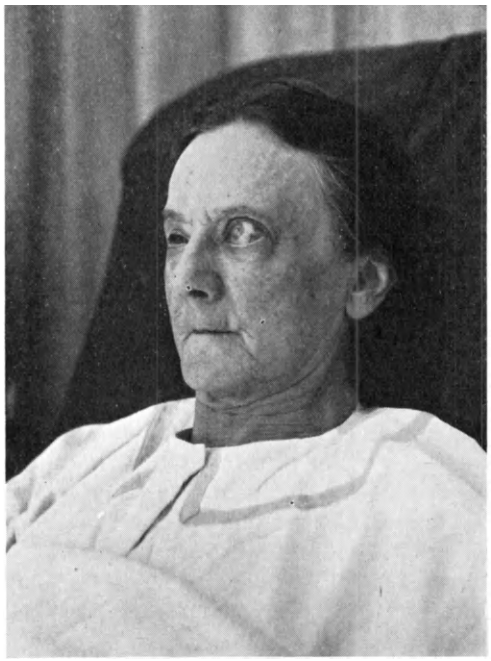


FIG. 99.—Loss of the right eye due to corneal ulceration, hypopyon and ophthalmitis. Six months previously she had been advised to come into hospital because of severe thyrotoxicosis and extreme exophthalmos but she had refused to do so.

is made well behind the hairline in the temporal region, the skin and subcutaneous tissue being mobilized forward from the surface of the temporal muscle. The latter is cleared from the outer orbital wall, which is then resected. The lateral bony margin of the orbital entrance is not taken as in the Krönlein operation. Harvey Jackson now carries out much the same radical decompression as Naffziger through this temporal incision and without turning down cranial bone flaps. In competent hands these operations carry a negligible mortality. The operations for the two sides are done on different occasions.

A temporary tarsorrhaphy is advantageously combined with orbital decompression. It reduces the post-operative conjunctival reaction and safeguards against new exposure ulcers. In addition, it renders safer the application of elastic pressure bandages, which do so much to promote good recession during the post-operative period.

There is a valuable place too for the removal of orbital fat from in front through incisions in the periphery of the upper and lower lids, as done by Piercy (1949) and by Juler (1945). Haemostasis must be meticulous. The fat from outside the muscle cone can be removed quite safely and this is particularly easy to do, and quite a lot can be got away from beneath the lower lid. The cosmetic result of this procedure may be excellent.

Irradiation of the pituitary and orbits is, however, of doubtful value. Ravdin *et al.* (1949) used the method "in 10 patients of this type without obviously harmful effect" (!).

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CHAPTER XVI

BIOCHEMICAL ABNORMALITIES IN THYROID DISEASE

WITH SPECIAL REFERENCE TO

DIAGNOSTIC TESTS

BY

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Introduction — Basal Metabolism — Method of Estimation — Sources of Error — Normal Limits — Values in Disease — Serum Cholesterol Estimations — Blood Iodine Estimations — Liver-Function Tests — Miscellaneous Metabolic Changes.

Introduction

In theory the ideal method of assessing thyroid function from the laboratory angle would be an estimation of the concentration of thyroxin in the circulating blood. At the present time this is not a practical procedure, although the newer methods of blood iodine determination are approaching nearer to this ideal. All the other tests which will be described depend upon secondary changes in metabolism resulting from the primary thyroid disturbance. Although many of them are of great value in diagnosis, none is completely specific, and it is therefore necessary to interpret them with due regard to the clinical picture. This proviso really applies, of course, to all laboratory tests but is perhaps particularly appropriate to those used in thyroid conditions. Thyrotoxicosis and myxoedema should both be regarded as syndromes presenting signs which are both clinical and biochemical; it is probably wise to regard the special tests in this way as physical signs which should be given their due place in diagnosis. No one sign, either clinical or biochemical, should be allowed undue weight in the assessment of any particular case. Thus, although striking metabolic changes may frequently raise a very strong presumption of thyroid disease, they can rarely be accepted as the sole evidence for it.

In the ensuing account the tests will be discussed in order of usefulness in the ordinary general hospital without specially elaborate laboratory facilities. For this reason the technically difficult blood iodine determinations appear rather lower on the list than their future possibility might be thought to warrant. The important recent work on diagnostic tests involving the use of radioactive iodine is dealt with in another chapter (Chapter I).

Basal Metabolism

The basal metabolism may be defined as the metabolic rate under certain standard (basal) conditions as compared with the normal for the patient under investigation. It is not therefore the lowest possible rate, as values below basal have been recorded in sleep. However, the suggested alternative term of " standard metabolism " does not appear to have gained general acceptance.

Methods of determining basal metabolism may be classified as follows:

Direct. Attwater-Benedict-Rosa Calorimeter.

Indirect. (a) Open. Douglas Bag.
(b) Closed. Spirometers of various types. (Tissot, Krogh, Knipping, Benedict-Roth).

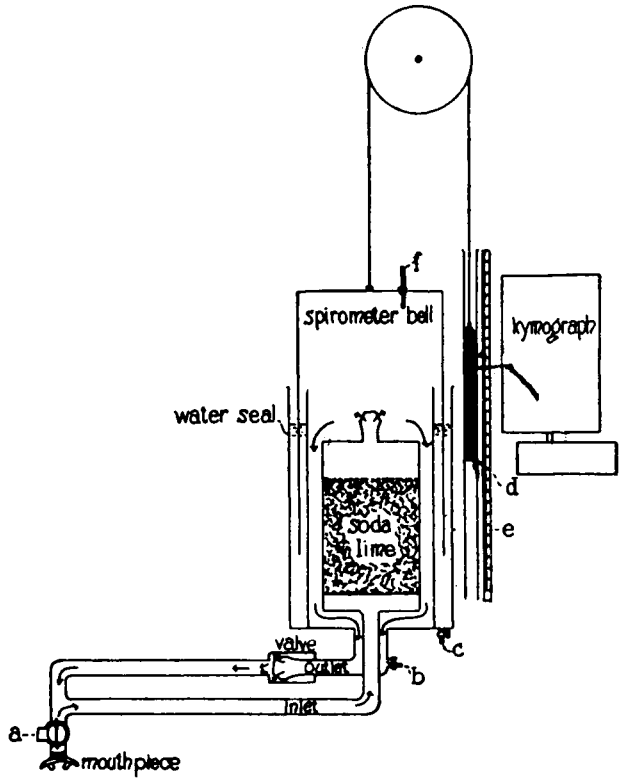
The direct method has been of immense service in pioneer studies but is too expensive and elaborate for ordinary diagnostic purposes. The open method—Douglas Bag (1911)—is convenient for physiological studies but is generally considered too time-consuming for routine clinical use. Thus, if any number of tests are to be performed on the same day the labour of gas analysis is considerable and, worse still, no inkling of the result is available until late afternoon. If therefore duplicate records fail to agree, the patient must be given a fresh appointment. For these purely practical reasons most workers who do any considerable number of tests prefer the closed method, and the Benedict-Roth machine will be described as the most popular type.

The apparatus is illustrated in Figs. 100, 101 and 102. It consists essentially of a spirometer attached to the patient in a closed circuit. A soda-lime tower in the circuit absorbs all the CO_2 in the expired air which passes through it, and an arrangement of valves maintains one-way passage of the expired air so that re-breathing of CO_2 containing air is prevented. Thus, only a small portion of the apparatus—" a " to soda lime—contains CO_2 and the patient re-breathes a CO_2-free mixture. A gradual contraction of the system occurs as the oxygen is used up and this is recorded graphically by the ink pen on the moving drum recorder. It is necessary for the air in the spirometer to be enriched with oxygen before the test is started so as to avoid the development of anoxaemia as the oxygen is used up. Instruments without a graphic recorder are on the market but their use is not advised.

The conduct of the test is as follows:

1. **Metabolism room.** Although tests are sometimes carried out in the ward with a portable apparatus, this is in general undesirable and the best results will be obtained by reserving a special room for metabolism tests. This should be in a quiet situation and may have several small curtained cubicles with couches and with provision for weighing and measuring the patients. A good writing desk and a mercurial barometer are also desirable adjuncts.

2. **Calibration of apparatus.** The parts of the machine requiring calibration are the spirometer bell, the clocks, and the minute rulings on the record charts. In the writer's opinion the spirometer bell can be calibrated with sufficient accuracy by measuring the circumference at several places with a steel tape-measure as recommended by Peters and Van Slyke (1932).



Diagrammatic representation of the Roth-Benedict apparatus for the determination of basal metabolism.

FIG. 100.—From Peters and Van Slyke (1932).

No appreciable lack of uniformity should be allowed. The thickness is also measured with a caliper, and the area of cross-section can then be calculated from the usual πr^2 formula. If the mode of calculation indicated below is to be used, this area should be 20·72 sq. cm. If more or less than this, a factor is worked out equal to $\frac{\text{cross-section area}}{20{\cdot}72}$, and the observed millimeter rise in 6 minutes is multiplied by this as explained below. The use of

this figure of 20·72 involves certain assumptions as to the respiratory quotient as noted below.

The clock and paper rulings can be checked simultaneously during any

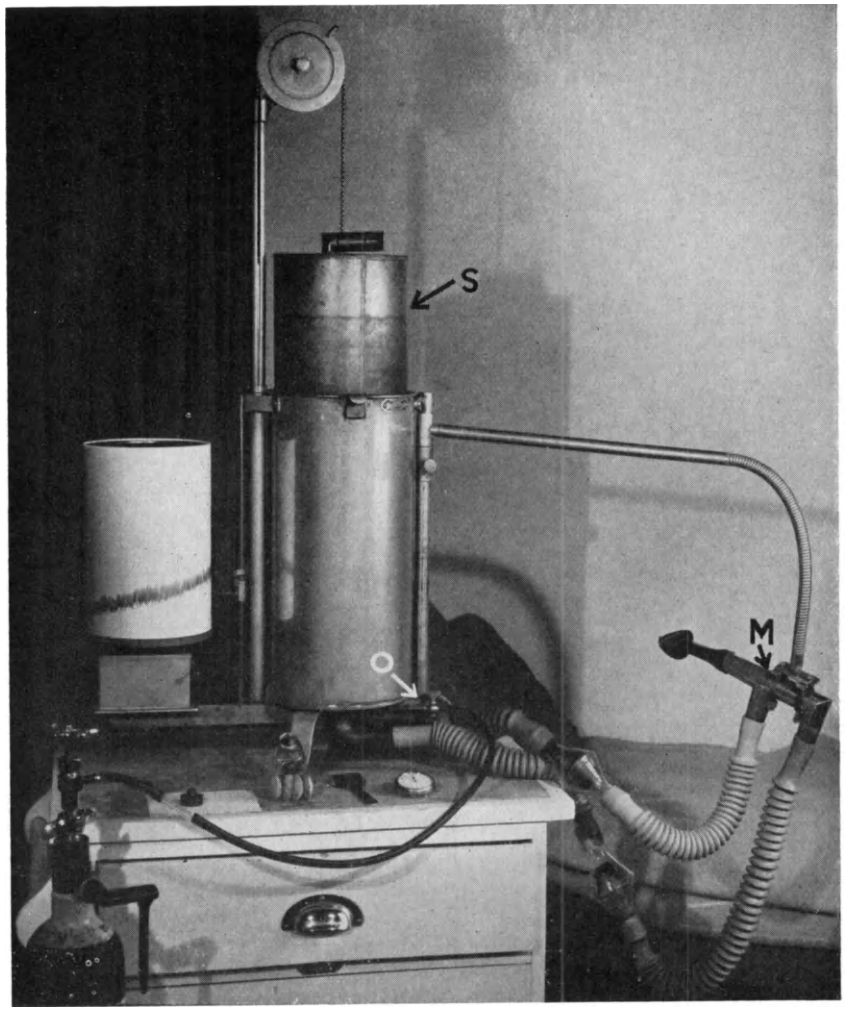


FIG. 101.—Roth-Benedict apparatus.

record with a good stop-watch. The only essential is that the pen should take exactly six minutes to traverse six lines. This check should be made at weekly intervals. Errors of less than three seconds on six minutes may be neglected.

3. **Sterilization of apparatus.** It is very important to sterilize, by boiling, the rubber mouthpieces and the metal connecting part (M) (Fig. 101) after each patient, so as to avoid the possibility of conveying infection from one patient to another. The machine should also be ventilated between the patients by raising and lowering the spirometer bell to its full extent three times. In addition to these precautions it is, in general, inadvisable to perform the test on any patient with an obvious respiratory infection. In the absence of these precautions there is a real risk of the development of throat infections as a result of the test, but a rigid adherence to them will prevent any trouble of this sort.

4. **Preparation of patient.** The patient should abstain from food and drink for twelve hours before the test, which is best carried out in the forenoon. No bath or vigorous exercise is allowed on the morning of the test,

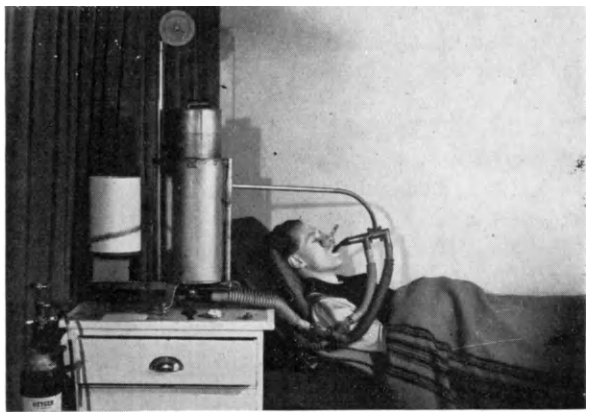


FIG. 102.—Roth-Benedict apparatus in use.

but the teeth may be brushed and the patient may get up for toilet purposes. In addition, he or she should be familiarized with the apparatus by preliminary runs on the instrument the day before the final test. Robertson (1938) has shown that it is important for the initial tests to be exactly similar to the final one in respect of fasting and weighing routine, in order presumably to convince the patient that " there is no deception".

The mouth temperature and body weight are taken before the preliminary rest. Sufficient clothing should be removed for weighing so that the error is reduced to less than 1 lb. when allowance is made for clothing. A definite inquiry as to the time of the last meal is advisable as a check on the carrying out of instructions as to fasting. In the case of out-patients printed instructions as to the preparation required should be given.

5. **Preliminary rest period.** After the above preparation, the patient should rest lying down on the couch where the test is to be performed for at least thirty minutes before any records are taken.

6. **Test procedure.** A rubber mouth-piece is first attached to the metal tube (M) (Fig. 101), and the rubber tubes from the spirometer are firmly attached to the other two limbs of the tube. The spirometer bell (S) is now depressed to its lowest level and oxygen is admitted from a cylinder via rubber tubing attached at (O) until the bell is half-way up. The mouth-piece is now inserted in the patient's mouth and a nose-clip applied to the nose. A rough test for leaks from the nose is made with a polished metal reflector, the nose-clip being readjusted if necessary. More oxygen is now admitted until the pen reaches near the bottom of the paper on the drum and after disconnecting the oxygen supply the record is started. The temperature of air in the spirometer is noted at the time.

Two to three minutes later a test for leaks is made by placing a 50 g. weight on the top of the spirometer bell and leaving it on for two minutes. The time during which the weight is in place is marked on the record and during this time it is convenient to record the pulse rate and to mark off a tally which shows how many times the soda-lime has been used. The permissible number varies with different brands, but is around twenty or twenty-five.

After about eight minutes the record is stopped and the machine is disconnected from the patient. The final spirometer temperature is now noted and the record is blotted and the best possible line is drawn to touch the bottom parts of the respiratory record. The slope of the line is measured by measuring the distance of the line from the bottom of the paper in millimetres at two points six minutes apart. This " millimetre rise in six minutes " is used as a basis for the calculation of calories per hour and also serves as a rapid check on the concordance of duplicate readings (Fig. 103). The barometer must be read at some time during the session.

7. **Number of records needed.** There has been wide variation in the practice in different clinics, varying from the acceptance of the first " good " record by some American workers to the more time-consuming routine recommended by Robertson (1938) in this country. The writer would subscribe to the view that a single tracing is of little value and has in general relied upon two or more tracings taken on the second day of attendance. It seems beyond doubt that the first-day reading is usually higher than subsequent readings, but the extra reliability which may possibly accrue from prolonging the period of observation beyond two days is outweighed by the extra labour and by the inconvenience to the patient. If two tracings taken on the second day agree within 10 per cent. of each other (approximately 6 mm. rise in six minutes) then either the mean or the lower of the two readings may be accepted. If the readings are not concordant, further study is necessary. A small proportion of patients may completely fail to give acceptable curves owing to some respiratory irregularity. In such cases the results are probably of little value and no report should be made. In practice the great majority of patients will give duplicate tracing agreeing within 5 per cent. or less on the second day of attendance. It is the great virtue of the Benedict-Roth method that this agreement can be ascertained

immediately after the second record is taken by the simple measurement of " millimetres rise in six minutes," the final calculation being done later at leisure.

Calculation. The millimetres rise in six minutes is equal to calories per hour after suitable corrections have been applied as follows: Firstly, if the rise in spirometer temperature during the test exceeds 1° C. add on 1 mm. per 2° temperature rise. This is because expansion of the air due to temperature rise will partly counteract contraction due to oxygen absorption. Secondly, the final figure for millimetres rise is multiplied by the calibration factor for the instrument and also by a temperature and pressure factor given in Table XX, p. 272, the latter factor correcting the observed volume to dry

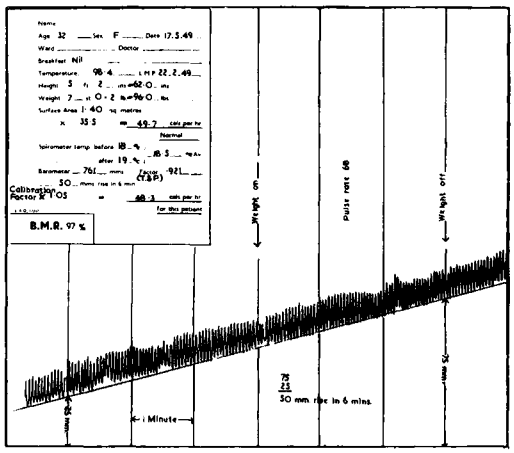


FIG. 103.

oxygen at 0° C. and 760 mm. barometric pressure. The final figure is now calories per hour.

This method of calculation involves an assumption with regard to the respiratory quotient. The value assumed is 0·82 corresponding to a calorific value of 4·825 calories per litre of oxygen absorbed. This figure is accepted as appropriate for the normal patient in the post-absorptive state and may occasionally be in error, for example, in diabetes mellitus. However, it is generally agreed that it is better to assume a respiratory quotient in this way rather than try to calculate the quotient from a short-period experiment.

It is next necessary to determine the ideal normal calories per hour for the patient. Numerous tables are available for this purpose embodying data worked out by observations on normal persons, but the writer recommends the use of the Aub and du Bois body surface formula or nomogram (Fig. 104), (Table XXI), used in conjunction with the age and sex table of Boothby and Sandiford (1929), (Table XXII), p. 272.

TABLE XX

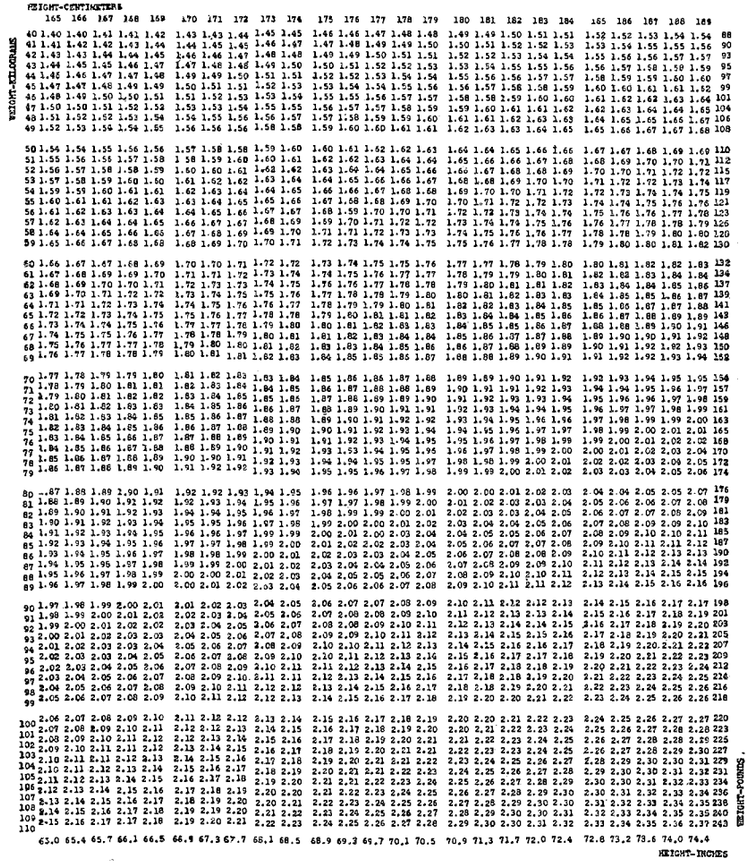
Factors for Reducing Volumes of 80% Saturated Air to 0°C. and 760 mm.

$$\text{Formula:-}\ \frac{1}{1 + 0.00367t} \times \frac{P - 0.80\ Pw}{760}$$

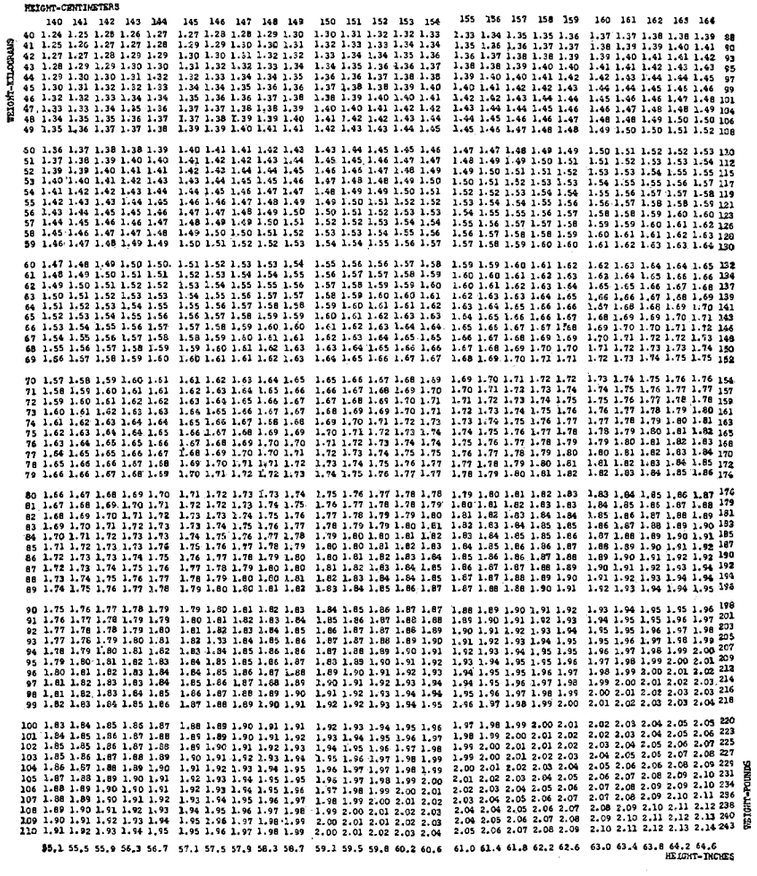
Temperature in degrees Centigrade

mm	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
720	.885	.881	.877	.873	.869	.865	.861	.857	.853	.849	.845	.841	.836	.832	.828	.824	.819	.814	.810	.805	.800
721	.886	.882	.878	.874	.870	.866	.862	.858	.854	.850	.846	.842	.837	.833	.829	.825	.820	.815	.811	.806	.801
722	.887	.883	.879	.875	.872	.868	.863	.859	.855	.851	.847	.843	.838	.834	.830	.826	.821	.816	.812	.807	.802
723	.889	.885	.881	.877	.873	.869	.865	.861	.857	.853	.849	.845	.840	.836	.832	.828	.823	.818	.814	.809	.804
724	.890	.886	.882	.878	.875	.871	.866	.862	.858	.854	.850	.846	.841	.837	.833	.829	.824	.819	.815	.810	.805
725	.891	.887	.883	.879	.876	.872	.867	.863	.859	.855	.851	.847	.842	.838	.834	.830	.825	.820	.816	.811	.806
726	.892	.888	.884	.880	.877	.873	.868	.864	.860	.856	.852	.848	.843	.839	.835	.831	.826	.821	.817	.812	.807
727	.893	.890	.886	.882	.878	.874	.870	.865	.861	.857	.853	.849	.844	.840	.836	.832	.827	.822	.818	.813	.808
728	.895	.891	.887	.883	.880	.876	.871	.867	.863	.859	.855	.851	.846	.842	.838	.834	.829	.824	.820	.815	.810
729	.896	.893	.889	.885	.881	.877	.873	.868	.864	.860	.856	.852	.847	.843	.839	.835	.830	.825	.821	.816	.811
730	.897	.894	.890	.886	.882	.878	.874	.869	.865	.861	.857	.853	.848	.844	.840	.836	.831	.826	.822	.817	.812
731	.898	.895	.891	.887	.883	.879	.875	.870	.866	.862	.858	.854	.849	.845	.841	.837	.832	.827	.823	.818	.813
732	.900	.896	.892	.888	.884	.880	.876	.871	.867	.863	.859	.855	.850	.846	.842	.838	.833	.828	.824	.819	.814
733	.901	.898	.894	.890	.886	.882	.878	.873	.869	.865	.861	.856	.852	.848	.844	.840	.835	.830	.825	.820	.815
734	.903	.899	.895	.891	.887	.883	.879	.874	.870	.866	.862	.857	.853	.849	.845	.841	.836	.831	.826	.821	.816
735	.904	.900	.896	.892	.888	.884	.880	.875	.871	.867	.863	.859	.854	.850	.846	.842	.837	.832	.827	.822	.817
736	.905	.901	.897	.893	.889	.885	.881	.876	.872	.868	.864	.860	.855	.851	.847	.843	.838	.833	.828	.823	.818
737	.906	.902	.898	.894	.890	.886	.882	.877	.873	.869	.865	.861	.856	.852	.848	.844	.839	.834	.829	.824	.819
738	.908	.904	.900	.896	.892	.888	.884	.879	.875	.871	.867	.863	.858	.854	.850	.846	.841	.836	.831	.826	.821
739	.909	.905	.901	.897	.893	.889	.885	.880	.876	.872	.868	.864	.859	.855	.851	.847	.842	.837	.832	.827	.822
740	.910	.906	.902	.898	.894	.890	.886	.881	.877	.873	.869	.865	.860	.856	.852	.848	.843	.838	.833	.828	.823
741	.911	.907	.903	.899	.895	.891	.887	.882	.878	.874	.870	.866	.861	.857	.853	.849	.844	.839	.834	.829	.824
742	.912	.908	.904	.900	.896	.892	.888	.883	.879	.875	.871	.867	.862	.858	.854	.850	.845	.840	.835	.830	.825
743	.914	.910	.906	.902	.898	.894	.890	.885	.881	.877	.873	.869	.864	.860	.855	.851	.846	.842	.837	.832	.827
744	.915	.911	.907	.903	.899	.895	.891	.886	.882	.878	.874	.870	.865	.861	.856	.852	.847	.843	.838	.833	.828
745	.916	.912	.908	.904	.900	.896	.892	.887	.883	.879	.875	.871	.866	.862	.857	.853	.848	.844	.839	.834	.829
746	.917	.913	.909	.905	.901	.897	.893	.888	.884	.880	.876	.872	.867	.863	.858	.854	.849	.845	.840	.835	.830
747	.918	.914	.910	.906	.902	.898	.894	.889	.885	.881	.877	.873	.868	.864	.859	.855	.850	.846	.841	.836	.831
748	.920	.916	.912	.908	.904	.900	.896	.891	.887	.883	.879	.875	.870	.866	.861	.857	.852	.847	.843	.838	.833
749	.921	.917	.913	.909	.905	.901	.897	.892	.888	.884	.880	.876	.871	.867	.862	.858	.853	.848	.844	.839	.834
750	.922	.918	.914	.910	.906	.902	.898	.893	.889	.885	.881	.877	.872	.868	.863	.859	.854	.849	.845	.840	.835
751	.923	.919	.915	.911	.907	.903	.899	.894	.890	.886	.882	.878	.873	.869	.864	.860	.855	.850	.846	.841	.836
752	.924	.920	.916	.912	.908	.904	.900	.895	.891	.887	.883	.879	.874	.870	.865	.861	.856	.851	.847	.842	.837
753	.926	.922	.918	.914	.910	.906	.902	.897	.893	.889	.885	.881	.876	.872	.867	.863	.858	.853	.849	.844	.839
754	.927	.923	.919	.915	.911	.907	.903	.898	.894	.890	.886	.882	.877	.873	.868	.864	.859	.854	.850	.845	.840
755	.928	.924	.920	.916	.912	.908	.904	.899	.895	.891	.887	.883	.878	.874	.869	.865	.860	.855	.851	.846	.841
756	.929	.925	.921	.917	.913	.909	.905	.900	.896	.892	.888	.884	.879	.875	.870	.866	.861	.856	.852	.847	.842
757	.930	.926	.922	.918	.914	.910	.906	.901	.897	.893	.889	.885	.880	.876	.871	.867	.862	.857	.853	.848	.843
758	.932	.928	.924	.920	.916	.912	.908	.903	.899	.895	.891	.887	.882	.878	.873	.869	.864	.859	.855	.850	.845
759	.933	.929	.925	.921	.917	.913	.909	.904	.900	.896	.892	.888	.883	.879	.874	.870	.865	.860	.856	.851	.846
760	.934	.930	.926	.922	.918	.914	.910	.905	.901	.897	.893	.889	.884	.880	.875	.871	.866	.861	.857	.852	.847
761	.935	.931	.927	.923	.919	.915	.911	.906	.902	.898	.894	.890	.885	.881	.876	.872	.867	.862	.858	.853	.848
762	.937	.932	.928	.924	.920	.916	.912	.907	.903	.899	.895	.891	.886	.882	.877	.873	.868	.863	.859	.854	.849
763	.938	.934	.930	.926	.922	.918	.914	.909	.905	.901	.897	.893	.888	.884	.879	.875	.870	.865	.861	.855	.850
764	.940	.935	.931	.927	.923	.919	.915	.910	.906	.902	.898	.894	.889	.885	.880	.876	.871	.866	.862	.856	.851
765	.941	.936	.932	.928	.924	.920	.916	.911	.907	.903	.899	.895	.890	.886	.881	.877	.872	.867	.863	.857	.852
766	.942	.937	.933	.929	.925	.921	.917	.912	.908	.904	.900	.896	.891	.887	.882	.878	.873	.868	.864	.858	.853
767	.943	.939	.935	.931	.926	.922	.918	.913	.909	.905	.901	.897	.892	.888	.883	.879	.874	.869	.865	.859	.854
768	.945	.940	.936	.932	.928	.924	.920	.915	.911	.907	.903	.899	.894	.890	.885	.881	.876	.871	.866	.861	.856
769	.946	.941	.937	.933	.929	.925	.921	.916	.912	.908	.904	.900	.895	.891	.886	.882	.877	.872	.867	.862	.857
770	.947	.943	.939	.935	.930	.926	.922	.917	.913	.909	.905	.901	.896	.892	.887	.883	.878	.873	.869	.863	.858

From Beaumont and Dodds (1936).



Body Surface Calculated from DuBois' Height-Weight Formula.



Body Surface Calculated from DuBois' Height-Weight Formula.

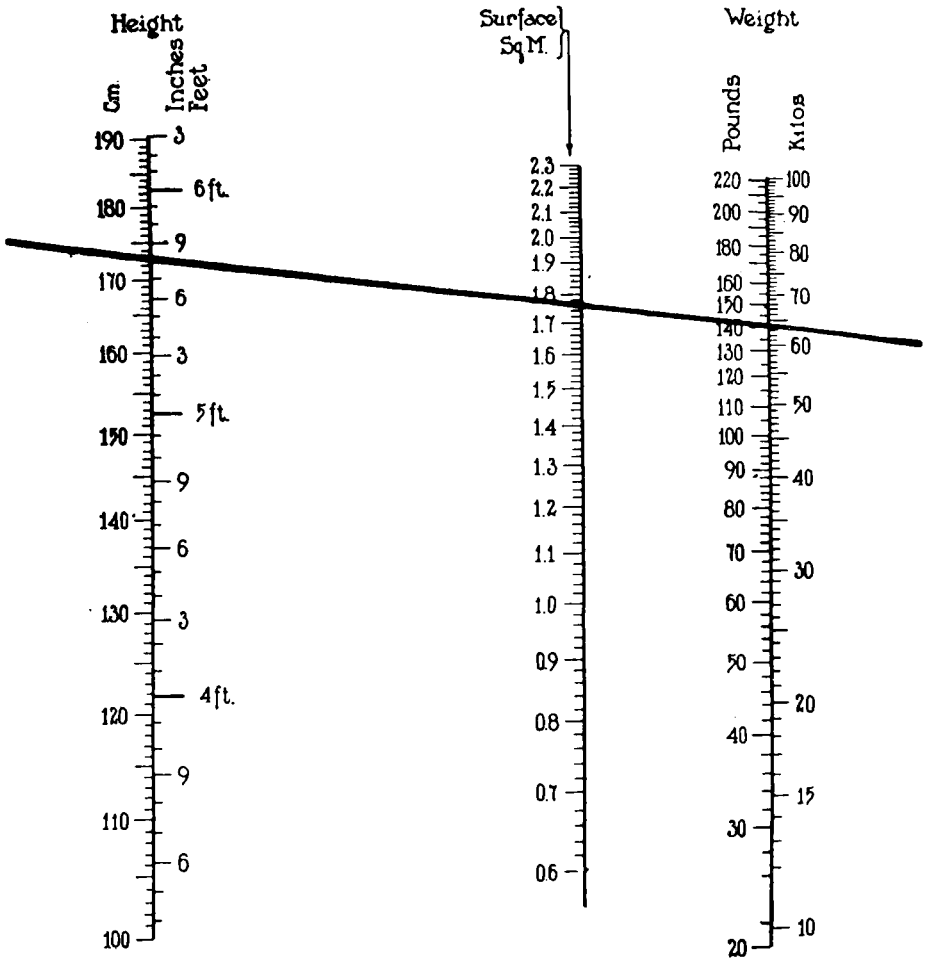
The DuBois Normal Standards as Modified by Boothby and Sandiford (1929)

(Cal. per Sq. M. per Hr.)

Age	Males	Females	Age	Males	Females
5	(53·0)	(51·6)	20–24	41·0	36·9
6	52·7	50·7	25–29	40·3	36·6
7	52·0	49·3			
8	51·2	48·1	30–34	39·8	36·2
9	50·4	46·9	35–39	39·2	35·8
10	49·5	45·8	40–44	38·3	35·3
11	48·6	44·6	45–49	37·8	35·0
12	47·8	43·4			
13	47·1	42·0	50–54	37·2	34·5
14	46·2	41·0	55–59	36·6	34·1
15	45·3	39·6	60–64	36·0	33·8
16	44·7	38·5	65–69	35·3	33·4
17	43·7	37·4			
18	42·9	37·3	70–74	(34·8)	(32·8)
19	42·1	37·2	75–79	(34·2)	(32·3)

In using this table, the age should be determined to the nearest year. That is, 4 years 6 months to 5 years 5 months, inclusive, is taken as 5 years; to do this correctly the actual birthday must be known and is important for children. The DuBois height-weight formula for surface area was used.

[*facing p.* 272.



Nomogram permitting direct estimation of surface area from height and weight by Du Bois' formula $A = H^{0.725} \times W^{0.425} \times 71.84$. When A = surface area in square centimeters, H = height in centimeters and W = weight in kilos. (sq. cm. = sq. m. × 10,000.) The surface area is found at the point of intersection of the middle scale with a straight line drawn from the observed height on the left hand scale to the observed weight on the right hand scale.

FIG. 104.—From Peters and van Slyke (1932).

The body surface in square metres is multiplied by the approximate factor from the age and sex table to give ideal normal calories per hour.

Mode of Reporting. To avoid ambiguity of signs, the following formula is advised:

B.M.R. 140% of normal (plus 40%).

It is very important to abstain from making any definite numerical report if the curves in any particular case are too irregular to justify it.

Sources of error. These fall into two groups: those depending on the handling of the patient and those concerned with technical matters. Many of the latter have already been considered, such as leaks and calibration errors. Inefficient CO_2 absorption can be tested for at the end of any record by expelling a sample of residual air from the tap (O) (Fig. 101) through a baryta bubbler. This should not be a source of error if the soda-lime is changed regularly, but will be suggested by progressively increasing over-ventilation during the test. A somewhat similar result occurs if the rubber valves are perished and the patient re-breathes without air circulation.

As regards the patient, every care must be taken to ensure co-operation by reassurance, but a watch must be kept for signs of obvious mental or physical unrest. For this reason the test is best carried out, or at least supervised by a medically qualified person. Pyrexia or gross dyspnoea, for example, will usually contra-indicate the test. It is usual to postpone the test if the patient is menstruating.

Normal limits. The limits conventionally accepted are from 115 to 85 per cent. of normal, but in using the standards suggested above on normal students in this country the writer has obtained a range of normal from 110 to 82 per cent., suggesting that the American standards are somewhat too high for use in this country. The difference is relatively unimportant in practice but the tendency should be remembered in interpreting the results.

Changes in disease. Thyroid conditions are of course the most important causes of deviations from the normal. Values up to 200 per cent. of normal or more may be seen in thyrotoxicosis and values down to 60 per cent. of normal or slightly less in myxoedema. Borderline values may be difficult to interpret and the relatively wide range of normal values introduces a difficulty here. Thus one patient may have a normal level of 85 per cent. and be abnormal at 110 per cent., while another may have the converse finding. In the latter case the effect of iodine on the basal metabolic rate may resolve the difficulty (Means, 1933, Robertson, 1938). Thus if a patient with a basal metabolic rate of 110 per cent. falls to 85 per cent. with iodine treatment this is regarded as evidence of thyrotoxicosis. However, this test requires a large number of carefully controlled readings under ideal conditions to be reliable, and is of course not applicable if iodine has been administered beforehand. No analogous procedure is available for cases of suspected myxoedema.

A number of other diseases are associated with changes in basal metabolism and are listed below. In many of these cases the effect is probably

mediated via the thyroid and those may be regarded as examples of secondary hyper- or hypothyroidism.

Conditions with raised basal metabolism	*Conditions with lowered basal metabolism*
Acromegaly	Starvation
Leukaemias	Gross malnutrition from any cause
Polycythaemias	Nephritis with oedema
Heart failure if dyspnoea present.	Pituitary atrophy (Simmonds' disease)
Fever (10 per cent. per 1° C.)	
Pregnancy (later months)	

Basal metabolism is also affected by the following drugs:

Drugs raising basal metabolism	*Drugs lowering basal metabolism*
Thyroxine or thyroid extracts	Thiouracil and homologues
Anterior pituitary preparations	Hypnotics
Adrenalin	Morphine and derivatives
Caffein	Iodine (in thyrotoxicosis only)
Nitrophenols	

It is desirable to note specially certain conditions in which basal metabolism is usually normal, such as exogenous obesity, hysteria and heart failure without dyspnoea. Normal findings in cases of this type are often of great help in excluding the participation of the thyroid.

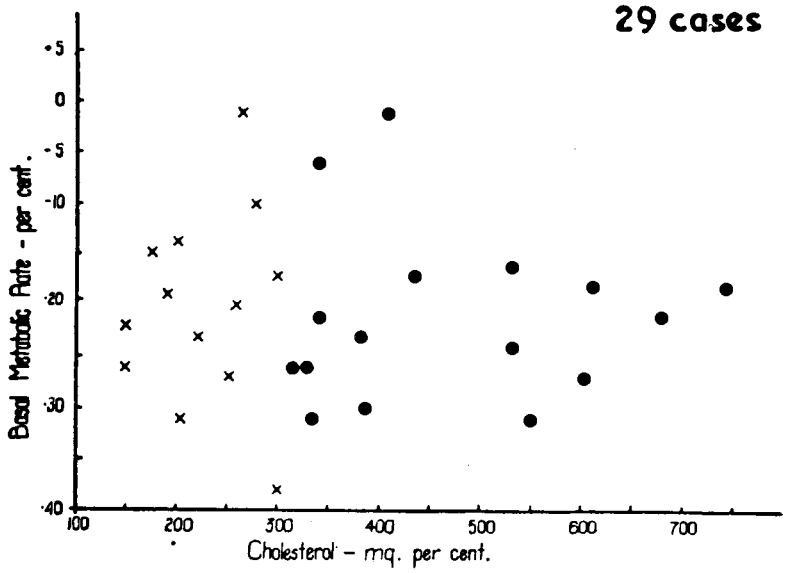
In conclusion therefore we may accept the estimation of basal metabolic rate as a valuable aid to the diagnosis of thyroid conditions if interpreted with due regard to the general clinical picture.

Serum Cholesterol Estimations

Changes in the blood cholesterol level in thyroid diseases have been recognized for a number of years following the work of Gardner and Gainsborough (1928), and Mason, Hunt and Hurxthal (1930). Later work has defined the relationship more exactly and has included studies of the other blood lipid fractions. The general tendency is for blood fats and cholesterol to rise in myxoedema and to fall in hyperthyroidism. The deviation in myxoedema is, however, more striking and of great diagnostic importance.

The mechanism of lipaemia in myxoedema appears to be obscure. A combination of lipaemia and low metabolism is not peculiar to myxoedema as it occurs, for example, in nephrosis, and it is interesting to note that it was this association of findings in nephrosis which originally led Epstein and Lande (1922) to suggest the existence of an inverse relationship between metabolic rate and blood cholesterol. However, the lipaemia of nephrosis is much more intense than that of myxoedema and there are many other examples of lipaemia without lowered metabolism, such as diabetes mellitus, xanthomatosis and obstructive jaundice. Conversely, the hypolipaemia of hepatogenous jaundice and severe anaemias is not associated with a high metabolic rate so that the proposition of a general inverse relationship between the two is not tenable.

Some typical results for the serum cholesterol level in myxoedema are shown in Fig. 105 which is taken from a paper by Gildea, Man and Peters, (1939). It will be seen that in this series twenty-one out of twenty-nine cases of suspected myxoedema had serum cholesterol values above 250 mg. per 100 ml. All the sixteen patients who showed clinical improvement on thyroid treatment had values above 300 mg. per 100 ml. and the authors of this paper suggest that the cholesterol estimation is of more value than the



BASAL METABOLIC RATE AND SERUM CHOLESTEROL AS INDICATORS OF SUBSEQUENT THYROID THERAPY

Circles indicate values in patients before treatment who improved on thyroid therapy.

Crosses indicate values in patients before treatment who did not improve on thyroid therapy.

FIG. 105.—From Gildea, Man and Peters (1939).

basal metabolic rate in determining whether or not a patient will respond to thyroid treatment. They regard values below 275 mg. per 100 ml. as almost excluding the diagnosis of myxoedema. They also demonstrated a fairly close correlation between serum cholesterol on the one hand and total fatty acids or lipoid phosphorus on the other.

Cholesterol has been preferred to other lipid estimations by most workers for technical reasons. These findings are on the whole very similar to those of other workers; for example, Mason, Hunt and Hurxthal (1930), found that twenty of their twenty-two cases of hypothyroidism had plasma

cholesterol values above 230 mg. per 100 ml. which was their upper normal limit. They also noted patients with low metabolic rates but without clinical evidence of myxoedema with normal cholesterol values.

In hyperthyroidism a low normal value is the usual finding but results actually outside the normal range are not so frequent. Thus, Mason, Hunt and Hurxthal (1930) in forty-seven cases found values for plasma cholesterol ranging from 71 to 183 mg. per 100 ml. with nine cases below 100 mg. per 100 ml. Man, Gildea and Peters (1940), in a series of thirty-eight cases reported values below 150 mg. per 100 ml. for the serum cholesterol in their thirteen " uncomplicated " cases, but twelve further cases had values between 150 and 200 mg. per 100 ml. (see Fig. 106). These were patients with marked

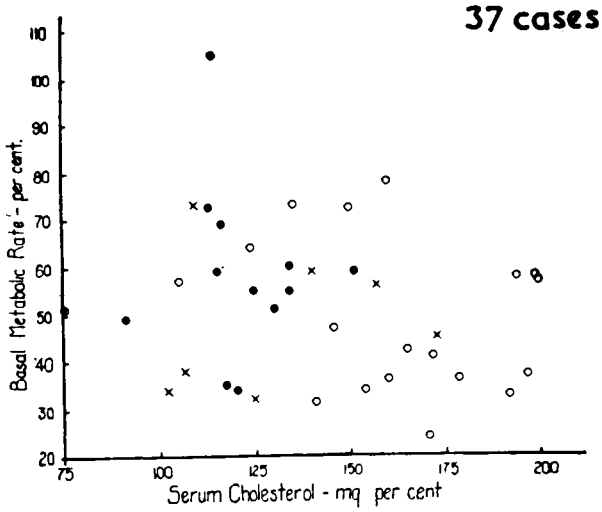


FIG. 106.—Basal Metabolic Rates and Serum Cholesterols before Treatment
• Uncomplicated cases. OX Cases complicated by other diseases.
From Man, Gildea and Peters (1940).

disorders of the vegetative and central nervous system or some other complication such as repeated exacerbations of hyperthyroidism. It would appear from this work that values above two hundred are very much against the diagnosis of hyperthyroidism but that results below the normal range will only occur in a proportion of cases.

We may therefore conclude that the serum cholesterol estimation is a valuable diagnostic aid in cases suspected of disturbances of thyroid function and particularly in myxoedema. It has found many useful applications both in spontaneous myxoedema and in that resulting from thyroidectomy or thiouracil therapy. The main difficulty in interpreting the results lies in the rather wide normal range. Varying figures for this are given by different authors, for example, Peters and Van Slyke (1932) give a range of 100 to

230 mg. per 100 ml., whereas the normal values given by Peters and Man (1943) extend from 107 to 320 mg. per 100 ml. and others have reported an even wider range (Foote and Merivale 1949). It would appear that for practical diagnostic purposes a range of 150 to 300 mg. per 100 ml. might be accepted with the reservation that occasional subjects might exceed these limits. There is the further difficulty that the patient's normal blood cholesterol is usually unknown. Thus a patient may have a " normal " level of 150 and be " abnormal " at 250, while another may have a " normal " level of 250 and be " abnormal " at 150 (mg. per 100 ml.). It is of course also necessary to consider the possibility of the other causes of hypo- and hypercholesterolaemia noted above.

It will be seen from this that a number of factors need to be considered in interpreting results but nevertheless values below 250 mg. per 100 ml. of serum will usually exclude the diagnosis of myxoedema and values above 250 will usually exclude the diagnosis of hyperthyroidism.

Blood Iodine Estimations

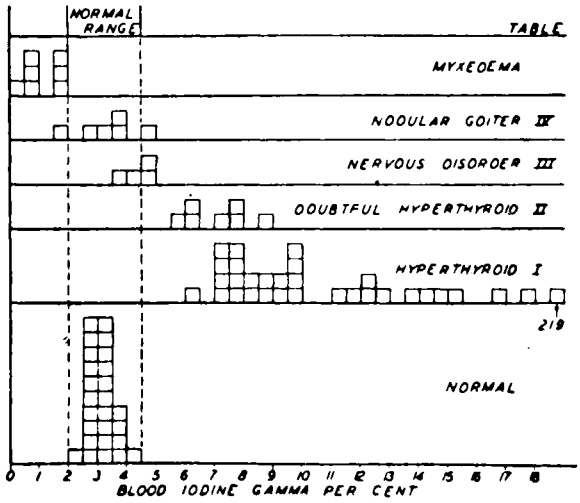
As noted above this type of estimation approaches nearest to the theoretical ideal of the determination of blood thyroxine, but the technical difficulties of the method are considerable on account of the very small amounts of iodine involved and their association with relative large amounts of protein. It has been known for many years that the blood iodine content is altered in various thyroid diseases, but the fact that thyroxine may at times represent only a small proportion of the blood iodine is a limiting factor in these studies. The earlier work is reviewed by Elmer (1938) who describes methods for estimation of total, alcohol precipitable, and " thyroxine " iodine. The latter fraction was estimated by butyl alcohol extraction of the dried blood after alkaline hydrolysis, and it appeared to bear a definite relation to thyroid function, being raised above the normal level of about 5 μg. per 100 ml. in thyrotoxicosis. The method was, however, laborious and 250–300 ml. of blood were required for the estimation in normal subjects.

More recent work has concentrated chiefly on the " precipitable," " protein-bound " or " hormonal " iodine in blood serum. These terms indicate the iodine found when the serum proteins are precipitated. A variety of different precipitation methods have been used by different workers. The methods are laborious and technically difficult but do not use inconveniently large amounts of material. A typical study is that of the Yale group (Riggs, Gildea, Man and Peters, 1941, and Winkler, Riggs, Thompson and Mann, 1946). These workers used zinc hydroxide for protein precipitation and found a normal range for precipitable serum iodine, from 4–8 μg. per 100 ml. The total serum iodine does not exceed this by more than 1 μg. unless iodine has been administered to the patient within the previous ten days, in which case large differences up to 50 μg. per 100 ml. may be seen. The precipitable iodine is therefore the safer estimation. Whole blood iodine is somewhat lower since the cells probably do not contain iodine.

The serum iodine undergoes the expected deviations in disease, i.e. it is above normal in thyrotoxicosis and below normal in myxoedema. These findings are illustrated by Fig. 107 from the paper by Riggs, Gildea, Man and Peters (1941), which gives the results of whole blood iodine determinations in some sixty-four subjects in whom recent iodine therapy was excluded.

In this study all patients with definite thyrotoxicosis were above 6·4 μg. and those with myxoedema were below 1·7 μg., the normal range being from 2·4 to 4·2 μg. per 100 ml.

A similar distribution of values in hyperthyroidism for the precipitable serum iodine was recorded by Winkler, Riggs, Thompson and Man (1946). These authors do not report full details of their findings, but give a value of



A Comparison of Blood Iodine Values in Normal Subjects, and in Patients with Hyperthyroidism, Myxedema, and Nervous Disorders

Fig. 107.—From Riggs, Gildea, Man and Peters (1941).

13·85 μg. per 100 ml. for the average serum precipitable iodine in thyrotoxicosis with a standard deviation of 2·63. They state that 95 per cent. of these cases may be expected to give values above 6·63 μg. per 100 ml. but actually only three of their fifty thyrotoxic patients were below the upper normal limit of 8 μg. per 100 ml. and two of these were probably in a state of spontaneous remission. There was a significant but not very close correlation with basal metabolic rate. Treatment with iodine usually produced a fall towards normal levels. These workers conclude that the estimation is superior to the basal metabolic rate in diagnosis.

Very similar results were reported by Salter, Bassett and Sappington (1941), who precipitated their proteins by heat coagulation (Fig. 108). Their

normal range for protein-bound plasma iodine was identical with that given above and twenty cases of myxoedema all gave results below normal and thirty-five out of thirty-six cases of hyperthyroidism gave high results. On the other hand, Curtis and Swenson (1948) obtained somewhat different results using acetone precipitation for the proteins. Their normal range for protein-bound blood iodine was 0·88 ± 0·2 μg. per 100 ml. and most of their thyrotoxic cases gave values above these limits. In spite of the apparent qualitative similarity between this work and the other two studies, the very much lower normal range with acetone precipitation strongly suggests that a different iodine fraction is being studied in this way.

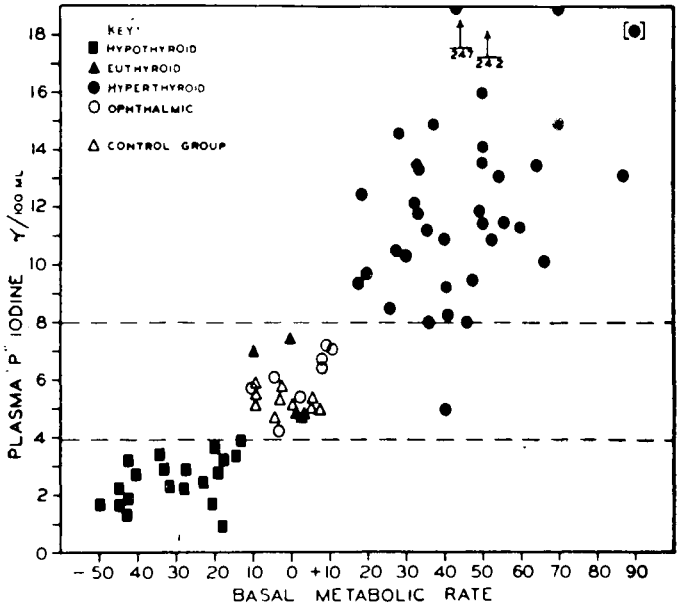


FIG. 108.—From Salter, Bassett and Sappington (1941).

Most workers have demonstrated a general relationship between basal metabolism and serum precipitable iodine in thyrotoxicosis (Lowenstein, Bruger and Hinton, 1944; Curtis and Swenson, 1948). This is further illustrated in Fig. 109 taken from Curtis and Swenson's paper. The effect of iodine treatment in thyrotoxicosis is usually to lower the protein-bound iodine, although according to Curtis and Swenson this result is only obtained in diffuse hyperplastic goitre. In toxic-nodular goitre, on the other hand, these workers found an actual rise in protein-bound iodine following treatment with potassium iodide. This is an extremely interesting difference which, if confirmed, would need to be taken into account in any theories on the aetiology of these conditions.

It would appear from this work that the serum precipitable iodine estimation is an extremely attractive one which goes a long way towards the ideal of a blood thyroxine determination. The principal limiting factors are of a technical nature but these difficulties are in fact probably sufficiently formidable to prevent the general adoption of the procedure as a routine diagnostic aid. The more recent method of Connor, *et al.* (1949) claims to overcome some of these difficulties. It should be noted that even this test cannot claim to be completely specific for thyroid diseases since raised values, up to 11 μg. per 100 ml. are seen in pregnancy in the absence of thyrotoxicosis (Heinemann, Johnson and Man, 1948), and in severe hypoalbuminaemia very

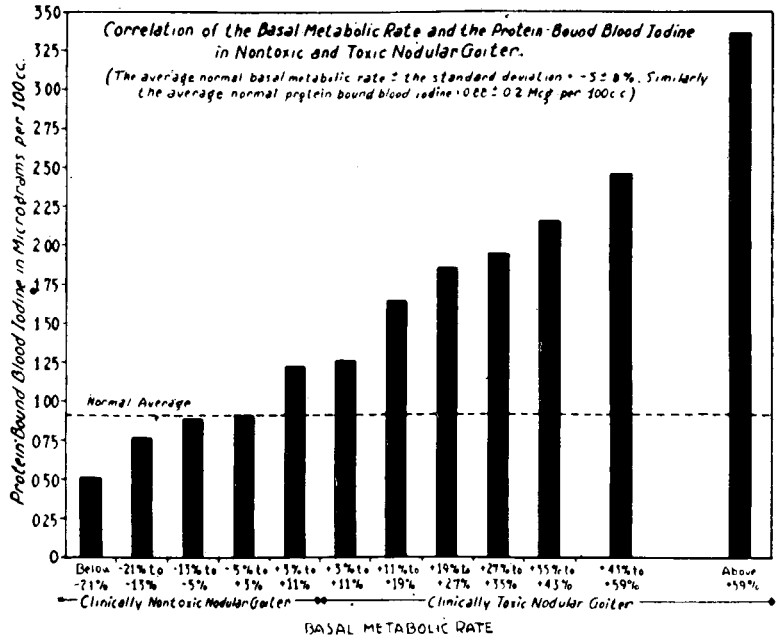


FIG. 109.—From Curtis and Swenson (1948).

low values may occur in the absence of myxoedema (Peters and Man, 1948). It may perhaps be argued that these results imply a " physiological " or compensatory alteration in thyroid function and this idea is supported by the parallel changes in basal metabolic rate in these conditions.

Liver Function Tests

The general pathology of the liver in thyrotoxicosis is discussed in Chapter XIV and we are only concerned here with those tests of liver function which appear to have diagnostic possibilities in this condition.

(a) **Galactose tolerance tests.** Impairment of hepatic glycogenesis in thyrotoxicosis has been recognized for many years and the frequency of lag

storage curves in the ordinary glucose tolerance test is no doubt associated with this impairment. To demonstrate the effect it is, however, preferable to use a sugar such as galactose whose conversion to hepatic glycogen is independent of the insulin supply. Abnormal galactose tolerance in thyrotoxicosis was apparently first noted by Hirose (1912) by the urinary excretion method. Interest in this subject was revived by the work of Althausen and Wever (1937), who studied blood galactose levels after oral administration of the sugar, and in 1940 further studies by this method were reported by Althausen, Lockhart and Soley and by Maclagan and Rundle. Fig. 110 is taken from Maclagan and Rundle's paper and gives a general impression of the results obtained.

The Galactose Index, which is charted in Fig. 110, is defined as the sum of the four half-hourly blood galactose values obtained after a standard dose

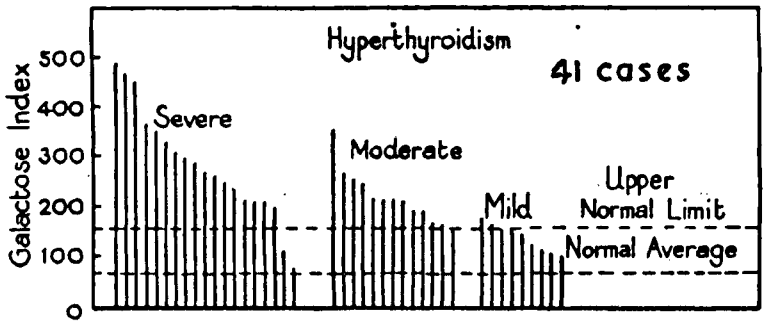


FIG. 110.—From Maclagan and Rundle (1940).

of 40 g. of galactose orally, expressed as mg. per 100 ml. It will be seen that the galactose index was above the normal average in all the forty-one patients with hyperthyroidism, and thirty of these were actually above normal limits. There was a rough correlation with the severity of the disease and a less close correlation with basal metabolic rate. It appeared that the duration of illness was of some significance, most of the normal results being obtained in cases with a short clinical history. The results of Althausen and his colleagues were very similar to these although they accepted a different normal range (maximum blood galactose 30 mg. per 100 ml), and general confirmation of this work has been forthcoming from a number of later workers (Wilson, 1942, Rosenkrantz, Bruger and Lockhart, 1942, Meranze, Likoff and Schneeberg, 1942).

There has, however, been considerable divergence of opinion on the mechanism responsible, Althausen ascribing the results mainly to accelerated intestinal absorption and Maclagan and Rundle mainly to liver damage. In favour of the former theory is the fact that the tolerance to intravenous galactose is usually normal in thyrotoxicosis (Althausen, Lockhart and Soley, 1940, Barnes and King, 1943), but the latter is supported by the abundant

collateral evidence of liver damage in this condition. In this connexion it should be noted that most of the work on intestinal absorption in thyrotoxicosis has been done on animals and a recent human study failed to reveal any accelerated intestinal absorption of galactose (Moseley and Chornock, 1947). It may well be that both factors are responsible; possibly in varying degrees in different subjects.

From the diagnostic standpoint the mechanism is unimportant and the test has proved of some value, particularly in borderline cases. The technique is, however, somewhat laborious and it appears doubtful whether it is worth retaining for routine purposes. The test has, however, made a contribution to our understanding of liver function in thyrotoxicosis and can be recommended for use in any special study of this question.

A number of other liver function tests have given abnormal results in thyrotoxicosis but no special claims have been made for their diagnostic value. They may be listed as follows:

Cinchophen oxidation test	(Lichtmann, 1932)
Hippuric acid test (oral and intravenous)	(Bartels, 1941; Haines, Magath and Power, 1941; Mills, 1942)
Bromsulphthalein test	(Haines, Magath and Power, 1941)

It may be noted that two of these tests—bromsulphthalein and intravenous hippuric acid—are certainly independent of the absorptive factor and hence afford general confirmation of the existence of liver damage in hyperthyroidism.

Miscellaneous Metabolic Changes

The work reviewed in this section has not yet produced any test of proved or accepted diagnostic value but forms an interesting sidelight on the general nature of the metabolic disturbance in thyroid diseases.

The *chief urinary pigment*, " urochrome " is related to metabolic rate. This is an old observation dating back to the work of Mellanby and Thomas in 1920 and was further studied by Drabkin (1927) and by Ostow and Philo (1944). It has been established that the chief pigment is an endogenous product and bears some relation to body surface and to basal metabolism. An attempt to exclude the effect of body surface was made by Ostow and Philo who measured the ratio of the urinary pigment concentration to the urinary creatinine concentration, the latter serving as a rough measure of muscle mass. This ratio showed a general correlation with basal metabolic rate. Work carried out in the writer's laboratory by Eden (1948) gave some support to these general conclusions but also revealed many difficulties in standardizing the measurements. The instability of the pigment and the lack of precise knowledge of its chemical structure are factors mitigating against the use of any such method as a substitute for estimations of basal metabolic rate at the present time.

Creatinuria has been recognized as an accompaniment of thyrotoxicosis for many years but the irregularity of its appearance particularly in women

makes the estimation of little diagnostic value (Brøchner-Mortensen and Møller, 1939). It appears that this creatinuria is due to the action of thyroxin in facilitating release of muscle creatine (Wilkins and Fleischmann, 1946). The blood creatine level may be raised in thyrotoxicosis and the renal threshold is only about 0·5 mg. per 100 ml. (Tierney and Peters, 1943).

Related to this question is the use of the urinary excretion of creatinine as an index of muscle mass (Shaffer, 1908). Much recent work, however, is against this conception (Hobson, 1939; Beard, 1943) and the reported relationship between urinary creatinine and basal heat production in children (Talbot, Stewart and Broughton, 1938) does not appear to have been confirmed.

A marked rise in the *non-diffusible serum magnesium* level in thyrotoxicosis has been noted by a number of workers (Soffer, *et al.*, 1937, 1941; Dine and Lavietes, 1942). While in normal subjects from 3 to 20 per cent. of the serum magnesium is non-diffusible, in thyrotoxicosis values up to 60 per cent. were frequently seen and in a few cases of myxoedema zero values were obtained. There was, however, no general correlation with basal metabolism. These results are of the greatest theoretical interest and the mechanism underlying the change appears to be quite unknown. The method of estimation is technically not very suitable for routine use.

Finally, the *procaine-esterase activity of the serum* has been reported above normal in thyrotoxicosis (Koster and Kisch, 1943). This estimation does not yet, however, appear to have found general application.

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CHAPTER XVII

THE TREATMENT OF THYROTOXICOSIS

Prophylaxis — Control of Hyperthyroidism — Principles of Treatment — The Management of Patients — The Effect of Iodine on the Toxic Gland after Anti-thyroid Therapy — Definitive Anti-thyroid Therapy — Drug Reactions — Clinical Manifestations of Anti-thyroid-Drug Sensitivity — Pathology of the Drug Reactions — Treatment of the Drug Reactions — Treatment of Special Clinical Groups of Thyrotoxicosis — Radio-iodine Therapy and Thyrotoxicosis.

The mechanism underlying Graves' disease being unknown, we cannot strike at the root of the disease. Fortunately, however, the hyperthyroid component, which produces most of the damaging effects, can be completely controlled, and with its control there is often cosmetic if superficial improvement in the ocular component, due to diminution of lid retraction. In fact, the results of correct treatment are very satisfactory.

The need for early treatment is paramount and this in turn depends upon early diagnosis. In its classical form, Graves' disease is obvious. In low-grade thyrotoxicosis, however, and especially where one system is selectively affected by some damaging complication, attention may be confined to it and the general disorder overlooked. The practitioner must therefore be on the look out for " formes frustes " of the disease. Thus, thyrotoxicosis should be considered in patients with auricular fibrillation, changes in personality, myopathy, wasting and persistent attacks of diarrhoea.

In complicated cases the best treatment may demand the close collaboration of the general practitioner, the physician, the surgeon, the ophthalmologist, the psychiatrist, the cardiologist and others. Thus a many-sided team must be in readiness and there should be no harmful delay in getting the most expert help and advice for any problem that may arise.

Prophylaxis. The relationship between nodular goitre and secondary thyrotoxicosis has already been noted (Chapter X). Presumably, if endemicity were wiped out and if the " residual " incidence of simple goitre were sufficiently reduced by the elimination of all known goitrogenic factors, the frequency of secondary thyrotoxicosis would also be minimized. The use of iodized salt in endemic areas is recommended, especially during pregnancy, puberty and adolescence.

Control of hyperthyroidism. There are three methods of controlling hyperthyroidism effectively at the present day, they are:

(i) Subtotal thyroidectomy, hereafter referred to as thyroidectomy.
(ii) The anti-thyroid drugs, thiourea and its derivatives, hereafter referred to as anti-thyroid therapy.
(iii) Radio-active iodine (radio-iodine).

Their pros and cons may now be summarized.

The advantages of thyroidectomy are that it involves removal of the goitre with all its local and general effects and that it results in permanent " cure " in 85 per cent. of cases. It is a well-established treatment; hospitals are organized to carry it out. The results are fairly predictable and the duration of treatment is well defined. The method is one of the safest, best and simplest of handling patients with toxic goitre on a large scale (Thompson *et al.*, 1948).

As against these advantages surgery carries the risk of sudden death, though nowadays this risk is slight, the mortality rate being only about 1 in 500 in expert hands (Cattell, 1949; Pemberton *et al.*, 1949). There is also a definite morbidity factor with thyroidectomy, about one patient in ten being left with tetany, post-operative myxoedema, paralysis of one or both recurrent laryngeal nerves, or recurrent thyrotoxicosis. Then there is the psychological ordeal of a major operation. Further, the patient is left with a scar, and though the scar is usually inconspicuous, this cannot be guaranteed. Moreover, since it is usually the mother who is affected, admission to hospital and operation involve an upheaval in the family life.

With the anti-thyroid drugs as a definitive form of treatment, the operation is avoided. The patient may remain ambulatory throughout, or at most needs a very short period in hospital. There is no scar. The drugs are easily and widely available. Compared with surgery and radio-iodine, anti-thyroid therapy has the precious advantage that its effect on the gland is reversible and so its dosage can be adjusted to the latter's variations in activity (Barr, 1948). It has a valuable place in the treatment of recurrent thyrotoxicosis (Reveno, 1949).

As against these considerable advantages, however, must be set the fact that the goitre remains *in situ*. Its local problem, especially that of pressure, may, indeed, be increased by the treatment. Also, the permanency of the general " cure " remains uncertain (Table XXI). Prolonged specialist supervision is necessary. In fact, though the drugs themselves are freely available and easily prescribed and taken, an organized approach by a competent team is still necessary. It is these facilities for controlling the effect of the anti-thyroid drugs which are not generally available (Austin *et al.* 1948). Over-dosage quickly leads to hypothyroidism and under-dosage or neglect of treatment, to persistent smouldering thyrotoxicosis. One or other of these results will follow quite frequently, unless there is continuity and personal supervision of treatment. We agree with Bartels (1948c) that the treatment is worse than useless in many cases if thyrotoxicosis is only partially controlled. Toxic reactions to these drugs may also occur and even prove fatal. It is known (Purves and Griesbach, 1946) that prolonged treatment of normal rats with thiourea results in the development of thyroid carcinomata, which may metastasize via the blood-stream to the lungs, an example of prolonged, severe hyperplasia giving place to neoplasia. Such metaplasia, however, is fortunately rare and it is now clear (Barr, 1948; Williams, 1947) that carcinogenesis from thiouracil therapy in man is an altogether negligible risk.

Radioactive iodine for therapeutic purposes is at present limited to a few

special centres, but its availability may be expected to increase greatly within the next decade, and, unless unforeseen objections arise, it promises to be by far the simplest, quickest, and cheapest method of controlling hyperthyroidism in most cases. Once the diagnosis is established, and the dose estimated, the latter is merely taken in a glassful of water, as a virtually tasteless drink. An operation, the scar, hospitalization and tiresome specialist supervision are avoided.

There is, however, another side to the picture; the difficulties of estimating the dose necessary in individual cases have not been overcome, and still appear

TABLE XXI

THE RESULTS OF ANTI-THYROID THERAPY

Methylthiouracil (Mt.) *Propylthiouracil* (Pt.) and *Thiouracil* (T.)

Author	Date	Agent	Remarks
Barfred . . .	1947	Mt.	Sustained remission in 26 per cent. Average working time lost, 5 weeks.
Barr	1948	Pt.	Sustained remission rate of 45–50 per cent. Myxoedema in 4 out of 81 cases.
Danowski *et al.* .	1948	Thiourea and iodine.	Fibrillation persisted in all but one of 12 patients with this complication.
Fowler . . .	1948	Pt.	50–75 per cent. of prolonged remissions following 6–9 months' therapy.
Grauer *et al.* . .	1948	Pt.	Two-thirds of patients showed remission.
McGavack . .	1948	Pt.	67 per cent. of prolonged remissions.
Poate	1948	Mt.	88 per cent. of prolonged remissions.
Reveno . . .	1948	Pt.	28 per cent. of patients in sustained remission.
Rinkoff and Spring	1948	Pt.	66 per cent. sustained remission.
Thompson *et al.* .	1948	Pt.	58 per cent. sustained remission.
Williams . . .	1948	Pt.	50 per cent. remissions after a year's treatment.
Kjerulf-Jensen and Meulengracht.	1948	Mt.	Goitre decreased in size in most cases. 90 per cent. remissions but "later recurrences may be expected." Duration of treatment 5–37 months.
Frisk . . .	1948	Mt.	83 per cent. remissions (includes recurrences given a second course of treatment successfully.
Beierwaltes and Sturgis . . .	1949	Pt.	77 per cent. remissions of average duration at follow-up of 17 months.

formidable. Over-dosage by causing excessive destruction of the gland, leads to irrevocable myxoedema. Neighbouring structures, including the parathyroid glandules, the recurrent nerves and the trachea may be severely damaged (Gorbman, 1947), though this was not confirmed by Goldberg *et al.* (1949). Under-dosage will, of course, necessitate a second treatment, or supplementary anti-thyroid therapy. The follicular epithelium may regenerate if only partially damaged by irradiation (Goldberg *et al.*, 1949). Radioactive iodine may also precipitate crisis in hyperacute cases. Its use involves intangible

hazards to patients and staff, among which are carcinogenesis, the production of blood dyscrasias, genetic changes and the shortening of life (Nickson, 1948).

Principles of treatment. (i) Treatment should be adapted to the individual patient, her personality, social and economic circumstances, and the particular character of her disease. Most patients will, however, fit into one of the general or special groups provided for below.

(ii) Now that the anti-thyroid drugs can be used to control hyperthyroidism completely, there is no longer any justification for undertaking thyroidectomy on an exhausted or wasted patient. All goitres should first be converted into non-toxic goitres and the patients should be rehabilitated physically. The timing of operation so important in the old days of preparation with iodine is no longer a matter of nicety. Provided the patient is maintained in a euthyroid state thyroidectomy can be done at any convenient time. In order to achieve maximal physical and mental rehabilitation it is often advantageous to delay the operation for several months.

(iii) Associated conditions, psychic, cardiovascular, endocrine, and so on, should be searched for and, if present, treated. It should be emphasized that thyrotoxicosis is a key psychosomatic disorder, and, especially in the older

TABLE XXII

MANAGEMENT OF THYROTOXICOSIS

1. Careful history-taking—especially social, economic and psychological factors.
2. Examination—characters of goitre, evidence of systemic damage, of local or associated disease.
3. Measurement of lid retraction, ocular prominence, eye movements.
4. Metabolic rate, haematological examination, etc.

age groups, is often associated with other ailments, psychic or physical. It is wrong to concentrate attention on the metabolism to the exclusion of all else. When thyrotoxicosis is not the major factor in the total illness, the tendency should be towards medical control.

(iv) Further experience will establish the exact role of radio-iodine in therapy. Meantime, in toxic goitre, we incline towards thyroidectomy as the definitive treatment, especially if the goitre is producing local symptoms, is large, or retrosternal. Exceptions are made if the patient is very old and afflicted by other diseases.

If thyrotoxicosis is mild and of short duration, and if the goitre is small and diffuse, carefully supervised anti-thyroid therapy is often preferable to surgery. In the highly intelligent and co-operative subject also, anti-thyroid therapy offers a satisfactory alternative treatment. The need for individual supervision must, however, be emphasized.

The management of patients. We usually admit patients for two or three days when they first attend. By careful history-taking and physical examination, as well as special tests, we establish the diagnosis, which must include a full assessment of any complication or associated disease. This short period

of observation also provides an opportunity for the establishment of *rapport* between the patient and the doctor, and at the same time, the definitive treatment most appropriate to the patient can generally be decided on. Barry (1948) emphasizes that a thyroid clinic is often a " clearing house " and that the doctor in charge must sort out the genuine cases of thyrotoxicosis from the large number of other diseases which may simulate it.

We then proceed forthwith to control the thyrotoxicosis. The anti-thyroid drugs in common use at the present day are propylthiouracil, methylthiouracil, thiouracil and thiourea. Stanley and Astwood (1947) have determined that the anti-thyroid potency of these and other agents is as follows:

TABLE XXIII

Anti-thyroid Potency of various Drugs, Thiouracil being used as a Standard of Reference and given a potency of 1.

Thiouracil	1
Thiourea	1
Propylthiouracil	0·75
Methylthiouracil	2
Mercaptoimidazole	10

The two in most common use are propylthiouracil (in the Americas) and methylthiouracil (in Europe and the British Commonwealth); methylthiouracil is the more readily manufactured.

We have obtained very satisfactory and rapid responses with an initial dosage of 150 mg. daily of methylthiouracil followed by a maintenance dosage of 75 mg. The drug is given in three equal doses, one being taken on rising in the morning, one in the early afternoon, and the other just before retiring at night. The aims and general technique of treatment should be explained simply and reassuringly to the patient, and her co-operation should be sought in carrying it through.

The responsiveness of individual patients varies, and accordingly, the foregoing standard dosage will often require modification. We agree with Poate (1947) that the minimal effective dose is also the safest dosage. Undoubtedly many of the toxic reactions to these drugs have been due to gross overdosage.

Stanley and Astwood (1947) have shown that with most of the anti-thyroid compounds the extent of the inhibitory effect is directly proportional to the dose, over the therapeutic range. With heavy dosage full control is rapidly obtained. There is, however, seldom any urgency, and like Reveno (1948) we have for many years tried only for rather gradual control. Toxic hazards are thus minimized. With the dosage of methylthiouracil mentioned, we have found that eight to ten weeks elapse before full metabolic control is achieved. The larger the goitre the greater the dose required but it is important not to push the patient down to a hypothyroid level, since thereby further enlargement and vascularity of the gland are produced. Stanley and Astwood (1948) have recently described a technique using tracer iodine and potassium thiocyanate, by which the degree of control achieved with a given dose of

anti-thyroid substance can be measured exactly, but this will be beyond the facilities of all but a few centres (Chapter I).

A safe working rule is to start off with the small dosage recommended here and to be content to observe the effect. The rate of response is not predictable and seldom involves an average fall in the basal metabolic rate of greater than 1 per cent. per day. In general the small diffuse gland responds quickest, and the large nodular goitre slowest. The patient will be improving all the time, however, and he is encouraged to remain at his work.

If the physical ravages of thyrotoxicosis are severe, then the patient is advised to eat abundantly and to rest during the first month of treatment but in general patients are encouraged to remain ambulatory, and in most instances loss of work at this stage of treatment can be cut down to one to two weeks.

Should untoward symptoms, including general malaise, sore throat, skin rash or gastro-intestinal symptoms develop, she should be told to stop taking the tablets and report to hospital; but there is no need to labour the occurrence or gravity of sensitivity to the drugs. Doubtless, many patients have been alarmed unnecessarily on this score.

Like Kearns (1948) we see the patient weekly for the first six weeks of anti-thyroid therapy, thereafter she attends monthly and when she is euthyroid, the dose of methylthiouracil is reduced to the maintenance level. It is important to guard against incomplete control of hyperthyroidism, hypothyroidism, and the drug reactions. It is comparatively easy to overlook hypothyroidism. We find that estimations of the basal metabolic rate, which may be done on out-patients accustomed to the test, are a valuable guide to the response and appropriate dosage.

With their hyperthyroidism controlled and strength regained, the patients to be treated surgically now stop anti-thyroid therapy and take Lugol's iodine, m.v thrice daily, for two weeks; this corresponds to a total daily dose of a little over 100 mg. iodine. They are admitted to hospital forty-eight hours before operation, enabling the basal metabolic rate and granulocytes to be checked on the day before surgery. Patients for thyroidectomy include those whose goitre is nodular, very large, retrosternal, productive of local symptoms, or so firm as to suggest carcinoma. The psychological, social and economic circumstances often contribute to make surgery the most expeditious and appropriate form of treatment. The existence of thyrotoxic complications, *e.g.* auricular fibrillation, in comparatively young patients also indicates surgery.

The effect of iodine on the toxic gland after anti-thyroid therapy. This has already been discussed in Chapter IX. Two or three weeks' pre-operative treatment with Lugol's iodine increases the firmness of the gland and reduces its vascularity. If the thyroid has enlarged under treatment, or if the metabolism has been pushed to a minus level, the gland may be found to be alarmingly vascular at operation in spite of iodine therapy. Surgery should therefore be postponed until enlargement has ceased (unless pressure symptoms exist) while keeping the patient euthyroid.

Definitive anti-thyroid therapy. Patients whose thyrotoxicosis is mild, and of short duration, and whose goitre is small and diffuse, are eminently suitable

for this régime. In the very old and when there are associated diseases, it is also preferable. In the intelligent and co-operative patient it has many advantages, and it is the obvious method in patients who prefer to avoid or postpone surgery.

Euthyroidism must be maintained uninterruptedly in these patients for at least six months. At each monthly attendance, the dosage is regulated from a consideration of the clinical state and the basal metabolic level. Poate (1947) maintains the metabolism at minus levels for four months and in certain cases also gives thyroid extract throughout the period of maintenance. Penick (1947) uses the same combination for pre-operative preparation, the thyroid extract being designed to inhibit the anterior pituitary and thus minimize the vascularity of the goitre at operation.

If the goitre increases in size, while euthyroidism is maintained, and causes pressure symptoms, medical treatment should be abandoned; thyroidectomy should be done after the usual iodine therapy. According to McGavack (1948) the gland enlarges in about a third of patients, but in our series the proportion has been much lower. Enlargement can, however, regularly be produced if the metabolism is pushed down to minus levels, but this enlargement will regress if the dosage be adjusted correctly. Thus, metabolic control of fluctuations in the size of the gland during treatment help us to interpret their significance. If the patient fails to co-operate in treatment or manifests an intolerance to the anti-thyroid drugs, or if a remission has not occurred after maintaining full control for one year, the plan of treatment should also be changed, and surgery advised. Minor manifestations of drug intolerance, however, can often be countered by reducing the dose or by changing the agent employed.

When euthyroidism has been maintained for six months, it is often found that the dose of methylthiouracil can be reduced to 50 mg. and finally to 25 mg. without the recurrence of thyrotoxic manifestations or rise in the basal metabolic rate. Finally, the drug is omitted entirely, the patient continuing to attend monthly for clinical and metabolic assessments. After a further period of six months, three-monthly visits only need be made. Indications that the treatment can be stopped are that the gland has decreased in size during therapy, and that its vascularity, as judged by the thrill and bruit, has also diminished. If the patient remains steady under stress, and maintains her weight in spite of very low dosage, remission is probable and treatment may be stopped. If recurrence occurs subsequently, then anti-thyroid therapy may be recommenced at a dosage level appropriate to the severity of the recurrence.

On the other hand, patients who continue to require 75 mg. or more to maintain euthyroidism, whose exophthalmos increases, and whose goitre remains large and vascular, are certainly not in remission and require continued treatment.

After either surgery or anti-thyroid therapy it is advisable for the patient to attend at least monthly for one year. Thereafter, attendance need be only occasional but there is much to be gained in a thyroid clinic from

continued observation if only six-monthly for many years; the after-results of treatment and any delayed complications will become evident. Ravdin *et al.* (1949) likewise stress that thyroidectomy should not be regarded as the end point of all treatment.

Drug reactions. The weight of evidence shows that thiobarbital is one of the most dangerous of the agents used. With it, the incidence of complications has been about 30 per cent. as compared with about 10 per cent. for thiouracil and 2 per cent. for propylthiouracil (Bartels, 1948d). Fowler (1946) reviewed 1,573 cases in which thiouracil had been used. The incidence of toxic reaction of all types was 13·77 per cent.; in 4 per cent. there were serious toxic complications and the over-all mortality rate was 0·57 per cent.

The most important of the toxic reactions is agranulocytosis which occurs in about 2 per cent. of patients treated with thiouracil. It proves fatal in about one-quarter of the patients affected. Thiouracil agranulocytosis may be an example of drug allergy, though its course was not affected by antistin in Gubbay's case (1950).

Agranulocytosis generally develops in the third or fourth week of treatment and is heralded by progressive neutropenia. Usually the dosage has been heavy, but cases have been reported in which it has developed out of a clear sky with frightening rapidity, the patient being on a moderate maintenance dose. Occasional counts of the granular cells afford little protection against it. In view of the much greater safety of propylthiouracil, Barr (1948) correctly states that " to-day thiouracil has no place in practical therapeutics unless it be in an extremely rare situation when more generally applicable anti-thyroid drugs prove unsuitable."

Propylthiouracil therapy is, however, not entirely free from the risk of agranulocytosis. Bartels (1948a) found that it occurred in three of his 672 cases, in one at least of whom the dosage was quite moderate (150 mg. daily for five weeks). Livingston and Livingston (1947) reported agranulocytosis and hepatic jaundice in a patient treated with 150–200 mg. daily. In one of Hibbs and McCullagh's patients (1948) severe exfoliative dermatitis developed while she was taking 50–150 mg. propylthiouracil daily after thirty-four weeks of treatment. It is clear that even propylthiouracil requires care and supervision in its administration. Fortunately, such complications are exceptional and they should not prejudice us against making full and proper use of propylthiouracil.

The true hazard of toxic reactions with methylthiouracil has not been determined. Published data suggest that it has generally been used in the same dosage as propylthiouracil and that its incidence of toxic reactions has been about 7 per cent. (Barfred, 1947). It is now known, however, (Stanley and Astwood, 1947) that the anti-thyroid potency of methylthiouracil is over two and one-half times that of propylthiouracil. It is safe to say that when the dosage is scaled down proportionately toxic reactions will prove far less common. We have used it now in well over 300 cases and have yet to encounter any evidence of idiosyncrasy.

Clinical manifestations of anti-thyroid drug sensitivity. Skin reactions,

including urticaria, rashes and pruritus, are the commonest. There also occur pharyngitis, conjunctivitis, fever, neutropenia, agranulocytosis, purpura, swelling of the salivary and lymph glands, arthralgias, nausea, vomiting, diarrhoea, crystalluria and haematuria. Hepatitis, splenomegaly, nervous irritability and muscle spasms have also been described. The presence of urobilin in the urine is a useful indication that other toxic reactions can be expected (Barfred, 1947).

Pathology of the drug reactions. Williams and Kay (1947) measured the concentration of thiouracil and its derivatives in the various tissues and body fluids. About 15 per cent. of the ingested dose is broken down and destroyed by the gastro-intestinal juices. The remainder is rapidly absorbed, significant concentrations appearing in the blood within fifteen minutes of its ingestion. Nearly all the blood thiouracil is protein-bound and occurs in the blood cells. Its concentration is higher in the leucocytes than in the erythrocytes. About one-third of the drug is excreted unchanged in the urine. The remainder gets into all the cells and tissues of the body but is present in widely different concentrations. There is a remarkable tendency for these drugs to be concentrated in the thyroid gland; this is most marked with methylthiouracil. The bone marrow is one of the tissues most highly saturated.

Serial sternal punctures and blood studies fail to show any regularly occurring changes after thiouracil; abnormalities are found only in the relatively few and unpredictable cases in which neutropenia or agranulocytosis develops (Sikkema *et al.*, 1946). In these there is an extreme reduction of the granulocyte precursors and later, of even the mature granular forms. Blackburn (1948) also found the most striking changes in the myeloid series, the cells of which were constantly depressed and showed obvious discrepancies between the maturation of the nucleus and that of the cytoplasm. It is known (Warren, 1945) that thiouracil inhibits respiration of the rabbit's bone marrow cells especially that of the immature myeloid cells. It thus seems probable that neutropenia and agranulocytosis depend on the presence of the drug in the immature granular cells of the haemopoetic marrow leading to arrest of respiration and normal development.

Sikkema *et al.* (1946) advise prophylactic leucocyte counts thrice weekly and even daily if the values are low. As a routine throughout treatment, this would clearly be impracticable. Careful dosage and supervision will minimize toxic reactions but it must be admitted that neutropenia occurs at very different dosage levels and after short or prolonged periods of administration; nor can we rely on clinical symptoms to indicate dangerous trends in the blood picture (Blackburn, 1948).

Treatment of the drug reactions. The paramount need is for prophylaxis by carefully regulated dosage and proper supervision. When the reaction is mild it will usually suffice to reduce the dose (McCullagh and Schneider, 1948). Alternatively, another preparation may be tried.

The occurrence of agranulocytosis calls for immediate cessation of antithyroid therapy and the institution of vigorous restorative measures. The slow transfusion of fresh, packed, cells will raise the granulocyte count while

the myeloid marrow is recovering. Injections of pentnucleotide, plexan or pyridoxine will also help. Penicillin therapy is a valuable prophylaxis against infective complications. Rest and general supportive treatment are also indicated.

Treatment of special clinical groups of thyrotoxicosis.

(i) **Thyroid crisis threatens.** Thyroid crisis or " storm " is not so much a complication of thyrotoxicosis as a potentially fatal state into which severe cases inevitably drift if treatment is neglected. Any patient with long-standing severe thyrotoxicosis, whose physical and psychical reserves are nearing exhaustion, is in a vulnerable state and a relatively minor upset or trauma may push her over into storm with its delirium, uncontrollable tachycardia, hyperpyrexia and terminal coma. Rarely she just drifts into a state of extreme prostration with muscular flaccidity and mental apathy (the apathetic type). The only satisfactory treatment of crisis is prevention. It is of vital importance that the practitioner should appreciate the dangerous plight of the patient who is restless, highly excitable and talkative, and has a rapid pulse, vomiting and diarrhoea. Nocturnal delirium is an even worse sign. Such patients may die out of hand and treatment is urgently necessary. Both Lugol's iodine and an anti-thyroid drug should be given in full doses forthwith. Sedatives, a quiet darkened room, cold-sponging, oxygen therapy, water, chloride, glucose and vitamins B and K by mouth and parenterally are among the other measures employed. Treatment should be adapted to the requirements of the individual. Each is an emergency requiring constant care and attention.

It has often been claimed that the addition of iodine delays the response to the anti-thyroid agents but Hibbs and McCullagh (1948) found little evidence of this. The iodine acts promptly by promoting colloid storage and reducing hormone secretion, while the anti-thyroid agent blocks its further synthesis. A flare-up of toxicity has often been noted following radio-iodine therapy in thyrotoxicosis (Werner *et al.*, 1948); so this form of treatment is contra-indicated when crisis threatens.

Regrettably crisis is not an extinct phenomenon but with the proper use of the anti-thyroid drugs it should be. " Medical " storms could be prevented by an increased alertness of the profession, resulting in earlier recognition and prompt treatment of thyrotoxicosis. " Surgical " storms could be prevented by complete anti-thyroid control before operation.

(ii) **Cardiovascular complications exist.** Anti-thyroid therapy should be pushed until the basal metabolic rate is slightly sub-normal. The fibrillating heart will then switch back to a normal rhythm in about 50 per cent. of cases (Goodwin, 1949). Rapid fibrillation or oedema calls for rest in bed, and careful dietary management including restriction of fluids and salt. Since the advent of anti-thyroid therapy, the outlook for the thyrocardiac has been transformed, for time can be taken to rehabilitate her fully before thyroidectomy. Granted complete control of thyrotoxicosis, mersalyl and paracentesis are rarely necessary; oedema usually looks after itself, especially when the rhythm reverts to normal. Thyroidectomy is ultimately necessary

especially in young patients or when there is associated organic disease of the heart which is likely to be aggravated by thyrotoxicosis. Clarke (1948) claims that thyroidectomy is preferable also in the elderly thyrocardiac.

If fibrillation persists, in spite of the complete eradication of hyperthyroidism and absence of organic heart disease, quinidine may be tried. But its administration is not free from risk and should only be undertaken in collaboration with a cardiologist.

(iii) **Mental complications are present.** The unearthing of sources of worry and stress and gradual re-education of the patient will do much to alleviate the psychological disorders associated with thyrotoxicosis and to minimize post-thyrotoxic psychoneurosis and depressions. When mental derangement has been precipitated or aggravated by thyrotoxicosis prompt anti-thyroid therapy is indicated.

(iv) **Ophthalmic forms of Graves' disease.** In the ophthalmic forms, as indeed in any patient with Graves' disease, it is important to assess the degree of thyrotoxicosis without regard to the eye-signs and to treat it on its own merits. The eye-signs may be very severe, though hyperthyroidism is slight or absent. The former will not be benefited by thyroidectomy and may even be aggravated.

An ophthalmologist should be given the earliest and fullest opportunity of controlling conjunctival exposure and infection. Partial or complete tarsorrhaphy may be indicated. Unroofing of the orbits has been done in recent years to relieve forward pressure on the globe and lids (Chapter XV). Should this operation become necessary, interim control of such hyperthyroidism as exists can be achieved by an anti-thyroid drug.

(v) **Glycosuria and diabetes.** These are an added indication for early control of hyperthyroidism. Nearly always the diabetic state is greatly relieved but this cannot be predicted with certainty and sometimes it is unaccountably worsened (Chapter XIV). Careful therapeutic trials with an anti-thyroid drug should be undertaken to ascertain the effect of full control and the optimum level of metabolism.

(vi) **Gastro-intestinal crises.** These call for prompt control of hyperthyroidism by the simultaneous administration of iodine and propyl- or methylthiouracil. The immediate need is to restore the normal fluid and electrolyte balances. The patient's probable requirements of blood, plasma, salt and water, should be estimated from the degree of wasting and dehydration present and the estimated further loss in the vomit, stools and perspiration. A day-to-day budget should be kept, the oral and parenteral nutrition being adjusted to meet any deficit that remains. It should be emphasized that while the patient's requirements should be fully met the excessive administration of intravenous saline may do much harm by producing widespread tissue, including pulmonary, oedema.

(vii) **Thyrotoxicosis complicating pregnancy.** In general it is the thyrotoxicosis not the pregnancy which should be interrupted. The standard treatment adopted by Mussey *et al.* (1948) is Lugol's iodine followed by thyroidectomy. Early fears concerning the dangers of anti-thyroid therapy during pregnancy

have not been substantiated by clinical experience. All the same it is probably wise to minimize their use and, if thyroidectomy has not been done, to switch over to iodine during the last month of the pregnancy. The anti-thyroid drugs are also freely secreted in the milk and as Williams has emphasized it is desirable to wean the infants of such mothers.

The need for cautious dosage is sufficiently indicated by Hone and Magarey's case (1948). A young woman with thyrotoxicosis was given methylthiouracil in large doses throughout her pregnancy. She was eventually delivered of a cretin infant who died some hours after birth and at autopsy showed considerable thyroid hyperplasia and vascular engorgement. Goldsmith *et al.* (1945) have produced a similar condition experimentally in newborn rats.

Since the foetal thyroid is functionless before the fourth month, the mother may be treated with radio-iodine up to that stage of pregnancy without retention of radioactivity in the foetus's thyroid (Chapman *et al.*, 1948).

Where the thyrotoxicosis is mild we prepare the pregnant patient with iodine and then proceed to thyroidectomy. When it is severe or complicated we first control it fully with methylthiouracil and then undertake thyroidectomy after two to three weeks' pre-operative iodine.

In endemic regions there is often an added mechanical factor to be considered (Steiner, 1948). Local pressure effects are likely to be aggravated during labour. Consequently early thyroidectomy is indicated.

(viii) **The patient is a child.** Here, especially in the mild degrees of thyrotoxicosis, there is great scope for anti-thyroid therapy. Supervision, however, must be close to avoid hypothyroidism which may prejudice full physical and mental development. When thyrotoxicosis is severe and the gland greatly enlarged, recourse may be had to surgery after careful preparation; but too radical an excision should not be done, again because of the ill effects of hypothyroidism in the young.

(ix) **Myasthenia or myopathy co-exists with thyrotoxicosis.** If a response to prostigmine exists, then this drug should be administered in carefully regulated doses while steps are taken to combat thyrotoxicosis. Anti-thyroid therapy is indicated for a long initial period to allow the patient's strength to be regained. When the respiratory muscles are greatly weakened, secretions accumulate in the upper respiratory passages and should be aspirated at the beginning and the end of the operation, which may best be performed under local anaesthesia, with the patient propped up.

(x) **Recurrent thyrotoxicosis.** The mortality rate following surgery in this group is distinctly greater than after primary operations and there is accordingly great scope here for definitive anti-thyroid therapy. Where there is already paralysis of one or both recurrent laryngeal nerves, anti-thyroid drugs will indeed be the treatment of choice.

(xi) **A toxic single nodule is present.** In these patients it will be sufficient to resect the nodule with a minimum of the surrounding gland tissue. The latter tends to be atrophied and sub-normal in function (see Chapter XI) and it is therefore both unnecessary and harmful to resect it.

(xii) **Thyrotoxicosis exists in association with some unrelated disease.** The relative urgency of the two conditions must be estimated and treatment planned accordingly. We are fortunate nowadays in having available anti-thyroid therapy which may be used to control the thyrotoxic state while treatment of the associated condition is carried out.

Dental and tonsillar sepsis are often associated with thyrotoxicosis. The offending teeth or tonsils should not be removed before fully controlling the thyrotoxic state, otherwise crisis may be precipitated. In general, control of such minor foci of sepsis is best postponed until treatment of the goitre has been completed.

Radio-iodine therapy and thyrotoxicosis. There is enough evidence even at the present early stage to suggest that radio-iodine is a very promising method of treating thyrotoxicosis. Chapman *et al.* (1948) have reported on their results in forty-one patients treated with I–131. The dose was 8–14 millicuries by mouth or an average effective dose of 142 microcuries per gram of thyroid tissue. Brilliant results including disappearance of the goitre have been obtained in most cases. Myxoedema was produced in only 4–10 per cent. of the cases.

Of forty patients given a single dose of I–131 by Hawes *et al.* (1948), twenty-seven obtained good results, eight fair results, and five poor ones. The good results were obtained in those given the highest average dose of radio-iodine, namely 242 microcuries per gram of thyroid tissue. Their data suggest that there are great individual variations in the sensitivity of different toxic glands to irradiation.

Miller *et al.* (1948) draw attention to the fact that radioactive iodine therapy is not likely to be effective if the gland is already saturated with iodine. Nor is it useful for thyroiditis, non-toxic goitre or involutional thyroid nodules. It is only occasionally useful in the treatment of thyroid cancer.

Soley and Miller (1948) used doses of up to 10 millicuries of radioactive iodine in treating thirty patients with Graves' disease. They administered 2,000 microcuries to start with and repeated this dose monthly until the required effect was obtained. Some 75 per cent. of their patients had a satisfactory remission in from one to seven months.

Werner *et al.* (1948) report on the results in forty cases of unquestionable toxic goitre. The dosage used was 3–4 millicuries of I–131 and the treatment was successful in 75 per cent. of the cases. Most of the patients took one to three months to respond. Hypothyroidism occurred in 10 per cent. but was transient in all. Seven of the thirteen, whose initial response was unsatisfactory, were given a second dose and three more responded favourably. Thus of the thirty-four cases given a single dose or two doses when necessary, 30 or 88 per cent. had been put into remission. The success rate thus compares very favourably with that of surgery and is better than that from definitive anti-thyroid therapy. Where therapy was successful the size of the gland was reduced to within normal limits two or three months after therapy. Where the treatment failed the gland size was not reduced to normal.

However it is only fair to admit that the potential hazards of radio-iodine

therapy are great. Nickson (1948), a bio-physicist, asserts that " its use in the treatment of non-malignant diseases of the thyroid should be reserved for those patients in whom the other possible means of therapy have failed or cannot be used." Skanse's fundamental studies (1948) on the effect of radio-iodine on the normal functioning of the thyroid gland also serve to demonstrate how empirical is its therapeutic use at the present day.

Brilliant results from radioactive iodine therapy have been reported by Crile *et al.* (1949). In 90 per cent. of their 105 thyrotoxics, hyperthyroidism was controlled in two to four months by one or two treatments. Ten per cent. of patients required a third treatment. Hyperthyroidism associated with nodular goitre was more difficult to control than that with diffuse goitre and, though the nodular goitre diminished in size, unlike the diffuse goitre, it did not disappear.

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CHAPTER XVIII

DEVELOPMENTAL ANOMALIES OF THE THYROID GLAND

Classification of Congenital Anomalies

Aplasia and Hypoplasia of the Thyroid: Aplasia — Simple Hypoplasia.

Abnormal Descent of the Thyroid: Lingual Thyroid — Illustrative Case — Clinical Features — Pathology — Diagnosis — Treatment.

Arrested Descent of the Thyroid.

Mediastinal Ectopia.

Accessory Thyroid Nodules: Treatment and Prognosis.

Intralaryngeal and Intratracheal Thyroid Tissue.

Thyroglossal Cysts and Fistulae.

Suprahyoid Cysts and Fistulae: Pathology — Clinical Features — Treatment.

Infrahyoid Cysts and Fistulae: Pathology — Clinical Features — Diagnosis — Prognosis — Treatment.

Struma Ovarii: Treatment.

The origin of the thyroid gland has already been traced from a mid-ventral pharyngeal diverticulum, which, growing caudalwards, eventually becomes bilobed and spreads out laterally, to give rise to the adult type of gland. Arrest of development may occur at any stage, so that the gland may never reach the neck but develop wholly in the tongue, or fragments may be held up along the tract and grow independently.

On the other hand, thyroid tissue may reach situations some distance from the normal tract or much lower down than the normal limits of the gland. Numerous other abnormalities may occur in connexion with the original thyroglossal duct or tract, a detailed knowledge of the structure and relationships of which is necessary in order to permit of proper surgical treatment.

The *foramen caecum*, which can be seen in the normal tongue far back on its dorsum, lies directly over, but is not identical with, the site of the upper end of the thyroglossal tract. The tongue develops later than the thyroid *anlage*, and when the former is complete the original orifice of the thyroglossal duct is covered in, though it can be identified in the depths of the floor of the foramen caecum. The first detailed investigation of the thyroglossal tract was made by Bochdalek (1866). The tract passes downwards through the substance of the tongue in close relationship with the fibres of the geniohyoglossus muscle as far as the hyoid bone, which, developing at a later date than the thyroid *anlage*, pushes against the posterior wall of the developing duct in a downward and forward direction. The duct lies closely apposed to the anterior surface of the hyoid; it passes underneath the lower edge of the bone, and takes a course upwards and backwards behind the body of the hyoid, very soon turning downwards to resume its original direction. Subsequently, further growth of the hyoid bone produces an actual interruption in the thyroglossal tract, so that it can eventually be divided into a

supra- and an infra-hyoid portion. This account based on the work of Wenglowski (1912) Rémy Néris (1929), and others, differs from that of Keith (1909), who describes the hyoid bone as at once breaking up the developing thyroglossal duct into an upper and a lower portion, while His (1891) describes the duct as passing entirely posterior to the bone.

The *supra-hyoid* part of the duct may, in rare cases, persist as a canal (Bochdalek, 1867), though it seldom reaches as far as the hyoid, and rarely exceeds 1 in. in length. The main duct may have one or many branches or diverticula; one of these in particular passes backwards towards the epiglottis, and may be conspicuous, though Bochdalek, as Rémy Néris remarks, was in error in regarding it as the main duct, for the latter passes almost directly downwards with only a very slight inclination backwards. It is important to realize that, even when portions of the tract persist, a continuous canal or cord can seldom be found, but, rather, fragmentary remnants of such structures. Rémy Néris therefore doubts the accuracy of Bland Sutton's figures (1886) *viz.*, that a solid cord persists in 10 per cent. of cases.

The *infra-hyoid* portion of the tract becomes deflected to one or other side of the median plane of the body by the prominent laryngeal cartilages so that the pyramidal lobe is almost invariably placed somewhat laterally, usually on the left side.

Classification of Congenital Anomalies

1. Aplasia
   - complete (basis of sporadic cretinism).
   - incomplete.
2. Simple hypoplasia.
3. Abnormal descent
   - complete failure of descent.
   - arrested descent.
   - mediastinal heterotopia.
4. Heterotopia and persistence of small fragments of thyroid anlage.
   - (i) Accessory thyroid nodules
     - at foramen caecum.
     - intralingual
       - in tract.
       - apart from tract.
     - sublingual.
     - submaxillary.
     - near hyoid bone.
     - on surface or borders of gland.
     - inferior.
     - intra-laryngeal, intra-tracheal.
   - (ii) Thyroglossal cysts or fistulae.
     - in the region of foramen caecum.
     - intra-lingual.
     - sublingual and submental cysts.
     - suprahyoid cysts.
     - infrahyoid cysts and fistulae.

5. Struma ovarii { dermoid with thyroid tissue. / cystoma with thyroid tissue. / true thyroid tumour.

The expression, "accessory thyroid tissue," is used here to describe thyroid tissue which is separate from and present in addition to a normal thyroid gland in the usual anatomical location. "Aberrant thyroid tissue" is the description applied to gland tissue which has been side-tracked from the normal location; part or whole of the gland is therefore missing from the usual site.

Aplasia and Hypoplasia of the Thyroid

Aplasia. Complete aplasia is the usual basis of sporadic cretinism. Degenerate thyroid remnants are often identifiable in the region of the foramen caecum of the tongue.

Partial aplasia may affect the isthmus, or one or other lobe. As would be anticipated from its comparative anatomy, the isthmus is subject to considerable variation. It may be well developed and fleshy, rudimentary and composed only of connective tissue, or entirely absent. The last obtains in about 5 per cent. of cases.

Of greater interest is the far rarer anomaly, complete absence of one lobe, which occurs only once in about two thousand subjects (Pemberton and McCaughan, 1933). To date some twenty-nine instances have been reported. Its frequency in the two sexes is about equal. As with aplasia of other paired organs, such as the lungs and kidneys, it affects the left side much more often than the right. The corresponding thyroid arteries may both be present, though rudimentary, or one or both may be absent. The defect may originate from failure of the original anlage to send out cell processes to both sides, or in other words to become bilobed. In one of Poate and Wyndham's cases (1938) the isthmus, pyramidal lobe, and right lobe were all absent.

The absence of one lobe does not, of itself, produce symptoms, and as a result, it is generally discovered incidentally. Nodular enlargement of a unilobular gland may, however, greatly displace the trachea as in Lazarus's case (1948). Pemberton and McCaughan rightly emphasize that the surgeon should always expose both lobes before proceeding to thyroidectomy.

Simple hypoplasia. This may be responsible for some cases of congenital hypothyroidism.

Abnormal Descent of the Thyroid

Complete failure of descent results in a lingual thyroid. Verneuil (1853) is said first to have described one of these tumours, though the credit of priority is often given to Zuckerkandl (1879) or to Kadyi (1879).

Illustrative case. Amy P., twenty-six.

History. Swelling on the back of the tongue had been noticed eight years before, with bleeding from the tumour a year afterwards. It had increased

in size rapidly in the previous three or four weeks. There was occasional difficulty in swallowing solid food, but no other symptoms. *Examination:* a swelling, the size of a tangerine orange, was seen in the position of the foramen caecum. *Operation:* Preliminary laryngotomy; tumour removed. It was not definitely encapsuled, and had a broad base. There was free bleeding, controlled by packing. Both before operation and during laryngotomy, the neck was carefully examined for evidence of the normal gland, but it could not be felt. *Microscopically:* the tumour had the structure of the thyroid gland, with follicles of varied size. Hypothyroidism followed the operation but was corrected by the administration of dried extract, grs. v daily, and 15 years afterwards the patient was perfectly well.

Preliminary laryngotomy, much used in earlier days, is no longer necessary for the removal of the lingual thyroid. The trachea is now intubated through the nose and the pharynx packed off before the operation commences.

In 1936 Montgomery made an exhaustive analysis of the 144 cases of lingual thyroid reported in the literature to that date. There were seventeen males and 118 females, the sex being unrecorded in nine cases. At least fourteen more cases have been described since, but the following account is largely derived from Montgomery's monograph.

Clinical features. Symptoms generally develop between the ages of ten and thirty-two years and are mild. They include changes in the voice, interference with swallowing, bleeding, choking attacks and dyspnoea. In rare cases there have been general symptoms suggestive of hyperthyroidism. Much more frequently, however, indeed in about 15 per cent. of patients, there is moderate or severe hypothyroidism, and in these patients the menses are often delayed and scanty. With suitable thyroid therapy menstrual function may revert to normal and pregnancy occur (Goetsch, 1948). Dwarfism may be present.

The lingual thyroid is subject to the same physiological and pathological influences as is the normal gland. Pregnancy, menstruation, and the menopause may be associated with the onset of hypertrophy and aggravation of symptoms. Cyclic haemorrhage may occur with the menses and in one patient symptoms developed following an operation for bilateral öophorectomy. In another case, the lingual thyroid became evident following a severe psychic shock.

It is usually spherical and largely embedded in the tongue, but it may be pedunculated. It has ranged from the size of an orange or a fist down to that of a pea. Its surface is smooth or slightly irregular, its colour dusky-red or brownish, and its consistency hard, elastic or fluctuant. Large veins may be seen coursing over it. Its centre is not always in the midline of the tongue. The overlying mucosa may be normal, atrophic, ulcerated or necrotic. About 70 per cent. of such patients have no thyroid gland in the neck. In the remainder, there is a cervical thyroid either in the normal location or near the hyoid bone.

Pathology. The cut surface of the lingual thyroid is reddish to yellowish and sometimes shows cystic, fibrous, calcific or other degeneration. In 55

per cent. of cases the predominant histology is that of a normal thyroid; in 20 per cent. the structure is foetal in type; in 9 per cent. there is colloid or adenomatous degeneration. Haemorrhagic, fibrotic or calcific degeneration predominates in the remaining 15 per cent. Parathyroid tissue has been identified and at least one patient has developed tetany following excision of the lingual nodule. Carcinomatous degeneration of the lingual thyroid with metastases in the lungs has been reported in the male, but has not been proved to occur in the female.

Diagnosis. The lingual thyroid has to be differentiated from benign tumours such as adenoma, angioma, fibroma, lipoma and teratoma, from a lingual tonsil or cyst, and from malignant neoplasms, including lymphosarcoma and carcinoma. Formerly, the diagnosis of lingual thyroid could rarely be indisputably established without a biopsy and Montgomery (1936) believed that this should be a first step in all suspected cases. Now, using radioactive iodine and a suitably mounted Geiger counter, the precise localization of any functioning thyroid tissue can be determined. It was thus established in a case of lingual thyroid reported by Nachman *et al.* (1949) that there was no thyroid tissue in the neck.

Treatment. If non-malignant and non-degenerate thyroid tissue is found, every effort should be made to reduce the size of the swelling by medical treatment. It was an unfortunate whim of fate that one of the first instances of this anomaly ever described failed to respond to iodine treatment, for this has resulted in an undeserved bias against medical therapy. Goetsch (1948) considers that it would have been preferable to excision in at least one of his three cases. In Montgomery's own case there was a remarkable reduction in the size of the lingual nodule with Lugol's solution. The latter should be supplemented by desiccated thyroid to tolerance dosage, the rationale being to cause disuse atrophy of the lingual thyroid. Medical therapy must be continued for at least a year.

If bleeding is persistent or if the lingual thyroid has attained such a size as to cause dysphonia, dysphagia or dyspnoea, surgery is indicated. A therapeutic dose of radio-iodine has been used with advantage as a preliminary to surgery (Schilling *et al.*, 1950).

If a tracer dose of radio-iodine shows that there is no thyroid tissue in the neck, conservative resection of the lingual thyroid is indicated, especially in young patients, in whom myxoedema may lead to imperfect mental and physical development. If, however, the patient is a male beyond the age of thirty, excision should be complete, because of the risk of carcinomatous degeneration.

The operation has usually been undertaken through the mouth. A preliminary tracheotomy, for anaesthetic purposes, enables the surgeon to make at least a rough estimate of the condition of the thyroid tissue at the usual site, but under modern conditions an intratracheal tube passed through the nose provides the best method of administering the anaesthetic and of avoiding respiratory embarrassment due to haemorrhage or to the bulk of the tumour. The tongue must be pulled forwards firmly by means of traction

sutures introduced through its substance, the mouth gagged open widely and the pharynx packed off with a roll of soft gauze. The tumour can then usually be resected rapidly, haemorrhage being controlled by firm pressure with gauze, quickly followed by a series of catgut sutures. The immediate effect of such operation has almost invariably been satisfactory.

Splitting the tongue along the raphé to provide better access to the deeper parts of the tumour has been advised, but it appears to us an unnecessarily severe step. Patterson (1928) advocates the cervical approach to such tumours because opening into the buccal cavity is avoided, but while feasible for large tumours deeply embedded in the tongue it can hardly be a satisfactory method for a tumour the greater part of which projects into the mouth.

Arrested descent of the thyroid. The gland may fail to descend as far as its normal location in the neck and in this event it is usually ill-developed. In a woman aged thirty reported by Kidd (1945) the thyroid was represented by two separate nodules, one lying above the hyoid and the other just below its left cornu. Following excision of the former, the latter enlarged somewhat. The rings of the trachea could be felt with suspicious ease at the normal level of the thyroid.

Mediastinal ectopia. Too caudad migration is usually an atavistic manifestation; the thyroid gland normally lies on the pericardium in certain reptiles.

Accessory thyroid nodules. In addition to the normal gland, nodules of thyroid tissue may be encountered anywhere along the line of the thyroglossal tract from the foramen caecum of the tongue as far down as the heart and pericardium. Thus some patients with a lingual thyroid nodule have a normal gland at the usual site in the neck. Nodules in the tongue may lie in the line of the tract or quite apart from it. In the complicated growth shiftings of the pharyngeal floor parts of the thyroid anlage may be carried forward in the substance of the tongue. Montgomery quotes two cases of lingual thyroid occurring near the tip of the tongue. Rosedale's patient (1936) had a large thyroid nodule in the floor of the mouth and in 1912 Haynes removed a solid thyroid tumour from the sublingual region which bulged underneath the chin. In Guilliminet and Marion's case (1946) a swelling appeared in the left submaxillary region following excision of a large nodular goitre. At operation a nodule of aberrant thyroid tissue was found lying superficial to the mylohyoid muscle.

Accessory thyroid tissue may also be found in connexion with the pyramidal process, on the antero-lateral surface of one of the lobes, or below the thyroid. In fact, the commonest site of accessory tissue is probably in the last situation; if the lower pole of the thyroid is brought upwards it is common to find a nodule or two of thyroid tissue attached to the lower pole only by fascial tissue. Occasionally, a chain of such nodules passes downwards into the mediastinum. Intra-thoracic goitres both innocent and malignant may arise in such heterotopic tissue. In goitrous dogs described by Graham (1946), accessory thyroid tissue was found loosely

attached to the lateral borders and inferior poles of the gland, on the innominate vein, and even within the pericardium.

True aberrant or accessory thyroid tissue must be distinguished from the lymph glandular metastases of a papilliferous carcinoma of the corresponding thyroid lobe. The primary growth may be so small as not to cause any visible or palpable enlargement of the gland and formerly the lymph glandular metastases were often erroneously thought to be lateral aberrant thyroids undergoing malignant degeneration. This matter is referred to more fully in Chapter XXII.

Treatment and prognosis. Unless definite pathological changes occur accessory and aberrant thyroid tissue need not be disturbed; but if it undergoes goitrous development or grows to an unsightly size, it may require removal.

Intralaryngeal and intratracheal thyroid tissue. It is conceivable that during the process of differentiation of the larynx and trachea small fragments of the developing thyroid may become included within the upper respiratory tract, subsequently enlarging to form tumours which interfere seriously with the respiratory function (Bruns, 1904). It is also possible, as Paltauf (1891) holds, that the developing thyroid may penetrate the wall of the larynx or trachea at some weak spot, and that the supervention of goitrous changes may be associated with a considerable increase in size of what was previously a trivial or negligible mass of tissue. It is probable that intralaryngeal and intratracheal aberrant thyroid masses can originate in both ways. Direct penetration of the trachea can of course occur in carcinoma of the thyroid as in Szende's case (1939). Spread by lymphatics to the submucosa of the trachea is also not very unusual. Intratracheal hyperplasia of thyroid tissue often leads to fatal respiratory complications as in Pendl's case (1947).

Ziemssen, in 1875, reported the first case of laryngeal thyroid; it occurred in a female aged eighteen and was the size of a cherry.

In Dorn's case (1919), a male aged thirty-two, who had had a goitre from puberty, rapid growth of the gland and pressure symptoms had been noticed for six months; the patient was hoarse, and one vocal cord was paralysed. The goitrous gland was found at operation to have penetrated the cricothyroid membrane. The intralaryngeal mass was scooped out, but recurrence followed, and subsequently a dumb-bell shaped thyroid tumour, partly inside and partly outside the laryngeal cavity, had to be removed by laryngo-fissure.

In Gödel's (1921) patient, a woman of thirty-nine, death from suffocation occurred from a mass, the size of a hazel-nut, which had penetrated into the lumen at the junction of the larynx and trachea; it was in continuity with the goitrous gland in the neck and had a similar structure.

Maier (1923) was able to collect twenty-eight cases. He estimates that one-fifteenth of all intratracheal tumours are of thyroid origin. His case was operated on by von Haberer through a low tracheotomy incision, and the wall of the trachea was found to be intact, differing therefore in

character from the cases described above. It is noteworthy that this patient had been operated on for goitre about five months before, during late pregnancy.

Bundschuh (1925) collected thirty-five cases up to 1924, and described two in females aged fifteen and twenty respectively.

Syring (1927) reported a single case of intratracheal thyroid cyst among 1,018 operations for goitre.

Vacher and Denis's patient (1927) complained of respiratory distress with each successive pregnancy; the intratracheal tumour was attached to the second and third tracheal rings by a broad base, and was removed by morcellement through a tracheotomy incision.

Clinical Features. E. Meyer (1910) described a case in a child of five months, but the condition is mainly one of adolescence and early adult life. There is a strong preponderance among women, especially during and after pregnancy.

Signs and Symptoms. Severe respiratory disturbance, aggravated in women during pregnancy and labour, sometimes paroxysmal in nature; cough and expectoration, often severe and distressing; hoarseness: all these may occur but, as they are also common in goitrous conditions of the gland, the existence of an intralaryngeal or intratracheal mass is likely to be overlooked until the goitre has been removed, when persistence or recurrence of cough and dyspnoea may lead to the discovery of the tumour by endoscopic examination.

Huber (1948) advises laryngoscopy and tracheoscopy as a routine in patients whose symptoms persist after thyroidectomy. He claims that such endoscopic examination is an essential preliminary to any operation for recurrent goitre.

Diagnosis. This can only be made with certainty by the use of a direct laryngoscope or bronchoscope. The tumour usually appears as a small, dark red nodule projecting into the lumen of the trachea or the subglottic region of the larynx, and its exact site must be determined in order to permit of accurate surgical approach. It very rarely occurs lower than the fifth tracheal ring. Its colour and softness enable it to be differentiated from tumours arising from the laryngeal and tracheal cartilages.

Prognosis. The prognosis of this rare condition is very favourable, provided that complete removal of the tumour is effected. Fatalities, when they occur, are nearly always due to post-operative pulmonary complications.

Treatment. An intratracheal tube, if it can be passed well beyond the obstruction, will enable comfortable anaesthesia to be maintained. If this be impracticable, tracheotomy below the level of the tumour will permit the use of a Junker's inhaler, or local anaesthesia alone may be employed. Whenever possible, the operation should be conducted from without, exposing the thyroid gland or goitre, and separating it from the upper part of the trachea and larynx, so as to lay bare the site of the tumour previously determined by endoscopic methods. If continuity between the gland and the

intratracheal extension be established it may be possible to withdraw the latter after enlarging the gap in the membrane or cartilages. The importance of complete removal is indicated by the recurrences which have followed such operations as the curetting or scraping away of the intratracheal tumour. If the mass be *intralaryngeal*, laryngo-fissure may be necessary to permit successful extirpation, as in Beeson's remarkable case (1937). The patient, a male aged fifty-one, presented alarming dyspnoea and cyanosis. The glottis was almost completely occluded by a smooth pale pink tumour, which measured $4 \times 3{\cdot}5 \times 3$ cms. after removal. Baldenweck and Levy-Deker (1936), however, were able to remove a small nodule of tissue, showing the structure of colloid goitre, from the anterior angle between the vocal cords, under laryngoscopy. If the nodule is intratracheal but without any obvious connexion with the thyroid gland, tracheotomy near the site of the tumour will be the best method of approach.

Thyroglossal Cysts and Fistulae

A thyroglossal fistula results from the breaking down of the skin or mucosa overlying a cyst. Infection often exists in the cyst wall (McClintock, 1936) and probably determines the breakdown. Of forty-three patients studied by Hubert (1947), twenty-five had infrahyoid cysts, five had suprahyoid cysts and thirteen had developed a sinus or fistula.

Suprahyoid cysts and fistulae. In addition to the cysts which result from degeneration of solid thyroid tumours of the tongue, and are therefore properly classified and described under that heading, other cysts occur in the tongue in connexion with the thyroglossal canal. They may be found in any part of its course—high up near its point of origin, or low down just above the hyoid bone. They may be so small that they are found only when the tongue is searched systematically post mortem, or they may be large enough to produce a conspicuous swelling.

" Blind " fistulae are occasionally met with in connexion with the foramen caecum. They represent the uppermost part of the thyroglossal tract, are usually short, seldom give rise to symptoms, and therefore are discovered only after death. If post-mortem search is made, small but definite remnants of the thyroglossal tract can be found between the thyroid gland and the hyoid bone in over 50 per cent. of adults (Batson, 1946). Sometimes there is a solid mass of tissue, sometimes a small tube with a lumen.

Pathology. These cysts and fistulae originate from the duct itself, and are usually unilocular, with smooth walls and clear, mucoid contents, though occasionally they contain turbid fluid with numerous cholesterin crystals. Microscopically, they are lined by epithelium which may be stratified squamous, columnar, or ciliated; mucous glands are also commonly found. Such cysts are therefore distinguishable from solid thyroglossal tumours in that they usually show no trace of thyroid cells or vesicles in their walls. The epithelium is sometimes entirely or largely missing, owing to inflammatory changes, and it is in such specimens that cholesterin crystals occur in the fluid contents.

Hubert (1947) remarks that if there is a fluctuant lump in the midline of the neck the aspirating needle provides a reliable means of diagnosis. Epithelial cells and cholesterol crystals in the aspirate make the diagnosis of thyroglossal cyst certain. The wall of the cyst may contain lymphoid tissue in greater or lesser amount.

Seelig (1907) and Patzelt (1923) have shown that the thyroglossal tract is not a simple duct or canal, but that the lingual portion has very complicated ramifications and diverticula, so that not only may the main duct give rise to these anomalies, but so also may one or other of the branches and diverticula.

Clinical Features. When large enough to attract attention these cysts give rise to symptoms which depend on their situation. If high up, interference with swallowing, mastication, and speech may occur, though rarely to so great an extent as with the solid tumours of the thyroglossal apparatus, which far more often project into the pharynx or are pedunculated. In the case of cysts situated lower down, i.e., in the supra-hyoid region, a smooth, rounded swelling is found, median in position and more or less prominent according to its size. Swallowing movements influence the position of the cyst.

Treatment. When situated near the foramen caecum, a cyst can be removed by a slight modification of the method described for the extirpation of solid thyroid tumours of the tongue, but a freer incision of the mucous membrane over the cyst is necessary, and its enucleation intact should be the surgeon's aim.

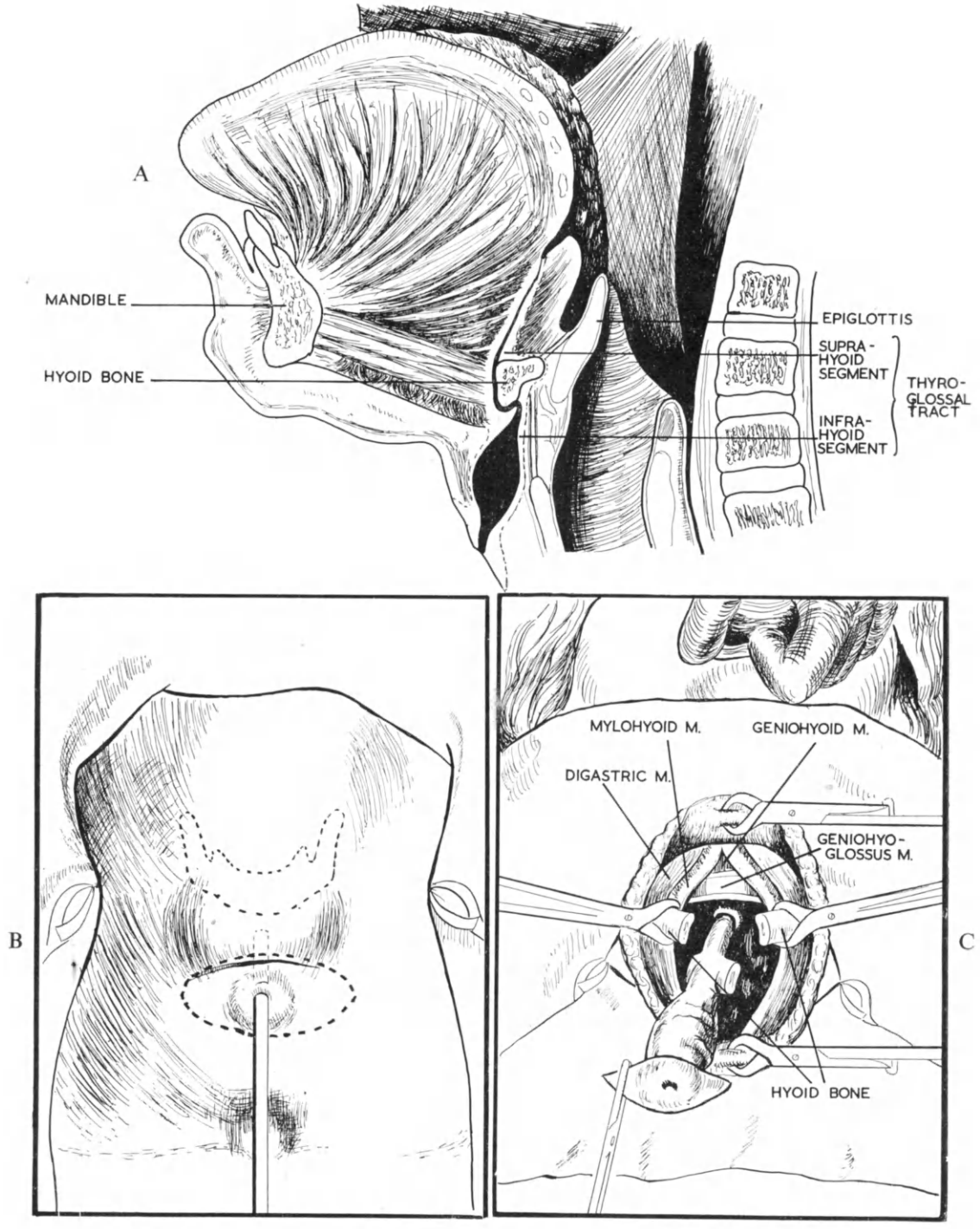
When the cyst is in the supra-hyoid region, a curved transverse skin incision, just above the body of the hyoid, gives adequate access. The skin and superficial fascia, with the platysma, are reflected, the deep fascia and mylohyoid divided, and the cyst wall exposed after separating the two geniohyoid muscles. The removal of such cysts is usually not difficult, as they have not the same tendency to possess the diverticula or prolongations found in the commoner subhyoid thyroglossal cysts and fistulae.

Infrahyoid cysts and fistulae. Thyroglossal cysts may be noticed soon after birth, but are more common in early childhood; occasionally they do not develop until late in life. We have removed one from a patient of seventy-five, in whom it had appeared only a year or two previously.

The cyst is generally smooth, rounded or ovoid, and placed exactly in the middle of the neck over the cricothyroid region, but it may lie rather higher up or lower down. Occasionally the cyst is lobulated and asymmetrically placed, probably owing to the pressure of a prominent thyroid cartilage. The largest in our series was the size of a tangerine orange.

Thyroglossal fistulae are very rarely, if ever, present at birth, but may develop soon afterwards. Three-quarters of Hubert's cases (1947) were under thirty years of age.

The fistulous opening is small, and is surrounded by atrophic skin, often reddened and adherent to the underlying structures. A crescentic fold of this atrophic skin usually overhangs and conceals the fistulous



THYROGLOSSAL FISTULA

FIG. 111.—A. To show general course of thyroglossal fistula and details of its relation to the hyoid bone. B. To show the elliptical incision for the excision of the unhealthy skin about the orifice of the fistula. C. To show the method of extirpation of the deeper part of the fistula. The central portion of the body of the hyoid bone has been excised and is left adherent to the tract. The index finger of the assistant's x right hand exerts pressure over the foramen caecum in the mouth. Modified from Sistrunk.)

opening. Rarely, the fistulous opening may be raised on a papilla. The discharge from the fistula is usually intermittent, and consists of clear fluid, which may contain considerable quantities of mucus, but the supervention of sepsis converts the discharge into a turbid or frankly purulent one. Mastication and swallowing increase the flow from the fistula. Iodine is said to have been detected in the discharge, though this is probably true of exceptional cases only.

These fistulae pass upwards towards the hyoid bone, and take the curious course which has already been described, *viz.* at first they pass behind the hyoid bone, but soon turn sharply downwards and forwards and continue over its anterior surface, and then upwards behind the mylohyoid muscle and between the geniohyoids, to pass almost vertically through the tongue to the foramen caecum, with which they only very rarely communicate. The association between the fistula and the hyoid bone is so intimate that for purposes of treatment it is convenient to adopt the view that they cannot be separated, and therefore that a portion of the bone needs to be removed with the fistulous track.

Emphasis has been laid on the extent to which these fistulae may correspond with the whole of the original thyroglossal canal and its ramifications and diverticula, but our experience is that many of them do not extend beyond the hyoid, and that careful extirpation of the fistula up to and including the median segment of the body of the bone is sufficient for cure. The lumen of the fistula may be irregular and so fine as scarcely to admit the finest probe, or it may be regular and wide enough to admit a small urethral catheter. The walls are generally smooth, but papillomata occasionally are present.

We have operated on twenty-five thyroglossal fistulae, of which only two were complete, while in eighteen the fistula extended only as far as the body of the hyoid, to which it was so closely connected that its central portion was removed in order to ensure complete extirpation of the tract. In five cases the fistula appeared to end abruptly below the hyoid.

Pathology. Thyroglossal cysts contain fluid which may be clear and mucoid, or dark and turbid from the presence of cholesterin, degenerated epithelial cells, and altered blood. There is never any evidence of sebaceous material or hair.

König (1895) first ascribed these fistulae to persistence of the thyroglossal tract. They are essentially derivatives of the canal, and therefore are usually lined with epithelium, though Patterson (1928) has established that the lining is often incomplete owing to the destructive action of inflammatory changes. His carefully compiled figures from the London Hospital prove that the majority of both fistulae and cysts are lined by stratified columnar, cubical, transitional, and squamous epithelium in varying proportions, while in a few it is columnar and ciliated, or purely squamous. The subepithelial zone of the wall of the fistulous track or cyst often contains lymphoid tissue, but this is scanty and discontinuous, and therefore unlike that occurring in the wall of a branchial cyst. Outside the epithelial lining

is a connective-tissue covering, rich in elastic tissue and blood vessels. Thyroid gland tissue in smaller or larger amounts, and in various stages of evolution, from solid cell masses to well-formed follicles, can be found in or near the wall of about one-half the cases of thyroglossal cysts, and in about one-third of fistulae. Patterson also records intracystic papillomata in two cases. Thyroglossal cysts are usually unilocular, but diverticula may be present. Multiple cysts are rare; Patterson observed three in one of his patients.

Clinical features. There is no clear evidence of a sex-preponderance in these conditions. Sistrunk (1920) states that in the Mayo Clinic most cases are seen between the ages of twenty and twenty-five. In our experience, thyroglossal *fistulae* are commoner than cysts in the first decade, and are therefore usually seen at hospitals for children, whereas in older patients thyroglossal *cysts* are much commoner than fistulae.

Diagnosis. Thyroglossal cysts are very easily recognized from their site and their attachment to the hyoid bone, but it is not always possible to distinguish them from certain solid thyroid tumours derived from the pyramidal process, though they may be translucent when examined by transmitted light. They must also be differentiated from enlarged lymphatic glands on the cricothyroid membrane, sequestration dermoids, sebaceous cysts, lipomata, and thyrohyoid bursae. When not placed strictly in the middle line of the neck, and especially if situated below the cricoid cartilage, differentiation from adenomata and cysts of the thyroid isthmus is almost impossible. Dermoid cysts are very rare in this region, though not uncommon in the supra-hyoid region.

Thyroglossal fistulae are not likely to be mistaken for anything but tuberculous sinuses associated with adenitis of the cricothyroid gland. Such sinuses lead directly backwards or to one side, and do not pass upwards towards the hyoid bone. There may also be evidence of disease in other cervical lymphatic glands.

Prognosis. All incomplete operations are futile. We have seen patients who have had as many as five operations for recurrences. Spencer (1914) quotes one case operated on eight times. We have had to operate twice in three cases; the remaining twenty-one were cured by a single intervention.

Owen and Ingelby (1927) have reported a case of malignant disease beginning in the thyroglossal duct; a solid tumour, the size of a hen's egg, was situated a little to the left of the thyroid cartilage, and on removal proved to be a papillary adenocarcinoma.

Treatment. Successful results are to be expected only if the whole of the cyst, fistula, or sinus, with any diverticula or side-tracks, is removed. If even a small part of the epithelium responsible for the production of the contents of the cyst, or of the secretion from the fistula, be allowed to remain recurrence is likely to follow.

For complete extirpation the full extent of the cyst or fistula must be known. Enough has been said to make it clear that the surgical anatomy of these conditions is complex, but it is wrong to assume that in all cases

the whole thyroglossal tract will need extirpation. Its upper portion is often already obliterated, so that the extensive operation described by Sistrunk may be unnecessary.

The injection of certain dyes, .e.g, 1 per cent. gentian violet, or 10 per cent. methylene blue, may help the surgeon in following the fistula to its termination. Collargol, lipiodol, or a 20 per cent. solution of sodium bromide, with the help of carefully orientated skiagrams, may serve to determine the exact limits of the developmental anomaly.

We have found the dye the more satisfactory, but both methods may fail when a complete interruption of the continuity of the tract is associated with its persistence above the obliterated segment. Injection methods may also reveal duplication of the thyroglossal duct over portions of its course, especially below the hyoid region. Spontaneous cure is rarely, if ever, seen, and the only satisfactory procedure is to extirpate the whole cyst or fistula, together with any ramifications which exist.

The *operation*, which should be conducted under intratracheal anaesthesia, is carried out through a slightly curved transverse incision, a natural crease in the skin being selected for the purpose if possible. A flap is fashioned above the incision, as it is in this direction that the dissection must proceed. If a fistula be present its orifice should be enclosed by the incision so that the unhealthy surrounding skin may be removed. The cyst wall or fistulous track is now separated from the surrounding tissues, care being taken not to attempt to clean off every trace of fascia and muscle, as the preservation of a thin layer of these tissues helps to avoid damage to the cyst wall or fistulous track, and facilitates complete excision. When the hyoid region is reached the central $\frac{1}{2}$ in. or so of the bone should be excised by means of two lateral cuts with bone-forceps or powerful scissors. The cyst wall is often adherent to the thyrohyoid membrane, damage to which must be avoided. Our experience is that, while many cysts, sinuses, and fistulae do not extend appreciably above the hyoid bone, the close association between the tract and that bone makes removal of a part of the latter essential to the complete extirpation of the former. This view is shared by Finochietto and Veppo (1939) and Gross and Connerley (1940). No disability follows. In fact, regeneration of the hyoid bone quickly results in union of the fragments (Bailey, 1931).

In those examples which extend far upwards into the tongue, Sistrunk (1928) advises " coring out " the whole tract as far as the foramen caecum, a finger in the mouth being utilized to give a precise indication of the direction of the duct and to enable the surgeon to gain readier access to its upper extremity. The term " to core out the duct " seems to us to be unfortunate, as it implies the existence of tissue of a different consistence in the neighbourhood of the tract, permitting its ready identification, whereas in fact the softness and tenuity of this structure are such that it is identifiable only with great difficulty, if at all. The essential feature, therefore, of Sistrunk's operation is the excision of a comparatively thick cylinder of tissue in such a way that the whole epithelial-lined duct is removed with some degree of certainty, very much as we have already described for those portions of the

tract which lie below the hyoid bone. This cylinder includes portions of the mylohyoid aponeurosis and of the genioglossus muscles.

The deeper parts of the wound are obliterated with interrupted catgut sutures, the hyoid bone united or its halves brought together by sutures which include the fascial tissue covering it, and the remainder of the wound sewn up except in its centre, where drainage should be provided for, during the first day or two. Healing is usually less rapid than in ordinary thyroid operations, but recurrence of discharge will follow only when incomplete operations have been performed.

Patterson (1928) advises deep cauterization of the region of the foramen caecum in all cases of complete fistula some weeks before any attempt at extirpation is undertaken. The upper half-inch or so of the fistula is thereby destroyed and replaced by scar tissue, so that it can be recognized when the formal operation from below is undertaken. The extirpation is stopped when this point is reached, so that the buccal cavity need not be entered, and thus an aseptic operation can be ensured. This method appears to be sound so long as it is used only for the rare *complete* fistulae: it is unnecessarily complicated for most thyroglossal fistulae.

Struma Ovarii. Nothing more than brief mention of struma ovarii will be necessary since this condition will rarely be encountered by the thyroid surgeon. The subject has been well reviewed by Emge (1940) and Smith (1946). The latter author classified ovarian tumours containing thyroid as follows:

(1) Dermoids containing thyroid tissue (52 per cent.).
(2) Cystoma with thyroid tissue (31 per cent.).
(3) Purely thyroid tumours (17 per cent.).

Thyroid tissue has been found bilaterally in six cases. All these thyroid tumours of the ovary are, of course, teratomatous in nature. The majority are benign but about 5 per cent. disseminate.

Histologically the ovarian thyroid tissue closely resembles the normal thyroid and is subject to all the same physiological and pathological variations. It should be regarded as part of the total thyroid tissue of the patient, reacting to iodine lack, thyrotropic and other stimuli in a manner similar to the parent gland.

Smith reviewed about 150 cases reported up to 1946. The average age of the patients was forty-two years and a goitre was present in the neck in 16·3 per cent. of cases. It is estimated that from 5 to 6 per cent. of ovarian strumas produce thyrotoxicosis (Gusberg and Danforth, 1944).

Metastases from an ovarian struma are nearly always confined to the abdomen. Ascites and peritoneal adhesions are frequent; about half these metastasizing strumata are fatal (Emge, 1940).

Treatment. Ovarian struma has very rarely been diagnosed before operation. Excision should be proceeded to in all cases.

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CHAPTER XIX

ACUTE INFLAMMATIONS OF THE THYROID GLAND

Suppurative and Non-Suppurative Varieties — Strumitis — Thyroiditis — Incidence — Causes — Routes of Entry of Micro-Organisms — Bacteriology — Morbid Anatomy — Microscopical Appearances — Clinical Features — Special Types — Differential Diagnosis — Prognosis and Sequelæ — Treatment — Illustrative Cases.

It is customary to differentiate that form of acute thyroiditis which subsides without suppuration, the so-called simple variety, from that in which pus is formed—the suppurative. The tendency to suppuration is greater in certain infections than in others. It is also usual to make a distinction between strumitis, or inflammation which involves a goitrous gland, and thyroiditis, which affects the normal thyroid. The distinction between acute non-suppurative thyroiditis and subacute thyroiditis is made on arbitrary clinical grounds and is often difficult.

The abundant blood supply of the thyroid enables circulating toxins and pathogenic micro-organisms to reach and to leave their mark on the gland, though the changes are seldom of such a nature as to be obvious clinically. In fact the thyroid seems to possess a definite resistance to local bacterial infection. Thus Womack (1944) cites experiments in which pure cultures of streptococci and staphylococci were injected into the superior thyroid artery of dogs; abscess formation rarely followed. Farrant (1914), who was among the first to observe the effects on the thyroid gland of bacterial toxins, describes the following changes:

(a) Diminution or disappearance of the colloid from the follicle.
(b) Degeneration and desquamation of the cells lining the follicle.
(c) Increased vascularity.
(d) Hyperplastic changes in the epithelium, which are sometimes sufficiently conspicuous to resemble those seen in certain stages of primary thyrotoxicosis.

Cole *et al.* (1929) confirmed Farrant's description, and Cole and Womack (1928) found that the phenomena he described may be prevented or minimized by the administration of iodine.

In addition to changes which are mainly of a microscopic order, the thyroid is occasionally the site of inflammatory processes of a more obvious nature, but varying widely in severity. Thus the gland may swell and become tender without any important constitutional upset, while in other cases suppuration follows, associated with grave toxaemia, which may have a fatal termination.

Incidence. Acute thyroiditis, at all events in the suppurative form, is a rare condition, even in institutions which deal specially with the acute

infectious diseases. Hagenbuch (1921) found that forty-three cases of acute thyroiditis occurred among 45,953 admissions to the medical and surgical wards of the Basle Clinic in a period of ten years. There were only two cases of acute thyroiditis among 10,000 operations on the gland reported by Torina and Carrocio (1947). It appears probable that the goitrous gland is far more susceptible to acute inflammation than is the normal thyroid.

Age. There is no age-limit for the condition, but, like other infections, it is relatively commoner in children and young adults than in elderly people. Demme (1878) reported a case in a newly-born child, and Burhans (1928) one in a patient aged seventy-seven.

Sex. Acute thyroiditis is commoner in women, owing to the relatively large number of puerperal cases, and to its special tendency to affect goitrous glands (which in general are more common in women).

Causes. A very large number of diseases, due both to known micro-organisms and protozoa and to causes which up to the present have not been traced to any specific organism, have been found in association with acute thyroiditis. The following are some of the more important:

Diphtheria
Typhoid
Paratyphoid
Vincent's angina
Acute miliary tuberculosis
Gonorrhoea
Bacillary dysentery
Cholera
Erysipelas
Pyaemia
Septicaemia
Furunculosis
Puerperal fever
Impetigo
Influenza
The common cold
Malaria
Trypanosomiasis
Helminthiasis
Ulcerative endocarditis
Acute rheumatism
Acute tonsillitis
Measles
Scarlet fever
Smallpox
Chicken-pox
Whooping-cough
Acute poliomyelitis
Broncho-pneumonia.

Trauma may be an added factor, though in itself it can hardly be a cause of an acute infective lesion of the gland. After attempted strangulation and other local injuries, inflammatory changes have been observed in the thyroid but in such cases bruising and haemorrhage into and around the gland must often occur, followed by infection of the damaged tissue either directly from associated injuries to the trachea and oesophagus, or indirectly from the blood stream. Formerly, the injection of irritant antiseptic fluids, designed to cure cystic tumours in the gland, was occasionally followed by acute strumitis.

Routes of entry of micro-organisms into the thyroid gland. Kocher, as far back as 1878, maintained that all forms of acute thyroiditis are secondary to foci of infection elsewhere in the body, and there is every reason to

suppose that his contention is correct. Sallick (1942) has reported suppurative thyroiditis following streptococcus viridans bacteraemia. Indeed, infection is usually haematogenous and only occasionally by the lymphatics or direct extension from some suppurative process in the neck. In their case of staphylococcal thyroiditis, Torina and Carrocio (1947) believed that the infection had spread to the gland from carious teeth via the lymphatics. In Kirshbaum and Rosenblum's case (1938) pneumococcal suppuration developed in an intra-thoracic goitre following lobar pneumonia. The mode of infection was probably by continuity, since the goitre was adherent to the mediastinal pleura, which in turn was adherent to the lung. Meeker (1925) has suggested the possibility of infection reaching the thyroid gland by way of a persistent thyroglossal duct, but such a route must be of extreme rarity.

Bacteriology. This can only be determined with any degree of certainty when suppuration supervenes. The pus from acute thyroiditis may yield pure cultures of a specific organism or a combination of several, some of which may be secondary or saprophytic. In Greenfield and Curtis's case (1939) the pus was foul-smelling and contained Gram-positive cocci and Gram-negative, fusiform bacilli.

Pure cultures of the pneumococcus have been isolated in a few cases. Roger (1907), Melchior (1914), and Milone (1942) found B. typhosus in cases following typhoid fever, and Gali (1913) isolated this organism from an abscess in the gland twenty-one years after the exanthem. Alain (1924), who reported sixteen cases of acute thyroiditis, obtained B. typhosus, either in pure culture or mixed with other organisms from the majority, but from a few of them B. paratyphosus A or B was isolated in pure culture.

Morbid anatomy. Usually only one lobe is involved. Often the acute inflammatory process spreads from one pole or one lobe throughout the gland (migratory thyroiditis of King and Rossellini, 1945). The affected parts of the gland are engorged with blood, and dark haemorrhagic foci and pale infarcts are scattered throughout its substance. Liquefaction occurs in the haemorrhagic areas and small scattered abscesses form, which may coalesce into one large irregular abscess cavity. The suppurative process may eventually involve an entire lobe or even the whole gland, spread into the fascial planes of the neck, or perforate the larynx, trachea, oesophagus, or skin. When virulent organisms are concerned, large portions of the gland may slough and be discharged with the purulent contents; in very rare cases, such as those of Gascoyen (1876), Richard (1909), Robertson (1911), Takahara and Wantanabe (1938), gangrene of the whole gland follows.

Microscopical appearances. In suppurative thyroiditis, areas of haemorrhage are numerous, with evidence of liquefaction and aggregation of leucocytes into definite purulent foci. The causative organisms may often be seen in large numbers in the sections. Indications of gas formation sometimes exist in cases due to anaërobic organisms.

In *non-suppurative varieties* the histological appearances are similar to the advanced stages described by Farrant in his experimental work. A

diffuse leucocytic infiltration of the gland is associated with proliferation and desquamation of the epithelial cells, which may be found in various stages of degeneration filling up the lumina of the follicles. The colloid is liquefied and stains poorly, or may be entirely absent. Giant-cells of the " foreign body " type are sometimes found enclosing, and apparently destroying, the masses of colloid. In very mild degrees of inflammation affecting the thyroid gland the most conspicuous changes are the hypertrophy and hyperplasia of the epithelium of the follicles.

Clinical features. Suppuration is rare in association with those forms of acute thyroiditis which follow scarlet fever, measles, mumps, acute rheumatism and malaria, and it seems probable that only in a small minority of cases of acute strumitis and thyroiditis is pus ever formed. Clute and Smith (1927) consider that suppuration is more likely to occur in acute strumitis than in acute thyroiditis.

Onset. The onset is usually acute, occasionally with rigors and a high temperature, but as a rule the pyrexia is moderate in degree and the onset gradual in the non-suppurative forms.

Signs and Symptoms. *Pain* in the neck, not necessarily localized to the thyroid gland, but often felt deeply and diffusely among the tissues of the neck, may be a prominent and early symptom. It is generally more severe on the side corresponding to the affected lobe, and may be referred also to the ear, occipital region, lower jaw, or shoulder; it is increased by swallowing. There may be marked spasm of the related neck muscles.

Swelling of the gland is noticed at an early stage. It may be diffuse or localized, and its degree depends on the virulence of the process and whether the gland was previously goitrous or normal. At first the swollen gland is firm or even hard, but if suppuration supervenes softening follows, and one or more areas of fluctuation may become obvious. When the inflammatory process is severe and diffuse, the whole of the neck may share in the features just described. The cervical glands are often somewhat enlarged and tender, and in rare cases the cervical veins may be engorged or thrombosed and the whole head and neck cyanosed.

In non-suppurative forms the disease reaches its climax within a few days and then gradually subsides but recurrence and relapses sometimes take place. It is unusual for any gross change in the gland to follow this form of inflammation, though Jensen (1943) reports a case in which residual nodules were palpable eighteen months later.

When suppuration occurs, pus may burrow in any direction unless the abscess be drained by surgical means. As a rule, the pus finds its way out through the skin over the affected part of the gland, but when deeply placed it may invade (i) the trachea near its upper end, giving rise to perichondritis and necrosis of laryngeal and tracheal cartilages or (ii) the pharynx, in close proximity to the glottis, broncho-pneumonia being likely to follow in either case; (iii) the mediastinum, giving rise to a fatal mediastinitis; (iv) the cellular planes of the neck burrowing among them and producing a diffuse abscess, which may point in situations far beyond the normal confines of the thyroid

gland proper. In a child, seen by the revisor, a large abscess had extended down into the mediastinum and was successfully drained through the second right intercostal space.

Dyspnoea may be severe and paroxysmal; it is due mainly to the direct pressure of the acutely enlarged gland on the trachea.

Cough is often troublesome, especially at night. Pus and blood may be expectorated when the abscess bursts into the trachea or larynx, or symptoms of asphyxia may supervene.

Alteration in voice, should it occur, is due either to involvement of the recurrent laryngeal nerve or to associated laryngitis and tracheitis. Oedema of the larynx is an occasional complication.

Tachycardia is common and results from toxaemia. It is not now believed that thyroiditis produces thyrotoxicosis, but rather that any such infection is likely to reduce thyroid secretion.

Pyrexia up to 104° F. has frequently been reported in suppurative cases; it is usually less in the non-suppurative.

Special types of acute thyroiditis and strumitis. The pneumococcal form is usually mild in type, and suppuration is rare, though Julian Taylor (1924) has described such a case. This type is usually referable to preceding broncho-pneumonia (Kirshbaum and Rosenblum, 1938; Pierangeli, 1947).

Typhoid thyroiditis often occurs weeks after the onset of the original disease; suppuration follows in about one-third of the cases. Alain (1924), found that goitrous patients were more liable to involvement of the gland than others. Gali's case of chronic typhoid abscess, occurring twenty-one years after typhoid fever, has already been referred to.

Puerperal thyroiditis occurs ten to fourteen days after the onset of puerperal infections but it rarely progresses to suppuration. Goitrous subjects are more susceptible to the condition than those with healthy thyroid glands.

Dysenteric thyroiditis was described by Thorburn in 1918. It was noticed during the convalescent stage of bacillary dysentery, localized to one lobe of the gland. In no case did suppuration follow. The thyroid gland became enlarged, hard, and both painful and tender.

Iodine thyroiditis. Prolonged administration of iodine and its compounds, both in goitrous subjects and in those with healthy glands, may give rise to a hardening and increase in the size of the thyroid sometimes associated with local pain and tenderness, which superficially simulate an infective condition.

Differential diagnosis. In acute congestion of the thyroid there is little or no fever, the gland is only slightly tender and painful, and there is an absence of leucocytosis. Acute haemorrhage into a thyroid cyst or adenoma has a much more rapid onset; it may be quite painful but pyrexia is slight or absent, though the gland or tumour is tender and tense. A history of strain or injury will be helpful and a leucocyte count will assist in excluding acute thyroiditis.

Plummer and Broders (1933) have drawn attention to the occurrence of congestion, oedema, and intense lymphocytic infiltration in the capsule of

thyroid nodules (" acute capsulitis "). The changes are often associated with haemorrhagic or necrotic degeneration in the substance of the nodule. They consider that the primary lesion is an acute non-suppurative inflammation of the capsule.

Malignant disease with an acute course, though very rare, may closely simulate an acute inflammatory condition of the gland as in Hallström's case (1942). The enlargement in this type of malignant disease may be diffuse and the pain and tenderness severe. Glandular involvement is, however, more obvious and more widespread than in acute thyroiditis, and eventually the mere bulk of the swelling serves to exclude an inflammatory nature.

Prognosis and sequelae. The primary mortality is difficult to estimate, and necessarily depends largely on the preceding infection from which the thyroiditis originates. If the inflammation be severe and the affection of the gland widespread, the resulting destruction of thyroid tissue may be extensive enough to lead to myxoedema, as Weeks (1920) has described, and this is true even in non-suppurative thyroiditis (Rasmussen, 1942). On the other hand, even when the whole gland appears to have sloughed evidence of hypothyroidism may be wanting (Gascoyen, 1876). The possibility of residual hypothyroidism should be remembered in children, since replacement therapy is essential to ensure normal growth and development as illustrated by Greenfield and Curtis's case (1939). Acute inflammation affecting an enlarged thyroid gland has been known to result in reduction of its size to normal (Petit, 1790; Lebert, 1862; Grimault and Brino, 1922). Bartels (1944) reports a patient with myxoedema and a small goitre, in which acute non-suppurative inflammation developed. After it had subsided the patient's condition was unchanged.

Treatment. The indications are:

(1) To institute chemotherapy in order to control bacterial activity and promote resolution. Use has thus been made of sulphadiazine (Candel, 1946), penicillin (Scheinberg, 1946), and sulphathiazole (King and Rossellini, 1945). Owing to the variety of causal bacteria, a combination of penicillin and sulphonamides or streptomycin seems indicated. Surprisingly, acute thyroiditis may respond rapidly to thiouracil therapy (King and Rossellini, 1945). Cantwell (1948) has reported two cases in which thiouracil quickly produced relief, though in the one, penicillin, and in the other, penicillin and sulphadiazine had been previously administered without effect.

(2) To evacuate the pus as soon as it has formed. Suppuration is not very common, but when it occurs, it is more rapidly localized, and pain is mitigated, if moist compresses are applied to the neck and changed frequently. No attempt to locate or to aspirate pus by means of a needle is justifiable, except as a preliminary step to a formal operation for the evacuation of the pus by free incision, followed by drainage. A general anaesthetic is desirable, because the pus is not always easily found and furthermore is not always localized to one area, being frequently loculated, so that it may be necessary to make counter-incisions in order to ensure its free exit. Womack (1944)

emphasizes that, in draining abscesses of the thyroid, the protective barriers against mediastinal spread should not be broken down.

Imperfect drainage may result in the formation of residual abscesses or persistent sinuses, for the cure of which it may be necessary later to resect portions of the affected thyroid tissue.

Illustrative cases. (1) Suppurative thyroiditis. Specimen in St. Bartholomew's Hospital Museum, No. 2319e. Trachea with the thyroid *in situ.* The latter has been laid open to show a condition of diffuse suppuration. The cut surface of the gland presents everywhere a mottled appearance due to the widespread deposit of purulent material within its tissue.

Microscopic examination shows that little glandular tissue remains. A few alveoli containing colloid material lie scattered among large areas of inflammatory exudate, which teems with cocci.

From a boy, aged sixteen, who died of pyaemia apparently secondary to a furunculosis. Post mortem he presented septic infarction of the myocardium, lungs, and kidneys.

C.A.J.'s Illustrative Case. C. C., male, 24; Oxford undergraduate; seen in consultation with Dr. Gwynne Lawrence, May 20th, 1926; operated on, May 21st, 1926.

History of impetigo for some weeks. On May 17th, 1926, sudden onset of pain over left side of thyroid, followed by swelling of gland and dysphagia. The left lobe of the thyroid gland was enlarged and tender, and the skin over it reddened and oedematous; deep fluctuation was detected.

Operation: Under ether anaesthesia an incision was made over the swelling, and 3 oz. of thick greenish-yellow pus were evacuated. Bacteriological examination revealed streptococci. The wound healed within three weeks.

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CHAPTER XX

GRANULOMATOUS DISEASES OF THE THYROID GLAND

Tuberculosis.—Acute Miliary — Caseous or Focal Forms — Miliary Focal Necrosis — Pathology — Incident — Clinical Features — Pressure Effects — Toxic Effects — Diagnosis — Prognosis — Treatment.

Syphilis.—Review of Cases — Clinical Features — Diagnosis — Prognosis — Treatment.

Actinomycosis.

Tuberculosis

Thyrotoxic subjects, especially when the actual goitre is small, are not uncommonly suspected of being tuberculous, if there are marked wasting, asthenia, and anaemia, but experience has shown that thyrotoxic patients have very little tendency to develop tuberculosis, either of the lungs or elsewhere. The converse is sometimes true, namely, that the wasting, asthenia, tachycardia, flush and sweating of tuberculous toxaemia are mistakenly ascribed to thyrotoxicosis. Those who are already suffering from tuberculosis seem rarely to develop thyrotoxicosis. Virchow held that there is a definite antagonism between goitre and tuberculosis, and that the existence of the former is proof of the absence of the latter. Both normal and goitrous glands may, however, become the seat of tuberculous lesions, so that any antagonism between the thyroid gland and the B. tuberculosis can be but relative.

Once the gland is infected, the local pathological changes depend on the number and virulence of the organisms and the allergic state of the host. Thus one may find isolated tubercles, extensive caseation, or a marked fibrous tissue reaction. Two forms are recognized by all pathologists:

(1) Acute miliary tuberculosis;
(2) Massive, focal, or caseous tuberculosis.

It is doubtful whether a third form here described as miliary focal degeneration is in reality tuberculous.

(1) **Acute miliary tuberculosis** of the thyroid occurs in association with generalized miliary tuberculosis. It is commoner in childhood, and, not being recognizable during life, its interest is chiefly pathological. The lesions in the gland are in all respects similar to those found throughout the body generally. Tubercle bacilli may be found in suitable stained sections, though usually only in small numbers.

(2) **Focal or caseous tuberculosis** of the thyroid was described by Lebert (1862) but it was not until after Koch's discovery of the specific bacillus that it became possible to identify such lesions in the thyroid with certainty. The condition must be considered as essentially secondary to tuberculosis of other organs or tissues, e.g. the lungs; but Weigert, in 1882, recorded an example

which he regarded as primary, the caseous mass in the thyroid gland having invaded a vein; generalized miliary tuberculosis followed.

Miliary focal degeneration. If sections of thyroid biopsies are cut and stained as a routine, foci of necrosis, strongly suggestive of tuberculosis, are occasionally found. A tuberculous aetiology has generally been assumed. Thus Ruppanner (1909) and Hedinger (1912) described localized areas of tuberculosis in goitrous glands in which no suspicion of tuberculosis had been entertained prior to operation. Uemura (1917) found twenty-four examples of this type of lesion in 1,400 adenomatous goitres removed surgically. Small areas resembling caseous foci were regarded as tuberculous but the diagnosis was not confirmed by the demonstration of the specific organism of Koch by acid-fast staining, by culture, or by inoculation tests. Such foci have also been regarded as tuberculous by McGregor and Peacock (1939). We have seen these tubercle-like foci several times both in nodular and diffuse toxic goitres but in the absence of tuberculosis elsewhere and failing the demonstration of the specific bacillus in the lesions locally, we feel that their nature remains doubtful. In some glands the giant cells within the lesions are clearly of the foreign-body type. Jaffé (1930) has examined the nature of these tubercle-like lesions carefully and concludes that they result from non-infectious focal involutional changes in newly-formed or old follicles. Crile describes similar tubercle-like foci of degeneration in subacute thyroiditis (cf. Chapter XXI).

Pathology. The disease affects the whole or a part of one lobe, seldom more. A hard, localized swelling results, which softens and subsequently breaks down, with the formation of thick pus which may contain stainable tubercle bacilli. The abscess cavity which develops has in its walls characteristic giant-cell systems, though these are sometimes scanty and have then to be sought for carefully. The caseation may spread beyond the confines of the gland and involve the superficial tissues or burrow into the deeper planes of the neck. In the former case the skin soon gives way and a sinus forms; in the latter, the trachea, larynx, or oesophagus may be perforated; the eventual result is the same, viz. secondary infection with pyogenic micro-organisms.

Incidence. Coller and Huggins (1926) recorded five examples of tuberculosis of the thyroid met with in 1,200 operations for goitre. Keynes (1938) encountered it but once in 1,225 operations. Rankin and Graham (1932) found tuberculosis in only twenty-one of 20,758 thyroid glands removed surgically at the Mayo Clinic (0·1 per cent.). In their excellent review Lindsay and Mead (1934) state that in all about 255 cases have been reported, more than half (130) being examples of miliary tuberculosis in which the thyroid lesions were discovered post mortem. Up to 1944 only twenty-six tuberculous abscesses had been described in the gland (Postlethwait and Berg) and only a few cases have been added since (Coggi, 1947; Klassen and Curtis, 1945; Stubbins and Guthrie, 1948).

Age. The youngest example yet recorded is Clairmont's (1902), in a child aged two years. Corner's patient (1904), a girl of nine, had an abscess containing

2 drachms of pus, and the lymphatic glands in the neck were also involved. Most of the records relate to patients between the ages of thirty and fifty.

Sex. There is a marked preponderance of females over males.

Clinical Features

As a rule, the localized form presents the features of a firm swelling in the thyroid gland, which, at first hard and indolent, later softens, the skin over it becoming reddened. Occasionally the tuberculous process spreads rapidly to the surrounding tissues before softening occurs. In Stubbins and Guthrie's case (1948) the affected lobe was firmly attached to the trachea, carotid sheath, infrahyoid muscles and apical pleura, the latter being opened during its removal. The mass may involve various cervical nerves, pain being referred to the ear, jaw or shoulder, and when this is associated with a hard tumour in the gland the clinical picture may closely simulate malignant disease. On the other hand, the progress of tuberculosis may be so slow and encapsulation so complete, that a chronic abscess, sometimes of large size, may result. It may be difficult to differentiate such a condition from a cystic adenoma with a thick capsule.

Clinical features may be grouped as follows:

(1) Local, due to the goitre and pressure or infiltration from it, and
(2) General, due to tuberculous toxaemia, hyperthyroidism or hypothyroidism.

(1) **Local effects.** Dyspnoea may result from pressure of the tuberculous mass on the trachea. The onset is gradual but, should the larynx or trachea be perforated by extension of the tuberculous process, sudden asphyxial symptoms may result from the discharge of the contents into the respiratory tract. Frassi (1929) described a case in which the rapid increase in the size of the thyroid led to a diagnosis of carcinoma.

Dysphagia is less common, though Rolleston (1897) has described the rupture of a tuberculous abscess of thyroid origin into the oesophagus.

The recurrent laryngeal nerve may be involved or the cervical sympathetic invaded producing characteristic changes in the voice and pupil respectively. Perforation of the wall of a vein was met with in Weigert's case (1882).

General effects. Mosiman (1917) recorded nine cases of tuberculosis of the thyroid gland, in seven of which thyrotoxic symptoms predominated. In this latter group all the patients exhibited nervousness, tremor, and palpitation, though in only two was exophthalmos present. Six had dilated hearts and wasting. Subtotal thyroidectomy was successfully performed in the seven thyrotoxic cases. Uemura (1917) described three cases of tuberculosis of the thyroid with symptoms similar to those of primary toxic goitre. The association of tuberculous thyroiditis and thyrotoxicosis has also been reported by Coller and Huggins (1926), Plummer and Broders (1920) Keynes (1938) and Comando (1942). But it is uncommon. Thus in only one of Postlethwait and Berg's twenty-six cases of tuberculous abscess of the thyroid were there symptoms and signs suggestive of thyrotoxicosis.

In many such cases, moreover, the diagnosis of thyrotoxicosis appears to have rested on such dubious evidence as " nervousness ", tremor, palpitations and slight loss of weight. Even the existence of a raised metabolic rate does not establish the diagnosis, since this may be the result of the tuberculous infection. The impression of exophthalmos, also, is often illusory.

Van Ravenswaay and Van Ravenswaay (1933), examined the problem of tuberculosis of the gland associated with thyrotoxicosis and concluded that " there is little aetiological relationship between tuberculosis and hyperthyroidism and their presence in the same individual is usually coincidental ". With this opinion we are in agreement.

Evidence of hypothyroidism was noted after resection of a tuberculous thyroid in three of Rankin and Graham's 115 cases (1932).

Diagnosis. This has very rarely been made before operation (in only three of the cases reviewed by Rankin and Graham). Usually it has depended on histological evidence, the finding of tubercle-like necrotic foci. The staining of acid-fast bacilli makes the diagnosis practically certain, though failure to find them does not exclude tubercle. Splinters of thyroid colloid may retain the stain and simulate the rod-like organism of tuberculosis (Jaffé, 1930). Final proof rests on culture and guinea-pig inoculation.

Prognosis. Good results are to be expected, except in patients with advanced tuberculosis of the lungs or other organs. The operation wound usually heals surprisingly well.

In Corner's case (1904) a fatal result from tuberculous meningitis followed the removal of the tuberculous mass together with a superficial sinus. In Comando's case (1942) convalescence was complicated by the development of tuberculous keratitis. But this rapidly resolved under treatment with Old Tuberculin.

Treatment. General treatment, aimed at raising the patient's natural resistance, is of supreme importance. The affected part of the thyroid gland should be extirpated together with any sinuses leading down to it and any diseased lymphatic glands in the neighbourhood. The extent of thyroidectomy will also depend on the symptoms present, e.g. if there are pressure symptoms the offending tissue must be resected. Keynes (1938) found the right side of the cricoid cartilage covered by granulations. When these were scraped away the cartilage was seen not to be eroded. Local anaesthesia, preceded by rectal avertin, or combined with nitrous oxide and oxygen, is most generally useful for this type of case.

Syphilis of the thyroid gland

Netherton (1932) and Laird (1945) have reviewed reported cases. Most fall into the category of solitary gummata. In some, skin ulceration follows. In others the gland and surrounding tissues show diffuse and dense fibrosis. Many of the earlier cases are open to the criticism that no indubitable evidence of the nature of the tumour was available, since the causative spirochaete had not then been discovered, nor had the Wassermann reaction been evolved.

Demme (1878) reported three cases of syphilis of the thyroid in children, in whom gummatous nodules appeared in the gland concomitantly with syphilitic lesions in other viscera. The nodules were described as being greyish-white or greyish-yellow in colour.

Barth and Gombault (1884) described a swelling of the thyroid occurring in a patient suffering from congenital syphilis associated with interstitial keratitis and tibial nodes, there being no evidence of tuberculosis in the lungs. Histologically, the mass consisted of a caseous centre, surrounded by a thick wall of connective tissue in which were a few giant-cells. Endarteritis obliterans was conspicuous in the surrounding vessels.

Fraenkel (1887) described a gumma of the isthmus in a woman of forty-one who died of syphilis. She also had necrotic gummata of the trachea and bronchi, liver and kidneys. The thyroid swelling consisted of a rather hard, yellowish-grey mass at the junction of the isthmus and right lobe. Microscopically, round cells but no giant cells were present.

Engel-Reimers (1891–92) described another type of syphilitic thyroid enlargement occurring in adults, the subjects of secondary syphilis. The gland was generally enlarged, but the goitre was soft and free from nodules. Lockwood (1895) observed a similar condition.

Köhler (1892) recorded a tumour of the thyroid, in a woman of forty-eight, which appeared to be syphilitic in character and was associated with myxoedematous symptoms. Both the tumour and the hypothyroid symptoms disappeared as the result of the administration of potassium iodide. A similar case was reported by Pospelow (1894).

Bruce Clarke (1897) reported the case of a woman aged thirty-eight, who had been treated four years previously for gummata of the arm and face; two weeks prior to admission to hospital she had difficulty in both swallowing and breathing, with hoarseness and occasional attacks of severe dyspnoea. A hard cylindrical mass was found in the middle of the neck, extending from the hyoid bone to the manubrium sterni; it moved on swallowing, and at its upper part a typical gummatous ulcer had formed. A few days later laryngo-tracheotomy became necessary, the symptoms being relieved thereby. The swelling rapidly subsided under treatment with potassium iodide.

Mendel (1906) refers to two cases of Küttner's, the first in a woman aged thirty-nine, who had a hard swelling in the thyroid, which was thought to be malignant but after removal showed the microscopical appearances of a gumma; the second case, in a man aged twenty-seven, exhibited similar features. Microscopically, there was much sclerotic connective tissue and round-cell infiltration, together with characteristic proliferative changes in the blood vessels. The lesion disappeared in three weeks under potassium iodide.

Thursfield (1908) described a case of gumma of the thyroid in a man of fifty-three, who had contracted syphilis thirty years earlier, and had had six months' treatment at that time; subsequently be developed tertiary syphilitic lesions, which cleared up under treatment with potassium iodide. The tumour

in the neck was in the right lobe of the thyroid; it was oval in shape, 2 in. by 1 in., and the skin was intact; it was painless, smooth, and hard, with a rounded margin ; complete disappearance of the tumour followed the administration of potassium iodide.

Davis (1910) stated that in the secondary stage, in addition to the soft and painless variety just referred to, a hard and sometimes painful swelling may occur. This, however, is possibly the effect on the gland of the iodides used in treatment.

Gaté and Aloin (1926) referred to an acute, painful swelling of the thyroid in secondary syphilis, the gland sometimes remaining permanently enlarged. In one case the rapidly developing tumour in the gland was diagnosed by a surgeon as cancerous. Pain, radiating to the ear, was a prominent feature. The patient was treated by injections of arsenobenzol, followed by mercury and potassium iodide, and the swelling disappeared slowly. No signs of interference with the function of the thyroid were observed. It seems that in this case treatment with iodides was beneficial, and that thyroid enlargement in secondary syphilis cannot commonly be the result of this form of medication.

In addition to acquired syphilitic lesions of the thyroid occurring in adults, congenital syphilis involving the gland has also been described. Menninger (1929) has reported three such cases, in patients aged respectively seventeen years, nine years, and one month. In all three cases the thyroid was normal in size and no gross change was visible on section, but microscopically there was an increase in the amount of interstitial fibrous tissue, and the vesicles were small in size.

There are several cases on record in which gummata of the thyroid produced such a degree of tracheal stenosis that tracheotomy became necessary. The mortality of such interventions is very high, owing to the difficulty of the operation and of keeping the tracheotomy tube in its place. Purulent bronchitis or broncho-pneumonia often follows.

Mention must also be made of Lancereaux' observations (1866) that in the case of patients dying from tertiary syphilis the thyroid gland appeared paler, smaller, and firmer than normal. A large amount of fibrous tissue was found surrounding the blood vessels in these glands.

In most of the cases described since the establishment of the Wassermann test as an important aid in the diagnosis of syphilis a positive reaction has been obtained. Anti-syphilitic treatment, even when the diagnosis has been confirmed by both clinical and laboratory methods, is not always successful, as the cases of Haeggström and Bergstrand (1902) and Lasch (1925) demonstrate.

In Senear's case (1918), as in the one described below, there was coincident enlargement of the cervical lymphatic glands.

Illustrative case: E. T., female, aged thirty-four; admitted November 17th, 1915, discharged December 3rd, 1915.

Past history: Three miscarriages in the last ten months; two children had died previously of convulsions; one, aged thirteen, was alive and healthy. The patient had noticed a swelling in the neck in May, 1915, together with palpitations, dyspnoea, dysphagia, irritation in the throat, hoarseness, and loss of

weight. On examination there were a smooth, very hard swelling in the right thyroid lobe, and a slight tremor in the hands. Diagnosis: malignant disease of the thyroid with mild thyrotoxic symptoms. At operation the tumour was found adherent to the surrounding structures, and the trachea was compressed antero-posteriorly. The right lobe of the thyroid was resected with considerable difficulty; the lymphatic glands were noticed to be enlarged, but were not removed. The tumour measured 2 in. by $1\frac{3}{4}$ in., and weighed 1 oz. It was very hard, and there was evidence of necrosis in its centre.

Pathological findings. The pathologist considered the mass to be gummatous. The necrotic area was surrounded by numerous round cells and giant cells and the vessels showed an extreme degree of endarteritis obliterans. There was no trace of any tuberculous change and no tubercle bacilli were found. The Wassermann test proved strongly positive.

Progress. The wound, which at first appeared to be healing satisfactorily, broke down, but healed rapidly when antisyphilitic treatment was instituted. The patient was re-examined in June, 1930, and no trace of recurrence of any thyroid lesion was detected.

Clinical features. Syphilitic lesions of the thyroid may occur at any age from early infancy until advanced life; Menninger's case was aged one month, and Thompson (1917) described one in a man aged seventy-two.

Gummata of the thyroid may occur within a year or two of the onset of the disease or may be delayed for as long as thirty years, as in the case described by Thursfield. The swelling in the gland is usually unilateral, and is characterized by its hardness. Pressure symptoms are usually found; they may be severe enough to require tracheotomy or resection of the affected part of the gland. At first the swelling is smooth, painless, and movable. When, however, the inflammatory process spreads to the surrounding muscles, or to the other important structures in the neck, immobilization of the mass follows, and with it an increase both in pressure symptoms and in the tendency to involvement of the recurrent laryngeal and sympathetic nerves. In a few cases thyrotoxic phenomena have been noted. In our case these were confined to palpitation, fine tremor in the hands, and loss of weight, but in other instances they may be more striking and associated with a significant rise in the basal metabolic rate.

Diagnosis. This must always be extremely difficult in the absence of evidence of syphilitic lesions in other parts, though a history of antecedent syphilis, together with a positive Wassermann reaction, will be helpful. It is, however, clear that the physical characters of a gumma of the thyroid resemble those produced by certain forms of malignant disease and also by a rather uncommon condition, chronic thyroiditis (Riedel's disease). The response to antisyphilitic treatment will generally, but not invariably, enable one to arrive at a correct diagnosis, as in Barber's case (1947). The patient, a woman aged thirty-seven, presented with goitre, hoarseness, dysphagia and mild symptoms of hyperthyroidism. At operation only a small portion of a very hard gland could be removed. Later gummata developed in the scar and on the shoulder and thigh and the Wassermann reaction was found to be

positive. All symptoms disappeared on treatment with potassium iodide and perchloride of mercury.

Prognosis. Excellent results follow antisyphilitic treatment but there have been cases, as mentioned above, where medical treatment has failed to cure. In such it is probable that secondary changes have occurred in the gland. The operation wound usually fails to heal soundly.

Treatment. The response to antisyphilitic treatment is generally dramatic. This was so in the gummata reported by Netherton (1932) and Laird (1945). In both patients the diagnosis was made without operation and with the appropriate treatment the thyroid lumps disappeared rapidly and completely. However it is advisable not to persevere with antisyphilitic remedies unless within a few weeks the tumour diminishes in size and the symptoms ameliorate: there are on record far too many cases of malignant tumours which have shown some temporary response to antisyphilitic remedies to justify perseverance with these beyond a limited period. If, therefore, within three or four weeks the change in the size of the mass is inconsiderable, it is wise to operate and to excise the tumour as widely as may be practicable.

Actinomycosis

Actinomycosis of the thyroid has the distinction of being the rarest of the inflammatory diseases of the gland. The one case on record of primary actinomycosis of the thyroid gland is Köhler's (1892); it was thought to be due to direct infection through the skin. The patient was a miller; the disease affected both lobes of the thyroid and pus was discharged through the skin. Myxoedematous symptoms supervened. An instance in which actinomycosis involved a thyroglossal cyst has occurred in our own practice:

J. G., 68, cattle farmer, previously healthy, seen March 14th 1929. He complained of swelling in neck for three weeks, gradually increasing in size, but without other symptoms. On examination there was a mass the size of a walnut, rather hard, slightly adherent to the skin, firmly adherent to the right side of the larynx, and moving on swallowing. Clinical diagnosis: Carcinoma, beginning in the pyramidal lobe. Wassermann reaction: Negative.

Operation: Excision of the mass, together with the adherent overlying skin. The interior of the tumour was occupied by a cyst, and its extent and anatomical relations were those commonly seen in that variety of thyroglossal cyst which lies at and below the hyoid bone.

The pathologist reported the presence of Streptothrix actinomyces in the wall and in the purulent contents of the cyst.

The wound healed rather slowly, but the patient was able to leave the hospital in twenty days. As soon as the diagnosis was established he was given 9 minims of Lugol's iodine by the mouth daily and was advised to continue this for some weeks. When last heard of, a year after the operation, he was quite well, and the wound had shown no tendency to break down.

Cases of metastatic actinomycosis of the gland secondary to generalized actinomycosis have been described by Kolaczek (1914) and Pätzold (1915).

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CHAPTER XXI

STRUMA LYMPHOMATOSA (HASHIMOTO'S DISEASE), RIEDEL'S STRUMA AND SUBACUTE (PSEUDO-TUBERCULOUS OR GIANT-CELL) THYROIDITIS

I. Struma Lymphomatosa

Historical Summary — Differentiation from Riedel's Struma — Incidence — Age Incidence — Sex Incidence — Geographical Distribution — Pathological Anatomy — Comparison with Riedel's and allied Disorders — Morbid Histology — Pathogenesis and Aetiology — Clinical Features of Hashimoto's Struma — Diagnosis — Treatment —Prognosis.

Historical Summary. Riedel, in 1896, 1897, and again in 1910, described a form of goitre which he referred to as " eisenharte " because of its peculiar consistency. In the limited series of cases which he observed young adults were affected, males more often than females, and the essential clinical feature was the widespread involvement of the extrathyroid tissues in a diffuse sclerosis which appeared to have originated in part of the thyroid gland—a state of affairs which precluded radical surgical excision owing to the danger of damage to the trachea, oesophagus, great vessels, and nerves. Riedel stressed the absence of evidence of functional disorder of the gland, whether before or after operation, and he made no mention of any lymphoid infiltration in his histological description of the tissue removed surgically.

In 1912 Hashimoto reported four cases of a peculiar type of " lymphoid goitre," by which term, he says, " I understand a growth of the lymphatic elements and a formation of lymphoid follicles together with certain changes both in the parenchyma and in the interstitial tissue of the excised gland." He expressly states that the lesion had not been recognized previously, and that he regarded it as distinct from Riedel's disease as well as from chronic thyroiditis, specific and non-specific. In 1925, and in greater detail in 1929, Williamson and Pearse described the same condition under the name " lymphadenoid goitre," to which the objection is cogent that eponymically Hashimoto's term " struma lymphomatosa " is undoubtedly correct, while in addition there is a faint suggestion implied in the word " lymphadenoid " of an association with lymphadenoma, to which in fact it has no real resemblance.

Between 1912 and 1922 scant attention appears to have been paid to Hashimoto's work, and, except for Heineke's article in 1914, little or nothing bearing on the subject was published until in 1922 Ewing, basing his opinion on the study of four cases only, came to the conclusion that Hashimoto and Riedel had described the earlier and later stages respectively of the same

disease, which he designated *benign granuloma of the thyroid*, a name previously used by Meyer (1913) for Riedel's disease itself. Ewing stated that in the four cases he studied, the gland was *bilaterally involved*, and that in one of them a *large goitre was present which receded after radium therapy*.

Ewing's views were apparently widely accepted, with the result that all attempt to differentiate between the two conditions ceased, and as a consequence nearly all the relevant cases since 1922 have appeared under one or other of the many synonymous titles for Riedel's disease such as:

1. Fibroid enlargement of the Thyroid (Semple, 1868–69).
2. Infiltrating fibroid tumour of the Thyroid (Bowlby, 1884).
3. Eisenharte Tumoren der Schilddrüse (Riedel, 1896).
4. Inflammation chronique primitive cancériforme de la glande thyroïde (Tailhefer, 1898).
5. Primary chronic inflammation of the Thyroid (Berry, 1901).
6. La dégénération fibreuse du corps thyroïde (Poncet, Ricard, 1901).
7. Riedel'sche Struma (Spannaus, 1910).
8. La thyroïdite ligneuse cancériforme (Alamartine, 1911).
9. La thyroïdite ligneuse (Delore and Alamartine, 1911).
10. Ligneous thyroiditis (Murray and Southam, 1912).
11. Thyroiditis chronica maligna (Meyer, 1913).
12. Die chronische Thyreoiditis (Heineke, 1914).
13. Benign granuloma (Ewing, 1922; Heyd, 1929).
14. Thyroïdite ligneuse chronique (Monod and Monod, 1923).
15. Chronic productive thyroiditis (St. George 1924).
16. Non-suppurative chronic thyroiditis (Hahn, 1925).
17. Riedel's struma (Meeker, 1925).
18. Riedel's chronic thyroiditis (Shaw and Smith, 1925).
19. Chronic ligneous thyroiditis (Smith and Clute, 1926).
20. Thyroiditis simplex (Riedel's tumour) (Bruce, 1931).

To mention one example of the confusion which has resulted we cannot do better than refer to Shaw and Smith's article which appeared in 1925 under the title of "Six Cases of Riedel's Thyroiditis." Graham (1931), after a careful analysis of these cases, is not satisfied that any one of them conforms to Riedel's description, an opinion with which we are in complete agreement, confirmed as it is by an examination of the pathological material from those cases.

If, then, Ewing's generalization is erroneous in that at least two different entities have been merged in this welter of titles, it seems hardly premature to attempt to define what in fact constitutes Hashimoto's struma: secondly, to contrast it with Riedel's disease, not ignoring the fact that the latter name has been applied very loosely, especially since 1912, and to a diversity of conditions more or less remote from what Riedel did in fact describe. Thus Eason (1928) makes the astonishing statement (for which we can find no published reference) that "some pathologists insist that Riedel's struma should not be diagnosed *unless they have satisfied themselves that the so-called germinal centres are present.*" He also states that Riedel's disease normally begins diffusely, although both Riedel and Hashimoto expressly deny this. Even more recently

Renton, Charteris, and Heggie (1938) assert that Riedel's disease is characterized by lymphocytic infiltration with or without giant cells, a view which explains why all their cases conform very closely indeed to Hashimoto's description but differ markedly from Riedel's.

It must not be concluded, however, that no attempt has yet been made to establish the soundness of Hashimoto's views, for Heineke (1914) certainly differentiated between the two groups of cases, and Reist (1922) could not agree that they were quite one and the same disease. Furthermore Perman and Wahlgren (1927), in reporting a case of true Riedel's disease, were able to show that the pathological tissue removed at two operations separated by a year's interval was of almost identical histological structure, thus combating the view that in the earlier stages of Riedel's disease the histological features correspond to what Hashimoto described. Graham and McCullagh (1931), and again a little later Graham (1931), first focused attention on the accumulated evidence that Riedel's disease and struma lymphomatosa are distinct and distinguishable diseases. Graham (1931) also pointed out the polygenous nature of the 104 cases which he reviewed from the literature, and was able to differentiate them into ten groups, only forty-one of the cases being acceptable as Riedel's disease and twenty-four as struma lymphomatosa, the remaining thirty-nine being attributed to various forms of chronic thyroiditis, atrophy and fibrosis, hyperthyroidism, etc.

Following on Graham's admirable analysis, other authors have described cases of Hashimoto's struma clearly differentiated from the Riedel conglomeration: among these are Howard (1934), Clute, Eckerson, and Warren (1935), Emerson (1935), Mallory (1935), Poer, Davison, and Bishop (1936), and McClintock and Wright (1937), though Polowe (1934) appears to have confused the lymphoid type of thyrotoxic goitre with struma lymphomatosa.

Many other recent writers have labelled cases which conform closely to Hashimoto's description under the term Riedel's disease or its cognomina, notably Renton, Charteris, and Heggie (1938) who in their otherwise exemplary report on the treatment of Riedel's thyroiditis by radium are certainly referring to Hashimoto's struma. Kreuzbauer (1930 and 1931) maintains, on the other hand, that there is no need to differentiate the two types of goitre, for he says some of them have lymph follicles and others not, and Jaffé (1937) also supports Ewing by urging that the differences between Hashimoto's struma and Riedel's disease are qualitative only, yet he finds justification for separating them on clinical grounds. Much of Jaffé's material was obtained at autopsy from the subjects of advanced systemic disease, and in none did the thyroid weigh more than 25 g., so that these cases, unlike Hashimoto's, cannot be regarded as goitrous, and his conclusions are therefore applicable more strictly to the atrophic forms of lymphoid infiltration of the thyroid met with particularly in elderly hypothyroid cases.

De Quervain (1904, 1906) and de Quervain and Giordanengo (1936), have done much to clarify the situation, though approaching it from another

aspect. In their comprehensive review of the whole subject of non-suppurative thyroiditis and strumitis they demonstrate the stages which lead from acute through subacute on to chronic thyroiditis, leaving open the question as to whether Riedel's disease is merely an advanced form of the last-named or a specific lesion of the gland. Schilling (1945) believes that Riedel's disease merely represents a sequel of subacute thyroiditis.

De Quervain and Giordanengo also amplify and modify the conclusions reached by Roger and Garnier (1900), Farrant (1914), Clute and Smith (1927), Burhans (1928), Cole, Womack and Gray (1929), Bérard and Dunet (1929), and Leffman (1932) as to the pathological effects of various toxic and infectious diseases on the thyroid gland. None of these authorities describes anything comparable to what is seen in struma lymphomatosa in any stage of development, a fact which argues strongly against its toxic or inflammatory origin, and de Quervain and Giordanengo add that they could find nothing to indicate that Hashimoto's struma is directly related to any of the forms of acute, subacute, or chronic thyroiditis or strumitis studied by them in their very complete survey, which includes both specific (i.e. tuberculous, syphilitic, actinomycotic, etc.) and non-specific forms.

Struma lymphomatosa with special reference to its differentiation from Riedel's struma. Most authors in recent years have described Hashimoto's and Riedel's disease as separate entities (Harry, 1940; McSwain and Moore, 1943; Womack, 1944; Schilling, 1945; Marshall *et al.*, 1948; and Crile, 1948). In the following account of struma lymphomatosa the features which distinguish it from Riedel's disease are emphasized. In addition, a short description is given of the insufficiently recognized entity subacute (pseudo-tuberculous or giant-cell) thyroiditis (de Quervain and Giordanengo, 1936).

The precise relationship between these three conditions is still quite obscure and further evidence may require us to revise our notions concerning them. Some cases defy strict classification (Brayton, 1948). Merrington (1948) and Oldfield (1948) have reported interesting cases which undeniably presented features of both Riedel's and Hashimoto's struma. Womack (1944) claims that it is more likely that the two changes represent parallel manifestations of the same underlying injury than that one *follows* the other. Whatever the ultimate relationship proves to be, the subdivision used here is convenient for descriptive purposes.

Incidence. It is difficult to assess the frequency of Hashimoto's struma, and Graham in 1931 was able to identify only twenty-four cases in the literature, a figure increased to fifty by McClintock and Wright in 1937, since when there have been many cases recorded. Inquiries made by us amongst surgeons in Great Britain who have had special experience in thyroid surgery led us to suppose that the condition is not nearly so rare as the figures quoted would imply. In addition, an examination of the material from pathological museums in London, Edinburgh, and the provinces, revealed a considerable number of specimens of struma lymphomatosa, and incidentally very few of true Riedel's disease. The relative frequency among thyroid diseases generally is shown as follows:

	Hashimoto's struma	Total thyroidectomies
J. Graham (Edinburgh)	6 cases (0·9 per cent.)	670
Renton, Charteris and Heggie (Glasgow 1938).	7 cases (1·7 per cent.)	418
G. Keynes	25 cases	1,600 (up to January, 1939.)
C. A. Joll	51 cases (0·9 per cent.)	5,650 (up to January, 1939.)
Marshall, Meissner and Smith (1948) .	78 cases (0.3 per cent.)	25,000
G. J. Crile (1948)	3 cases (0·33 per cent.)	900

Age incidence. Hashimoto's disease is rare before forty, but may occur into the eighth decade—thus Graham's oldest patient was seventy-five and one of ours seventy-four. We have, however, a note of a case in a girl aged ten, and a few on record between twenty and forty. In Riedel's disease, speaking generally, the incidence is certainly earlier, whereas on the basis of Ewing's views the reverse should be the case. It must not be forgotten that Eisen (1934a and b) takes a diametrically opposed view and believes that Riedel's disease is the earlier and Hashimoto's struma the later stage of one disease, though the evidence for this view seems too slender to require refutation.

Sex incidence. There is a striking preponderance of women among the cases of struma lymphomatosa, both in McClintock and Wright's and in our own series, the discrepancy between the two groups being negligible, whereas in Riedel's disease, although the later figures do not bear out the original contention that the disease is commoner in males, the disproportion between the sexes is much less than for the former disease, and probably bears some relationship to the sex incidence of thyroid disease generally in any particular district. The sex distinction between the two conditions is sufficient at once to indicate that they cannot be mere stages in one disease, unless it be assumed that in an inordinate number of females suffering from Hashimoto's struma there is spontaneous recovery, and that conversely in an overwhelming number of males similarly affected the lesion passes into Riedel's disease.

Geographical distribution. De Quervain, of Berne, and Haas, of Munich, state that Hashimoto's struma is almost unknown in their respective districts, yet it occurs elsewhere on the continent of Europe, but is certainly commoner in Great Britain and possibly in America and Japan than is either Riedel's disease or any other non-suppurative form of thyroiditis. These facts, few as they are, tend to support the view that Hashimoto's struma

and Riedel's disease are independent conditions, otherwise it seems incredible that their geographical distributions should differ so markedly.

Emerson (1935) states that the cases of struma lymphomatosa are equally divided between goitrous and non-goitrous districts, but from the figures available it would seem difficult to establish this as a general principle, and of our own series of fifty-one cases, only five came from districts where goitre is regarded as endemic.

So far as *social status* is concerned the cases in our own series were distributed among all classes, and there is certainly nothing to indicate that the disease has any connexion whatsoever with defective hygiene or with an insufficient or ill-balanced dietary as McCarrison (1929) suggests.

Pathological anatomy. In struma lymphomatosa the gland is enlarged, all parts of it sharing in this enlargement proportionally. The average weight of seventy-eight glands reported by Marshall *et al.* (1948) was approximately 100 gm. It is necessary to stress this point, since it has been alleged that one or other lobe may be affected either preponderantly or exclusively. It must be remembered that the normal thyroid may be asymmetrical, sometimes so much so that one lobe may be entirely absent; consequently if Hashimoto's struma affects such a lopsided gland, the asymmetry will be exaggerated. In none of the cases in our own series was the lesion other than generalized, a feature which at once distinguishes it from the focal lymphoid infiltration so common in certain types of thyrotoxic goitre. The pyramidal lobe, as well as substernal prolongations when present, also shares in the general enlargement, and very commonly indeed there is a striking degree of enlargement posteriorly, so that the lobes meet or even overlap behind the pharynx, larnyx, and oesophagus (" circular goitre "), resulting in antero-posterior compression of the trachea, though this is rarely sufficient to cause serious dyspnoea.

The surface of the gland is smooth and slightly lobulated, this lobulation being merely an exaggeration of the normal. The superficial veins are not as large as in many thyrotoxic and nodular goitres of comparable size and the capsule of the gland, though slightly thickened, is smooth externally and shows no evidence of adherent muscular or fascial tissue. After removal the solidity of the tissue is revealed by the depth of the groove for the trachea, which may consequently be bilaterally compressed in the larger and more fibrous goitres. There is often some thickening of the capsule where it lies in contact with the trachea, but nothing to indicate any direct fibrous infiltration of the tracheal wall from the goitre or vice versa. One of the main anatomical supports of the thyroid, possibly the most important, is the fascial attachment between the gland and the tracheal wall, and it is this fascial tissue which becomes hypertrophied in all large and heavy goitres, but however great this hypertrophy it bears no sort of resemblance to the solid block of dense fibrous tissue which engulfs the trachea in Riedel's disease.

In struma lymphomatosa the consistency of the gland tissue is quite uniform throughout, best revealed when complete thyroidectomy has been

performed in the erroneous belief that the condition is neoplastic. There is a wide difference between the relative friability of the early stage and the resilient toughness of the later stage, though this latter is never sufficient to justify the terms " iron-hard " or " woody " which are so apt for Riedel's disease. On section in the earlier stages the tissue may be as friable as that of a lymph-node, and it is only in the advanced stages that it can be said to grate on the knife, little, if any juice being then expressible.

The colour of the gland tissue varies from the palest pink to yellowish white, with a distinct brownish tinge in certain specimens. In fresh material in early stages of the disease there is often a suggestion of translucency.

The capsule shows slight to moderate thickening and the connective-tissue stroma is abnormally distinct even in the earlier stage, though later it stands out very clearly as thick fibrous bands; in the most advanced degree of fibrosis the pseudolobular structure may be obscured rather than emphasized.

The main blood-vessels are not as large as in either simple or thyrotoxic goitres of comparable size and the general vascularity is diminished. The blood-vessels show no special tendency to be thickened or otherwise abnormal.

There is no naked-eye evidence of normal colloid-containing tissue to be seen in any part of the gland and nodules and cysts are very rare, and doubtless when present their formation antedated the lymphoid change. We have never encountered necrosis, calcification, or abscess formation.

Comparison with Riedel's disease and allied disorders. Contrast with the above description the state of affairs in *Riedel's disease*, in which the pathological changes are usually unilateral, at any rate in the earlier stages: the mass is seldom as large as a goose's egg, and the shape of the gland is obscured by adherent fragments of muscle tissue, etc., while its hardness on section is sufficient to blunt the knife. The cut surface is a dull white or yellowish-white, there is no trace of " pseudo-lobulation," yet at some point or points areas of colloid-containing tissue may be clearly visible and even occasionally a cyst or small areas of calcification. In *chronic syphilitic thyroiditis* there is usually gross evidence of necrosis of a gummatous type which is characteristic, and in *tuberculous thyroiditis* (apart from miliary forms and the highly dubious " tuberculose inflammatoire " of Roger and Garnier) caseous foci are to be seen both in the gland tissue and in the regional lymph-nodes.

Morbid histology. Microscopically the characteristic feature is the *uniformity of the changes*, which at once serves to distinguish struma lymphomatosa proper from the numerous conditions in which some degree of focal lymphoid infiltration may be found; notably in certain thyrotoxic goitres, in myxoedema, in involutional and similar changes in the thyroid gland, as well as in many unclassifiable chronic inflammatory states. There is a *diffuse* lymphocytic infiltration as well as more or less numerous *focal aggregations*, some with, some without, *germinal centres* (Fig. 112). These changes are widespread, so that in all parts of the gland the appearances

under the microscope are very similar. This does not preclude considerable differences in detail according to the stage reached by the disease, as Hashimoto himself admits, and it is these that have led Ewing and others astray and into assuming that in the final fibrotic stage there is a pathological identity with Riedel's disease. Vaux (1938) has differentiated three stages—early, intermediate, and late—correlating these in a general way with the clinical features. In her opinion there is a definite gradation in the degree of parenchymatous destruction and the amount of fibrosis, the average age of patients corresponding with what would be expected in the three gradations.

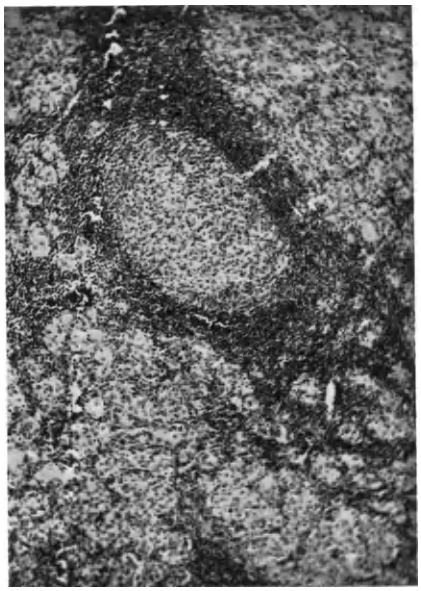

FIG. 112.—Section of thyroid isthmus removed from the patient in Fig. 114, showing lymphoid infiltration. (× 65.)

Vaux also maintains that in the early stage there is evidence of thyrotoxicosis in a majority of cases, this, however, diminishing in the intermediate stage, passing eventually into hypothyroidism in the last stage. Several of the cases included by Vaux as being in the earlier stages would not, in our opinion, be justifiably included under Hashimoto's struma, but should be classed with the advanced forms of lymphoid infiltration in Graves' disease, and the validity of her conclusions must be judged accordingly. Harry (1940) concludes that the thyrotoxic glands showing areas of dense lymphoid hyperplasia should be excluded from the class struma lymphomatosa, and with this opinion we agree. McClintock and Wright (1937) report a case in a woman of fifty-three on whom two operations were done

at an interval of two years, the extirpated tissue at both stages having essentially the same structure with a little added fibrosis in that removed later. We have had a similar case, the interval between the operations being more than four years, and although Heyd (1929) claimed to have observed a definite transformation of struma lymphomatosa into Riedel's disease from material similarly removed at intervals from the same patient, McClintock and Wright maintain that the extirpated tissue in both stages has the structure of Hashimoto's struma.

1. The Lymphatic Elements. A diffuse lymphocytic infiltration is constantly present and involves widely the intervesicular connective tissue.

*The lymph-follicles** vary greatly in size and number; they are usually rounded, but may be polygonal, fusiform, or irregular in shape. As a rule they possess a germ centre demarcated from the surrounding tissue by several layers of lymphocytes arranged fairly regularly in rows. In the germ centres are: (a) Reticulum cells, with large pale vesicular nuclei, some showing mitosis; (b) Plasma cells in small numbers, with eccentrically placed nuclei and a characteristic chromatin network; (c) Scattered lymphocytes.

These lymph-follicles must not be confused with the pseudo-follicles which are common in many types of goitrous glands and in myxoedema. These have a superficial resemblance to true follicles, but do not exhibit the germ-centre structure as described above, the central areas containing sometimes rather large pale cell remnants of thyroid epithelium or in others collections of phagocytic leucocytes. Both true and pseudo-follicles may be found in certain examples of struma lymphomatosa.

2. The Thyroid Vesicles. These also show great differences in size (Hashimoto's measurements were 30 to 360μ), but in our material large vesicles are rare, the majority being of the order of 70μ. In shape they may be oval, rounded, or irregular, or all trace of vesicular structure may be lost, a syncytium resulting. The interstitial connective tissue is hyperplastic and may contain epithelial cells either scattered or in groups. In one of our cases the vesicles show an extraordinary variety of metaplasia to squamous-celled tissue with well-marked keratinization, and a somewhat similar appearance is described by Kreuzbauer (1931).

The *cells* lining the vesicles are flat to low-columnar, according to the amount of colloid which persists. They are usually in a single layer, their protoplasm staining very variably with eosin. The nucleus is basal in the taller cells and central in the flatter; it is oval or rounded, with from one to four nucleoli. In the later stages the epithelial cells of the atrophic vesicles are large, acidophil, with excessive granular protoplasm and hyperchromatic nuclei. Occasionally the epithelial cells, both isolated and in vesicular formation, contain granules staining black with Flemming's solution or reddish with Sudan III or Scharlach R. These may, as Hashimoto states, correspond to Erdheim's granules (1903). According to Eisen (1934a and b)

* In this chapter, in order to avoid confusion, as far as possible the term *follicle* is restricted to the lymphocytic structures, while the term *vesicle* is employed for the epithelial thyroid unit.

rod-shaped mitochondria are to be found by Cowdray's method (1922) in the hypertrophic epithelial cells and in the syncytia of the lymphoid type of goitre which he includes with Riedel's disease, but which it is clear from his description corresponds to struma lymphomatosa. In cases which have been treated by iodine he believes there is evidence that these *mitochondria*, which he regards as criteria of cellular activity, are absent or represented by mere granules. Evidence of mitosis in the epithelial cells is conspicuous by its absence. There is considerable difference of opinion as to whether the epithelial cells show hypertrophy rather than mere hyperplasia. Shaw and Smith (1925) say that the cells are hypertrophic and show all the signs of increased functional activity, but that cellular degeneration keeps pace with the epithelial hyperplasia. Renton, Charteris, and Heggie (1938) deny the hypertrophic character of the epithelial cells and syncytia, asking why it is that these patients show *hypothyroid* and not *hyperthyroid* clinical features if there is even a moderate degree of epithelial hypertrophy. The answer would appear to be rather that the epithelial hypertrophy explains why a certain number of patients exhibit no hypothyroid phenomena, and also why in the early stages there may be a moderate elevation of the basal metabolic rate with transitory toxic symptoms such as wasting and tachycardia.

The *colloid* varies considerably in amount and in staining properties. It may be sufficient to cause flattening of the epithelial cells. Usually there are peripheral and occasionally central vacuoles present in the colloid. The staining reaction varies from vesicle to vesicle; it may be normal and eosinophil, there may be patchy basophil areas, or it may be entirely basophil. It may also be granular rather than homogeneous. Usually the colloid is much reduced in amount, and frequently absent altogether, though isolated masses surrounded by foreign-body giant cells or within lymph-spaces occur in some specimens.

Plugs of epithelial cells are common within the colloid-free vesicles. Such cells may retain their cell walls and staining characters or they may be shrunken or completely desquamated (Fig. 113). Mononuclear wandering cells in varying numbers may also be found within the vesicle as well as unmistakable plasma cells.

3. The Connective Tissue. This is everywhere increased in amount, showing up well with van Gieson's or Mallory's stain. It is widely infiltrated with lymphocytes, among which are a few plasma cells. Foreign-body giant cells were present in about 10 per cent. of our own material, though their presence or absence cannot be regarded as pathognomonic since thay may be met with in many forms of non-suppurative thyroiditis (Lee, 1935, de Quervain and Giordanengo, 1936), though rarely if ever in Riedel's disease. Giant cells, when present, have eosinophil protoplasm, are rounded, ovoid, crescentic, or irregular, with the nuclei arranged peripherally, their long axes tangentially or radially orientated, though not uncommonly the nuclei are grouped in the centre of the cell or are quite irregularly distributed. The role of these giant cells is, as Olper (1935)

showed, the elimination of colloid which cannot be otherwise absorbed, and it must be assumed that whereas in certain types of chronic thyroiditis the elimination of colloid by normal methods is so defective that many new giant cells arise for the purpose, in Hashimoto's struma there is seldom any necessity for the intervention of such cells and in Riedel's struma even less so. It is very doubtful indeed, therefore, whether a distinct " foreign-body giant-cell " type of thyroiditis need be split off as Lee has done.

4. The Blood-vessels. These are little altered in size or structure, and endarteritis is not met with in struma lymphomatosa. No micro-organisms, spores, or protozoa have been detected in the gland in any case of Hashimoto's struma, nor have the usual tests, bacteriological or biological, for

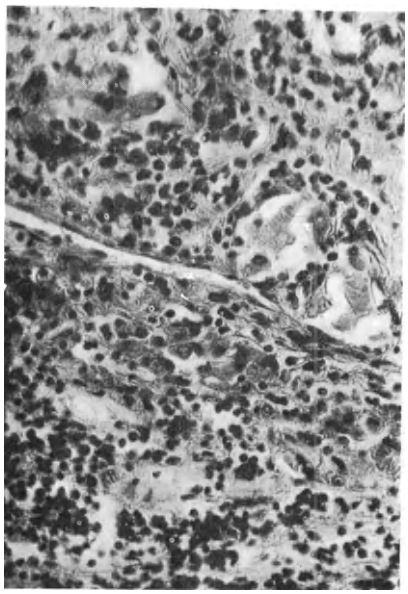

FIG. 113.—Part of section shown in Fig. 112 under higher magnification (× 350). Note degenerate follicles.

tuberculosis or syphilis proved positive, so that there is little or nothing to connect the disease with a micro-organismal cause.

The histological features of Hashimoto's struma may be briefly summarized thus: (1) Abundant infiltration of the gland with lymphocytes, together with many active germ follicles. (2) Profound changes in the vesicular epithelium, with eventual disappearance of colloid. (3) Widespread new formation of connective tissue.

Comparison with Riedel's disease. Contrasted with this, Riedel's disease is characterized by the *absence of diffuse lymphocytic infiltration* and of lymph-follicles, though, as in every other form of goitre, an occasional

lymph-follicle may be seen even in Riedel's disease, in which usually they are entirely wanting. The changes in the *parenchyma* are of a totally different nature. For the most part there are no traces of epithelium or colloid throughout the extirpated tissue, but at the periphery there are small groups of shrunken vesicles surrounded by dense fibrous tissue which has the appearance of strangling them. Giant cells are very rarely seen, but their presence cannot be allowed pathognomonic significance. Immediately outside the fibrotic area are to be seen well-formed vesicles containing normal colloid, and having all the appearances of being in full functional activity, a condition reflected in the fact that evidence of hypothyroidism either before or after operation is unusual. The bulk of the new tissue in Riedel's disease is composed of adult fibrous tissue often relatively poor in cells and extensively hyalinized, though at the periphery of the mass some fibroblasts are often visible, contrasting thus with the forms of non-suppurative thyroiditis described by de Quervain and Giordanengo in which the tissue in certain areas is rich in cells, oedematous, and only partly cicatrized. On the surface of the mass, striped-muscle cells can be seen infiltrated by fibrous tissue continuous with that in the thyroid.

In *syphilis* of the thyroid there is usually well-marked endarteritis in the blood-vessels and evidence of necrosis both macro- and microscopical, the parenchyma suffering very much as in Riedel's disease.

In *tuberculosis* the characteristic organism may be detectable, and there is little indication of the advanced fibrosis seen both in Riedel's disease and in chronic non-specific thyroiditis, many of the vesicles at the edge of the caseous tissue containing healthy-looking colloid.

Pathogenesis and Aetiology. The nature of the lesion in Hashimoto's disease is quite obscure, and it is mere obscurantism to refer to it as an inflammatory condition. It is clear from a study of the clinical histories of the proved cases that the goitre rarely if ever follows on an attack of one or other of the acute inflammatory diseases, nor does it exhibit any of the recognized features of an inflammatory state throughout its course. Histologically it reveals none of the varied pictures which de Quervain and Giordanengo (1936) have so fully and conveniently described for the several types of thyroiditis and strumitis. It is true, however, that Brünger (1915) and Eason (1927) regard the presence of lymphoid follicles in the thyroid as evidence in itself of an inflammatory process. Davison and Letton (1949) suggest that, as in other forms of goitre, emotional stress may play a part in its pathogenesis.

The source of the lymphoid infiltration is easier to account for than is the stimulus which induces it. It is unusual to find definite lymphoid aggregations in the normal thyroid gland, yet we have one or two histological preparations which exhibit it. Simmonds (1913), working with autopsy material from Karlsruhe, found lymphoid collections in 5 per cent. of apparently healthy thyroid glands. Such lymphoid foci did not occur in the thyroid glands of young people under thirty years of age, and were five times as common in women as in men. He found lymphoid tissue

in 15 per cent. of simple goitres as well as in 75 per cent. of the goitres from Graves' disease, and he concludes that it is impossible to say whether the disturbance leading to lymphoid infiltration is general or local, and again, if local whether it is chemical, mechanical, or inflammatory. He adds that the quantitatively and qualitatively altered secretions in Graves' disease may be a sufficient chemical stimulus to the formation of lymphoid tissue, as also may be iodine medication. In a later paper Simmonds (1923) describes changes in the thyroid glands of elderly obese patients resembling in certain particulars those of Hashimoto's struma, especially in the tendency to lymphoid infiltration and subsequently to destruction of the epithelial elements, terminating in myxoedema. These were, however, atrophic glands, and the two processes are quite dissimilar. On the one hand there is the small or shrunken gland described by Simmonds; and on the other the goitrous gland of Hashimoto, which may within a few weeks reach a very considerable bulk. At operation the lymphoid tissue appears not merely to be replacing something which has undergone shrinkage, but to possess enormous intrinsic activity, so that the tension within the gland in the prefibrotic stage is considerable, the pallid tissue bulging visibly when the capsule is incised.

Several authorities, *e.g.* von Werdt (1911), Reist (1922), Payr (1927), Kreuzbauer (1930, 1931), Boyden, Coller, and Bugher (1935), and Dunhill (1937), lay emphasis on the possible influence of iodine medication on the development of the lymphoid infiltration of Hashimoto's struma as well as the similar but focal changes so frequently seen in thyrotoxic goitres, but it should be remembered that in Hashimoto's cases there had been no iodine medication and the same remark applies to seventeen cases in our own series. It is also true that large focal areas of lymphoid infiltration may be discovered in goitres from Graves' disease which were removed in this country before it was the custom to prepare such cases with iodine. Jaffé is also very sceptical as to the influence of iodine therapy in struma lymphomatosa. It is not, of course, essential to prove that lymphoid follicles are present in the normal thyroid gland in order to account for the various lymphoid infiltrations met with in simple goitre, in thyrotoxicosis, and in Hashimoto's struma, since undifferentiated mesenchymal cells and possibly also reticulum cells are to be found widely scattered in the stroma of the thyroid. This accords with Maximow's views (1924) on the potentialities of the mesenchyme, which thus may provide an intrinsic source for the development of lymphoid tissue, an origin the more likely as there is so little to indicate any spread of lymphoid changes into the thyroid from without. Crile (1948) reports a case of Hashimoto's struma which showed generalized lymphoid hyperplasia post mortem.

Hashimoto compares struma lymphomatosa and Mikulicz's disease, but there appears to be no evidence that they are in fact related, and little, if any, similarity histologically between the two lesions.

Graham (1931) does not exclude the possibility of a relationship to lymphosarcoma, but although he thinks that he has seen at least one case

exhibiting a transition from Hashimoto's struma to sarcoma, no such development has appeared in any of our own series, some of which have been followed up for nearly twenty years.

Little is to be gained by pursuing the problem of the pathogenesis of Hashimoto's struma, which in effect appears to be neither inflammatory, neoplastic, nor degenerative in any way comparable with what is usually understood pathologically by such terms.

Clinical features of Hashimoto's struma

1. History and mode of onset. There is nothing in the series of cases under review to confirm Eason's (1928) view that struma lymphomatosa and Riedel's disease are late developments in a thyrotoxic type of goitre. Since 1928, when Eason raised the question, we have taken pains to inquire into this possibility in all such cases, with consistently negative results. It is in fact striking how little evidence there is of any pre-existing ill health in patients with Hashimoto's struma, either immediate or remote. Unlike what is common in most non-suppurative forms of thyroiditis and strumitis, there is seldom any preceding acute illness or other toxic or infective state, general or local. Fatigue, shortness of breath, and increase in weight are common symptoms, but they can legitimately be ascribed partly to direct pressure and partly to the hypothyroid tendencies so often revealed when the basal metabolic rate is estimated. It cannot be denied that certain toxic features may also occur in exceptional cases, exemplified by loss of weight, nervousness, and a moderate elevation of the basal metabolic rate, but these are explicable in relation to the degree of dyspnoea which exists and to the hypertrophic changes in the thyroid epithelium, which, however, are comparatively short-lived. In other words, toxic features do not precede the disease, though they may be associated with its onset, in which event they have no tendency to become aggravated or to lead to the complete picture of thyrotoxicosis, primary or secondary. There are of course many cases of advanced thyrotoxicosis in which more or less of the hyperplastic tissue is replaced by a diffuse lymphocytic infiltration among which there may be many germinal centres. These changes are, however, essentially focal, and considerable areas of actively hyperplastic colloid-bearing tissue invariably coexist with the lymphoid areas, indicating that it is a secondary phenomenon, whereas in Hashimoto's struma the evidence is all in favour of the lymphoid change being primary.

In many cases the patient is a woman in the late forties or early fifties, inclined to obesity, with the facies of early myxoedema and a rather dry skin, and is apathetic or torpid in habit, with a basal metabolic rate which suggests a moderate degree of hypothyroidism.

In Riedel's disease evidence of thyrotoxicosis or of myxoedema is almost invariably lacking, though as in all conditions associated with severe dyspnoea and nocturnal asthmatic attacks, the basal metabolic rate may be moderately raised and the patient exhibit nervousness and loss of weight. In those exceptional and late cases in which both lobes are affected, evidence of

hypothyroidism may be forthcoming even in Riedel's disease. Much the same applies to the non-suppurative form of thyroiditis and strumitis described so fully by de Quervain and Giordanengo, and for the same reason—namely, that in these lesions there is sufficient secretory tissue remaining to carry out normal thyroid activity.

There is very seldom any pyrexia or other evidence of inflammation at the onset of Hashimoto's struma, or for that matter in Riedel's disease, in spite of Clute and Lahey's (1932) view that the latter condition has an origin in acute thyroiditis, as undoubtedly is true for many other non-suppurative forms of chronic thyroiditis. The blood-picture is seldom altered, except for a mild degree of secondary anaemia in certain cases.

Localized pain and tenderness in the thyroid gland, as well as pain referred to the ear, nape of neck, and upper limb, are characteristic of acute and subacute thyroiditis, and particularly of the giant-cell type which Lee regards as an entity, but they do not occur in uncomplicated cases of struma lymphomatosa or in Riedel's disease. Headache, vertigo, and slight dysphagia may occasionally be complained of, but are unusual. The goitre develops, with certain striking exceptions, at a moderate rate, so that it may be months before it causes pressure symptoms, whereas in Riedel's disease it is more commonly a matter of weeks. Sometimes the goitre grows rapidly at first, followed by a slowing down, or it may steadily progress. Even in the largest goitres of Hashimoto's type there is seldom any evidence of pre-existing thyroid enlargement, except in those arising where goitre is endemic. In none of the cases in the series here reported does the disease appear to have been engrafted on an established goitre—colloid, nodular, or hyperplastic—though the prolonged history of goitrous enlargements in one or two instances might suggest that possibility.

2. Pressure symptoms. These are seldom prominent in Hashimoto's struma unless the goitre is exceptionally large, when the trachea may be subjected either to bilateral or to antero-posterior compression as revealed by appropriate radiographs. Usually the worst that happens is a moderate dyspnoea on exertion. Interference with swallowing is also most unusual. No instance of laryngeal paralysis occurred in the series of cases now under review, though some hoarseness and dysphonia of an intermittent character is often observed: this appears to be due not to interference with the function of the interarytenoid muscle, but to the mechanical effect of the very solid goitre, much of which lies behind the larynx.

In Riedel's disease, on the other hand, pressure effects dominate the picture and reveal themselves by intense dyspnoea, often worse when lying down, suffocative attacks, and nocturnal asthma, as well as persistent stridulous cough.

3. Type of goitre. The goitre itself in Hashimoto's struma is usually of moderate size (Fig. 114), every part of the gland taking a share in the enlargement, so that the pyramidal lobe is often palpable as an entity. It is smoothly lobular, the irregularities on its surface being an exaggeration of those normal to the thyroid gland in health. In the earlier stages the gland is

moderately firm, but hardly more so than in the hyperplastic goitre of Graves' disease, and it moves freely on swallowing. When fibrosis has developed the gland becomes firmly or toughly resilient, but never as hard as iron or wood, and while moving on swallowing may appear rather unusually tethered to the trachea. The thyroid shape of the goitre is well preserved in struma lymphomatosa and its outline and borders may be well defined (Sinaiko *et al.*, 1948). The pulsation of the carotid vessels is readily palpable posterolaterally, in which direction they are displaced by the growing gland.

In Riedel's disease the intense hardness and fixation of the relatively small and smooth mass are the features which distinguish the condition from all

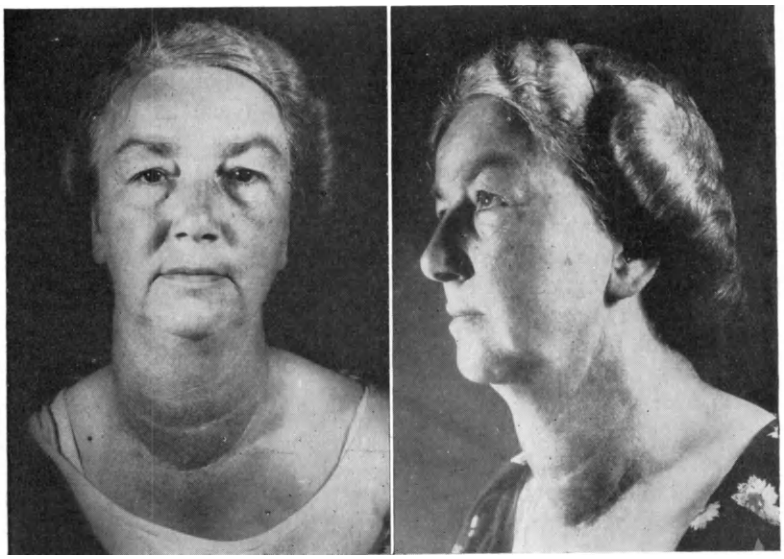

FIG. 114.—Struma lymphomatosa: The patient, aged 54, had an eighteen months' history of goitre with progressive fatiguability, sluggishness and inability to concentrate. The general appearance was suggestive of mild hypothyroidism. The photograph was taken shortly after a biopsy from the thyroid isthmus, and irradiation therapy.

other thyroid lesions. In no form of malignant goitre is the mass so hard as in Riedel's disease, though that form of secondary growth following post-cricoid carcinoma approaches it closely in this respect. Movement on swallowing may be entirely abolished, and the surrounding structures cannot be separately palpated. The carotid artery on the corresponding side is usually completely obscured and its pulsations almost entirely obliterated. Such a state of affairs, though it may be met with in extensive and advanced malignant goitre, is not encountered in neoplasms of a size comparable with the mass of tissue in Riedel's disease.

4. Conditions met with at operation. In struma lymphomatosa the

infrahyoid muscles and the surgical capsule of the thyroid gland are readily separable from the latter, which can be dislocated from its bed with no greater difficulty than is met with in any of the more solid hyperplastic glands of primary thyrotoxicosis. Vascularity is slight and the main thyroid veins and arteries can be readily secured, though owing to the friability of the thyroid tissue the smaller intrathyroid blood-vessels are more difficult to control than in most goitres. On the whole the haemorrhage encountered is less than in any other thyroid operation of comparable magnitude. Separation from the trachea is not difficult, for although the fibrous tissue binding gland to trachea is often markedly bulky and opaque, the plane of cleavage is never really obscured.

In Riedel's disease the mobilization of the fibrous mass may prove a matter of the utmost difficulty. Many operations have had to be abandoned, others have proved fatal on the operating table from haemorrhage, from suffocation, or from damage to vital structures, while yet in others it has been necessary to resect muscles, nerves, bones (such as the clavicle or portions of the sternum), the jugular vein, or common carotid artery, with dire consequences to the cerebral function, etc.

5. Hypothyroid phenomena. The progress of Hashimoto's struma even without operative treatment is towards myxoedema, as would be expected from its histology. We observed one such case (a woman now aged sixty-two) for some years, the diagnosis being sufficiently clear and symptoms of pressure so trivial that it has been possible to avoid operative treatment. The basal metabolic rate fell from −12 per cent. to −36 per cent. during the first year and a half, and then full doses of thyroid extract were required to maintain thyroid function. We have not observed any case of spontaneous retrogression such as undoubtedly occurs with the foreign-body giant-cell type of thyroiditis.

Sir T. Dunhill has reported an interesting thyrotoxic case in his Lettsomian Lectures for 1937: At a first intervention the extirpated tissue proved to be so extensively infiltrated with lymphoid tissue that supervention of myxoedema was anticipated. The patient lost all her symptoms, yet some years later developed further thyrotoxic symptoms necessitating a second operation, the tissue removed at this intervention showing all the characteristics of a hyperplastic goitre modified by prolonged iodine therapy. In this case, however, the primary lesion was not Hashimoto's struma but thyrotoxicosis, and the reappearance of thyroid hyperplasia with the disappearance of the lymphoid infiltration is explicable on the ground that at the first operation a portion only of the gland was extirpated and therefore tissue free from lymphoid infiltration (and capable of hyperplasia) was almost certainly present in the part of the thyroid which was conserved.

It is extremely difficult to estimate the *rate of progress* in a disease with so few symptoms, but one of the largest goitres of the Hashimoto variety which we have seen reached its maximum in a few months, considerable dyspnoea resulting, whereas in those glands of more moderate size little advance may be observed in the course of a year or more.

In Riedel's disease progress is relatively more rapid, but once serious pressure effects arise the danger to the patient has little relationship to the actual size of the thyroid mass. There is good reason to doubt whether those cases recorded as having spontaneously retrogressed were in fact examples of Riedel's disease. It is probable that they were inflammatory lesions of the thyroid without the adult fibrous tissue and the perithyroid involvement so characteristic of Riedel's disease, the more so as inquiry into the after-history of our own series of cases of true Riedel's disease and a review of the literature reveals that recurrence or relapse is not unusual. Myxoedema, however, is rarely the outcome of Riedel's disease even after attempts at radical extirpation, a point in sharp contrast to what happens in struma lymphomatosa.

Diagnosis. The difficulties in the diagnosis of Hashimoto's struma to a large extent are resolved when once its status *vis-à-vis* Riedel's disease is admitted. A firm goitre which appears in a middle-aged patient, usually a woman, reaches its maximum in a few months, and involves every part of the gland, causes only a moderate degree of dyspnoea, but produces neither serious pressure effects, thyrotoxic symptoms, pain, tenderness, pyrexia, nor other inflammatory phenomena, is almost certainly a struma lymphomatosa. If to these features be added the *absence* of any evidence of involvement of extrathyroid tissues and the *presence* of some degree of hypothyroidism, the diagnosis is placed beyond a peradventure.

Nevertheless struma lymphomatosa is rarely diagnosed correctly before operation and even when the gland is exposed the nature of its enlargement may not be recognized and too radical a resection done. Patterson and Starkey (1948) have rightly emphasized that chronic thyroiditis is not a pathological curiosity and that the clinician should be more mindful of its existence and the different types.

Differential diagnosis. 1. *From Lymphosarcoma and other Malignant Neoplasms.* From malignant disease the distinction is made by noting that in struma lymphomatosa all parts of the gland are affected, without serious encroachment on extrathyroid tissues, without involvement of the main vessels and nerves, and without any trace of the irregular bossiness of the surface of the gland or of enlarged lymph-nodes. Nevertheless the conditions are frequently confused, for Emerson (1935), in reporting nine cases of Hashimoto's struma, states that five were diagnosed as malignant goitre. This error has been made more frequently than might be expected, sometimes inducing the surgeon to perform complete thyroidectomy, an operation dangerously easy to carry out in struma lymphomatosa but rarely if ever feasible or desirable in malignant disease. In the latter it is extremely rare to find that the whole thyroid is involved without such a degree of infiltration of surrounding structures as to preclude the possibility of complete thyroidectomy.

The reaction of the goitre to radium therapy may also be employed to differentiate Hashimoto's struma, which is in fact remarkably radiosensitive.

From lymphosarcoma, into which Graham (1931) suggests it may become

converted, struma lymphomatosa is distinguishable by the absence of involvement of regional lymph-nodes, as well as by the bulky goitre resulting from lymphosarcoma.

2. *From Riedel's disease.* Diagnosis is made by a consideration of the numerous points of distinction already elaborated, but which may be tabulated as follows:

TABLE XXIV

DIFFERENTIAL DIAGNOSIS BETWEEN HASHIMOTO'S STRUMA AND RIEDEL'S DISEASE

	Hashimoto's Struma	*Riedel's Disease*
1.	Preponderates in women from 45 to 60 years of age.	Occurs in younger men and women than does struma lymphomatosa.
2.	There is a tendency to myxoedema.	There is little tendency to myxoedema except after radical operations.
3.	All parts of the thyroid gland are involved, but nothing outside it. The goitre is sometimes large but never woody hard.	The disease is usually unilateral with extension to extrathyroid structures. The goitre is small, intensely hard, and smooth.
4.	Pressure effects are seldom severe.	Grave pressure effects are the rule.
5.	The histological structure, which varies with the stage of the disease, is characteristic.	The mass is formed of dense scar tissue.

3. *From chronic thyroiditis, non-specific and specific.* From chronic thyroiditis of the giant-cell type described by de Quervain and Giordanengo, it is distinguishable by the absence of inflammatory symptoms throughout, by its bilateral character, the tendency to hypothyroidism, and the absence of any tendency to spontaneous cure.

From specific forms of chronic thyroiditis, i.e. tuberculosis, syphilis, and actinomycosis, it is differentiated by the absence of evidence of the specific causal organisms and of the special physical characters of the thyroid enlargement in these several diseases.

From calcified goitres of various kinds it is differentiated by radiographic evidence of the presence of this type of degenerative change.

Treatment. The main indications for treatment are: (1) To establish that the condition is not a malignant neoplasm; and (2) To relieve pressure symptoms.

It has already been pointed out that diagnosis is usually possible even without recourse to a biopsy, though the latter step is so easy to carry out and so free from risk that it may be argued reasonably that it is almost essential in order to avoid dangerous error. The naked-eye appearances of the gland, once it is exposed, are usually sufficiently characteristic to permit confirmation of the diagnosis without waiting for microscopical examination,

though with modern methods the delay of the few minutes necessary for such further confirmation is amply justifiable.

In order to relieve pressure a bilateral resection is usually called for, and it will be obvious from what has already been described that in many cases the " circular " character of the goitre calls for full dislocation of the lateral lobes in order to enable this bilateral resection to be carried out on a scale sufficient to relieve the antero-posterior tracheal compression which exists in such cases. It is of course clear that the more radical the operation, the sooner will the patient exhibit hypothyroid phenomena—or if indeed such already exist, the more rapidly will they reach that of high-grade myxoedema. The advent of hypothyroidism is, however, sooner or later almost inevitable, and it cannot be a matter of great moment, once this has appeared, whether the patient has to take a small or large dose of thyroid extract. It is, however, neither necessary nor desirable to perform complete thyroidectomy, an operation which is perhaps easier technically in struma lymphomatosa than in any other form of goitre with which we are acquainted. We have examined several museum specimens which illustrate this dangerous facility, dangerous not because of the inevitable myxoedema which in any case is only precipitated by such excessively radical methods, but because of the risk of damage to the parathyroid function as well as to the recurrent laryngeal nerves. Gilchrist (1935) quotes a case in which both myxoedema and tetany followed complete thyroidectomy in struma lymphomatosa, and we know of other similar cases. It is perhaps wise to avoid the ligation of the main thyroid vessels in carrying out the necessary extirpation, and this is rendered all the easier since the blood-supply is not sufficiently rich to make arterial ligation necessary on technical grounds.

There is very little risk or difficulty in resecting sufficient goitrous tissue to relieve pressure in these cases, and in our own series as well as those quoted by Graham (1931), McClintock and Wright (1937), and others, the operative risk proved negligible. This is in striking contrast to what is found in Riedel's disease, in which radical operations even if attempted have rarely been completed, although to achieve them the cervical muscles, the clavicle, and the sternum have been divided and the great vessels, the vagus, the thoracic duct, trachea, and oesophagus have been resected or accidentally damaged and tracheotomy has often proved necessary; as would be expected, the immediate mortality is high.

1. Surgical. It is a matter of considerable doubt as to whether surgical treatment is necessary in Hashimoto's disease, assuming that pressure symptoms are slight. Avoidance of resection will undoubtedly postpone the necessity for thyroid medication, and there are some who believe that the disease in certain cases may either cease to progress to the stage of thyroid deficiency or may even retrogress, though the evidence for this is very slender.

2. Radium therapy. Radium therapy was shown by Renton, Charteris and Heggie to be almost a specific for the type of goitre which is here identified as struma lymphomatosa; it appears to be exceptionally radiosensitive.

These authors give valuable details as to dosage, etc., and point out that the method affords a rapid differential test from malignant disease of the thyroid, which is in general much less radiosensitive, though this does not apply to lymphosarcoma. McEwan of Bradford informs us that he has also had a case which cleared up rapidly under similar methods. It will also be recalled that in one of the cases to which Ewing referred the goitre disappeared under radium therapy. Harry (1940) cites a series of six patients treated with radium who lost their symptoms over a period of two to four years without developing myxoedema.

3. X-ray therapy. There seems little reason to doubt that X-ray therapy also, if of only sufficiently high voltage, would affect struma lymphomatosa favourably, though Boyden, Coller, and Bugher, (1935), and Portman (1932), disapprove of it in such cases, while Means (1948) advocates its use. Schilling (1945) states that the treatment of choice for struma lymphomatosa is irradiation after diagnostic biopsy.

Prognosis

1. Tendency to myxoedema. If untreated, struma lymphomatosa may pass into myxoedema, the transition being so gradual that, unless repeated basal metabolic rate estimations be made, it is often overlooked. No medical treatment appears to have any effect whatever, and spontaneous regression in typical Hashimoto's disease has not so far been proved to occur though it is arguable that it has in fact occurred whenever the patient fails to exhibit hypothyroid phenomena after a period of years. After bilateral resection of a part of both lobes complete and permanent relief of pressure symptoms is to be anticipated even if the onset of hypothyroid phenomena is thereby hastened. Complete restoration to health was noted to be slow by Hashimoto, but this no doubt was due to failure to recognize that thyroid medication should be commenced early whenever there is reasonable ground for assuming that otherwise hypothyroidism would supervene.

2. Relapses. Recurrence after operation is most unusual, and when it occurs is due usually to the bilateral nature of the goitre not having been recognized, resulting in a unilateral resection which fails to relieve pressure adequately, this necessitating a further intervention on the contralateral side. It is a mistake in these cases to assume that the disease has in the interval merely spread from one lateral lobe to the other, for which view there is no reliable evidence: the explanation is most probably that in certain asymmetrical goitres (based on congenital asymmetry of the thyroid gland) one large lateral lobe may so overshadow the other smaller lobe that the latter is allowed to remain undisturbed, and the fact that it is equally affected pathologically is not recognized. This appears to be the explanation of several of the cases in which second operations were called for at intervals of from one to four years; it was certainly so in the one case early in our own series which required a second intervention. McSwain and Moore (1943) agree that true regrowth of a Hashimoto's struma after thyroidectomy is unknown.

3. Post-operative complications. These are very unusual, unlike what happens after attempts to extirpate the tissue radically in Riedel's disease. Laryngeal paralysis (*but see* Clute, Eckerson, and Warren) and tetany are both rare following operations for struma lymphomatosa except in the cases in which complete thyroidectomy has been performed in the erroneous belief that the condition was malignant. Post-operative myxoedema is to be expected sooner or later; it occurred in 64·8 per cent. of the series here

TABLE XXV

SUMMARY OF DATA RELATING TO HASHIMOTO'S DISEASE AND RIEDEL'S STRUMA

		HASHIMOTO'S STRUMA		RIEDEL'S STRUMA	
		McClintock and Wright (July, 1937) (47 cases)	Joll (1939) (81 cases)	McClintock and Wright (60 cases)	Joll (1939) (5 cases)
Sex	Male Female	4·2 per cent. 95·8 per cent.	3·7 per cent. 96·3 per cent.	18·2 per cent. 81·8 per cent.	20 per cent. 80 per cent.
Age	Youngest Oldest Average	26 years 75 years 49·2 years	10 years 74 years 57·6 years	23 years 78 years 40·3 years	27 years 62 years 44·4 years
Duration of symptoms	Shortest Longest Average	30 days 6 years 1·3 years	1 month 8 years 1·7 years	15 days 2 years 7·5 months	3 weeks 1 year 6·1 months
Duration of goitre	Shortest Longest Average	3 days 16 years 4·2 years	3 weeks 30 years 4·2 years	14 days 23 years 3·5 years	3 weeks 8 years 1·9 years
Thyroid involvement	Unilateral Bilateral	100 per cent.	100 per cent.	30·5 per cent. 69·5 per cent.	80 per cent. 20 per cent.
Pre-operative function	Thyrotoxic Hypothyroid	0 per cent. Not stated	0 per cent. 35·2 per cent.	Not stated Not stated	None None
Operative findings	Diffuse extrathyroid involvement	0 per cent.	0 per cent.	100 per cent.	100 per cent.
Post-operative function	Hypothyroid	78·8 per cent.	6·48 per cent.	27 per cent.	20 per cent.

Summary of data relating to Hashimoto's struma (C. A. J.'s cases, 51; communicated, but previously unpublished, 30; none of these appear in McClintock and Wright's series) and Riedel's disease (5 cases unpublished, not included in McClintock and Wright's figures).

reported, as well as in 78·8 per cent. of the cases reported by McClintock and Wright.

In our own series a daily dose of 1–3 gr. of thyroid extract (based on the dry gland) has proved adequate to control the hypothyroid symptoms. At present there is insufficient evidence to indicate whether after radium or X-ray therapy there is the same tendency to the supervention of myxoedema, as in Renton, Charteris, and Heggie's series no estimations of the basal metabolic rate appear to have been made, but nevertheless these authors state that no hypothyroid phenomena were detected though one of their cases was followed for as long as five years.

II. Riedel's Disease

Introduction — Incidence — Pathology — Pathogenesis — Signs and Symptoms — Diagnosis — Prognosis — Treatment — Table of Cases.

This disease is characterized by the appearance in the thyroid of a hard mass, which later tends to invade the surrounding structures, such as the tracheal wall, carotid sheath, and cervical muscles. Its clinical features closely simulate slowly-growing malignant disease, though pathologically it is undoubtedly an inflammatory condition in which fibrosis eventually dominates the picture. The cause is quite unknown.

Riedel's description of the condition, in 1896, led to its recognition as a clinical and pathological entity, although it is probable that Semple's case (1868) was of a similar type.

Bowlby, in 1884, had described a specimen obtained at autopsy from a woman of forty-two, in whom symptoms began three years before death. He drew attention to the fibrous appearance of the cut surface of the tumour and to the fact that the nerves, veins, and arteries were involved in the mass and the trachea compressed in an antero-posterior direction. He regarded the condition as an infiltrating fibroma, but it seems almost certain that it was really a chronic inflammatory condition, identical with Riedel's disease.

Riedel mistook his first case for malignant disease. In attempting to remove the mass he had to abandon the operation, owing to the involvement of the surrounding parts. In spite of the incomplete operation the patient recovered. This peculiar sequel attracted Riedel's attention to the condition, and he subsequently described a series of cases.

The pathological process in the gland is of the nature of a sclerosis which strangulates and destroys the secretory parenchyma; eventually a dense mass of tissue, variously compared to iron, stone, or wood, results, and the various planes of cleavage between the normal tissues become so obscured that they are impossible to define. In Jeannel's case (1898) fibrosis had invaded the carotid sheath and had extended to the base of the skull.

Incidence. The incidence is extremely difficult to estimate, but Heyd (1929) states that there were forty-eight cases among 10,500 patients with thyroid disease treated at the Mayo Clinic, and Richard (1947) reported that among 3,400 thyroidectomies there were nine cases of Riedel's struma.

Age and sex. The youngest case on record is that of Riedel's in a child of four; the oldest, in a man of sixty-three. Most of the cases occur in adults, and, although a considerable percentage develops in goitrous glands, the association with pre-existing goitre is far less frequent than is the case with malignant disease.

There appears to be a slight preponderance among females though of Delore and Alamartine's collection of fourteen cases (1911) ten were in males. Heineke (1914) also considers the disease to be commoner in men.

Pathological anatomy and Pathogenesis. The disease may begin in the interior of the gland and spread outwards, or it may start comparatively

superficially; in the latter event the surrounding tissue may be involved while recognizable thyroid tissue yet remains in the interior of the gland.

The origin and distribution of Riedel's disease are essentially focal. *Bilateral* laryngeal paralysis has, so far as we are aware, never been recorded; yet if it were true that the condition follows struma lymphomatosa, in which the whole gland is usually involved, such a complication might occasionally be expected.

In nearly one-third of the reported cases the disease has been confined to one lobe.

Macroscopically, the mass is white or pinkish-white in colour. Traces of the gland tissue can be recognized if the disease started in the peripheral part of the gland and has not yet penetrated deeply into the interior, or when the gland is already the site of an adenomatous or colloid goitre. In some cases cysts are found in the fibrous mass [as in Spannaus's case (1910), and in two of our own series].

According to Crile (1948) the dense fibrosis often appears to centre round a degenerating adenoma of the thyroid. Calcification has been described in one case by Heineke. On scraping the cut surface of the mass no juice can be expressed, in contradistinction to what is usual in carcinoma. The fibrous tissue can be traced into the infrahyoid muscles and the carotid sheath and its associated structures. The walls of the great vessels become particularly friable in this disease. In one of the recorded instances fibrous tissue reached as far as the pericardium; it often surrounds or invades the trachea and oesophagus, so that to define the normal planes of cleavage between the gland and these viscera becomes impossible. Crile (1948) aptly describes the condition as a diffuse fibrosis of the neck with the thyroid at its centre. It is therefore extremely difficult to avoid damage to other structures during attempts at extirpation of the mass.

According to Heineke, the most common site of the disease is the lower portion of the gland, and this accords with our own experience.

Microscopically, the parenchyma of the gland is seen to be invaded by a sclerotic process which involves both the capsule and the interstitial tissue. In the oldest part of the lesion there is no trace of thyroid tissue left, but merely a mass of adult fibrous tissue poor in cells. In places there are large collections of inflammatory cells, among them many mononuclears, large lymphocytes, plasma cells, and some eosinophils. Foci of lymphoid tissue may occur but they are never as prominent as in struma lymphomatosa. Again areas of relatively normal thyroid tissue may be found surrounded by dense fibrous tissue; or the uninvolved parenchyma may show definite hyperplasia. Rarely extensive metaplasia of the follicular epithelium exists (Fig. 115), the walls of the follicles being lined by typical stratified epithelium (Harry, 1940). Giant cells of histiocytic and epithelial origin may be prominent in the interstitial tissue and within the follicles. Hyaline degeneration may be a prominent feature in certain specimens. Suppuration is exceedingly rare, nor is there any sign whatever of caseation. Very few capillary blood vessels can be found, and endarteritis is common in such vessels as exist.

Minute haemorrhagic foci are sometimes present. At the spreading edge of the mass there is evidence that the fibrous tissue is compressing and strangulating the vesicles, but, in addition, there is invariably some trace of proliferation of the epithelial elements side by side with the degenerative and destructive processes. It is probable that the absence of hypothyroid symptoms can be correlated with this somewhat imperfect regenerative change.

A study of these histological appearances justifies the conclusion that Riedel's disease is a definite pathological entity, even though the causation

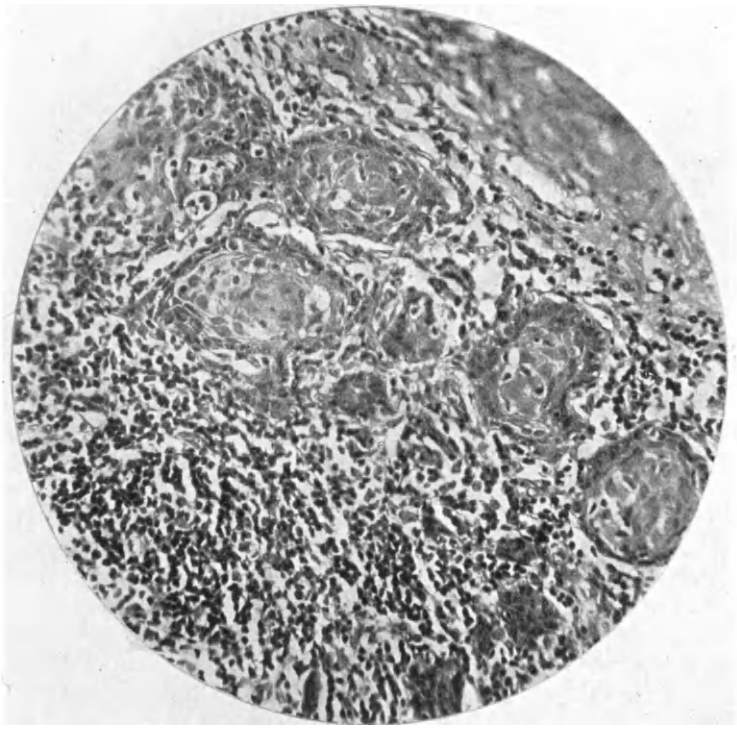

FIG. 115.—Section of thyroid tissue resected from a patient with Riedel's disease. Note squamous metaplasia and fibroblastic reaction. (× 120.)

of the condition is absolutely obscure. Marshall *et al.* (1948) accept the view that Riedel's struma represents the terminal stage of a non-specific thyroiditis but our own experience is that extra-capsular extension of the disease process is absent or trivial in the latter condition.

Signs and Symptoms. The disease is slow in its progress, though Delore and Alamartine (1911) consider that it is relatively less chronic than some forms of malignant disease of the thyroid. Pain is a common symptom, and may be localized to the gland or referred to the ear, the back of the neck, or the shoulder, of the corresponding side.

The gland may be slightly tender to palpation. Low-grade pyrexia may exist but is exceptional (Harry, 1940). Dyspnoea is a striking feature of most cases, and may be due either to lateral or to antero-posterior compression of the trachea. Lateral deviation of the trachea is unusual, differing in this respect from what is found in association with malignant disease or large innocent tumours. The resultant dyspnoea is often out of all proportion to the size of the tumour. Delore and Alamartine consider that the reason for the severe dyspnoea is the encircling of the trachea by the fibrous mass, but this can be the true explanation in only a minority of the cases.

Affection of the voice. This may occur early, and is due to involvement of the recurrent laryngeal nerve. Fortunately it is generally unilateral, but in exceptional cases both nerves may be affected, and attacks of acute suffocative dyspnoea occur from time to time.

Dysphagia is said to be met with less commonly than in the course of malignant disease, but it was a prominent feature in some of our own cases, and in many of those recorded by others.

The *sympathetic nerve* trunk appears, as a rule, to escape damage, though there seems to be no satisfactory explanation of this immunity in view of the intimate association between the inflammatory process and the structures in the carotid sheath. Pressure on vessels may occur, indicated by distension of the veins of head and neck and the formation of a *caput Medusae* on the chest wall, and in rare instances the carotid artery may be occluded; in fact, Tailhefer (1898) considered obliteration of the temporal pulse to be a diagnostic feature. Although the infiltrating mass often surrounds the carotid artery so as to render its pulsations difficult to feel, its complete obliteration must be an exceptional occurrence.

The *parathyroid glandules* usually escape. One, which was removed in a case of Harry's (1940), was normal histologically.

In the majority of cases the disease begins in one lobe of the gland and spreads later into the other, but it is not unusual for one lobe to escape, even at an advanced stage. In a few of the recorded cases the disease appears to have involved the whole gland at a very early stage. The size of the mass varies considerably, according to whether the disease attacks a previously normal or a goitrous gland, but in any case it is rare for it to reach the great bulk met with in many simple and in malignant goitres.

Nevertheless, the goitre is usually one of considerable size. The skin over the tumour is intact, except in a very small minority of cases. In one of Riedel's a sinus developed, and in one of our own cases (see Fig. 116) there was a similar condition which persisted for some months.

The surface is either smooth or only slightly lobulated, but exceptionally, especially when a goitrous gland is affected, it may show striking irregularity. The lymphatic glands are not enlarged; this provides a valuable diagnostic distinction from malignant disease.

A characteristic feature of Riedel's disease, however, is the involvement of the perithyroid structures, so that within a comparatively short time the

gland becomes fixed to surrounding tissues, with limitation of its normal movements and obliteration of its normal outline and of the surrounding anatomical landmarks.

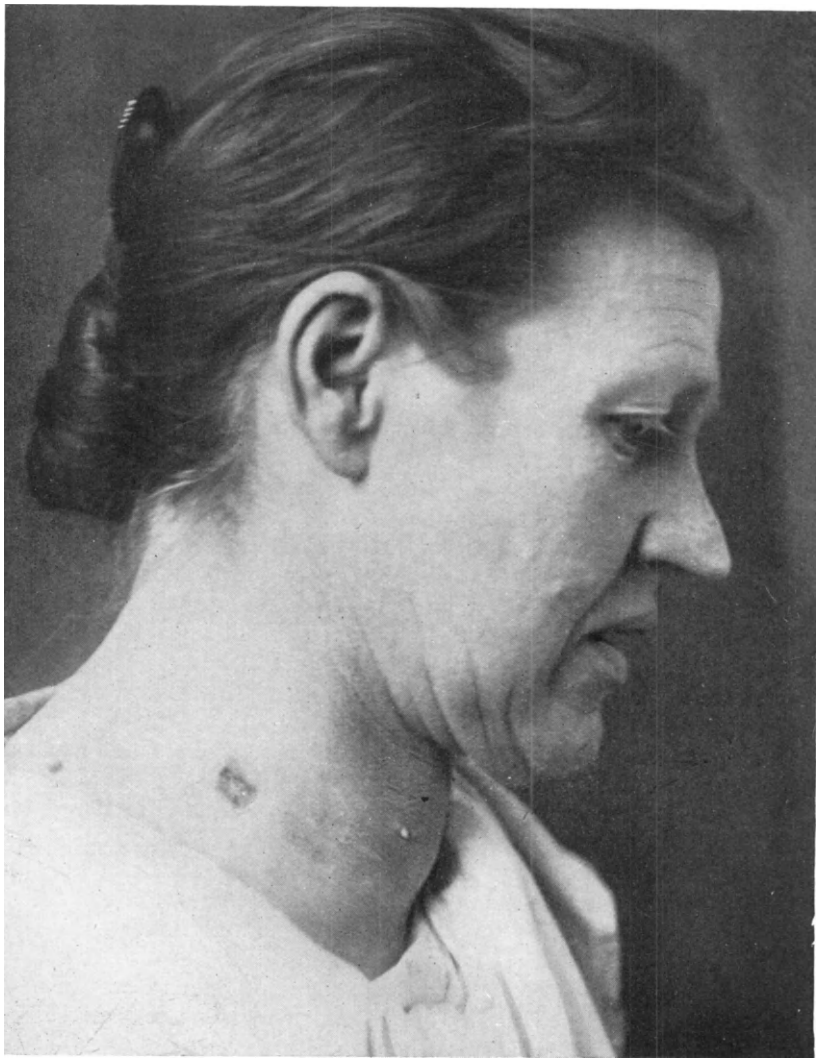

FIG. 116.—Riedel's disease with sinus formation.

Diagnosis. It is almost impossible to lay down any rule which will enable this disease to be distinguished from certain malignant neoplasms of the thyroid gland, but the intense hardness of the tumour, especially when occurring in a young adult, associated with pressure symptoms of a severity

out of all proportion to the size of the tumour, will make a diagnosis of Riedel's disease at least a possibility.

The absence of great irregularity of the surface and of enlargement of lymphatic glands are also helpful diagnostic features.

Other conditions likely to be mistaken for Riedel's disease are:

(1) Subacute and chronic simple thyroiditis, which occasionally occurs, but which does not spread outside the confines of the gland.

(2) Struma lymphomatosa, a disease usually met with in women at or about the menopause, and associated with hypothyroid symptoms, but usually without severe pressure symptoms or any tendency to involvement of the surrounding tissues.

(3) Tuberculous and syphilitic lesions of the thyroid, which should be distinguished by their tendency to break down, and by specific tests.

Prognosis. This is always doubtful. The gland in a few cases appears to have remained stationary after reaching a certain size. In others, cure has followed sometimes after partial and sometimes after radical resections of the fibrous mass. In rare cases the disease progresses whatever the treatment (as in Case 3, Table XXVI), and the patient dies in asphyxia.

Treatment. Riedel's disease is an extremely unsatisfactory condition to treat in view of the tendency to early involvement of the surrounding tissues.

Most authorities, including Riedel, are of the opinion that it is best to resect a part of the mass so as to relieve pressure symptoms as far as is possible, without attempting any radical extirpation of the whole, since this latter course involves risk of irreparable damage to important vessels, nerves, and viscera. Several observers have recorded very great relief following this partial intervention, and in a few cases the disease appears to have remained stationary afterwards.

It is remarkable how little haemorrhage occurs during the operation, owing to the strangulation of the vessels by the fibrous tissue; but it is also true that, should any *considerable* vessel be divided in the course of these operations, control of bleeding is very much more difficult than in most operations for goitre, owing to the fact that haemostatic forceps often fail to secure the bleeding point, embedded as it is in dense fibrous tissue. In such cases mattress sutures of strong silk are necessary to control bleeding, though the introduction of sutures undoubtedly involves risk of damage to important structures.

Almost all authorities agree that laryngotomy and tracheotomy should be avoided whenever possible, owing to the great difficulty and danger of these operations and the small degree of relief which follows. The extent of the involvement of the trachea makes it unlikely that a simple laryngotomy or tracheotomy will give permanent relief, even if a long flexible tracheotomy tube be introduced.

Other authors recommend that no surgical intervention whatever should be undertaken. Heineke recorded one case in which spontaneous regression occurred without any functional disability. Sloan states that these cases

TABLE XXVI EIGHT CASES

No.	Date.	Sex.	Age.	Previous Goitre.	Complaint.	Clinical Findings.
1	Dec., 1915	F.	53	Many years	A recent increase in size and hardness of goitre; dyspnoea, dysphagia, some anaemia. No alteration in voice, no pain.	Both lobes enlarged, smooth, and very hard; some restriction of movement on swallowing. Vocal cords normal. Carotids could not be felt.
2	Sept., 1917	F.	44	None	Swelling left side of neck 5 weeks, with pain, weakness and fatigue. No dyspnoea or dysphagia.	Nodular, extremely hard mass in left lobe, somewhat fixed to deeper tissues. Vocal cords normal.
3	Feb., 1920	F.	38	Always a full neck	Neck harder 3 years. Dyspnoea on exertion 9 months. Pain later. Some loss of weight in past few months. Alteration in voice 5 weeks.	Thyroid enlarged, hard, and nodular, especially left lobe and isthmus; fixed to deep structures. Tenderness over left lobe. Left vocal cord paralysed.
4	Jan., 1927	F.	45	Two years	Swelling very prominent 5 weeks; stifling sensation in throat; husky voice. No dysphagia, no pain.	Hard, irregular swelling in right lobe, fixed to deeper structures; only slight movement on deglutition. B.M.R.—17 per cent.
5	July, 1927	F	44	Full neck all her life	Swelling in midline 5 years, with attacks of severe dyspnoea, orthopnoea, nervousness, and palpitations.	Thyroid greatly enlarged and very hard.
6	Jan., 1928.	F.	50	None	Tender swelling right side of neck 2 months. No dyspnoea, dysphagia, or hoarseness. Some loss of weight.	Tender, very hard swelling in right lobe and isthmus; no movement on deglutition. Oesophagus normal.
7	Aug., 1929	M.	37	None	Swelling in neck 6 weeks.	Hard lump in right lobe; movement on deglutition. Trachea displaced to left in neck.
8	Oct., 1929	F.	31	Always had a thick neck	Swelling left side of neck 2 months; much larger 2 weeks. No pain; little dyspnoea; no alteration of voice; no nervousness.	Hard mass in left lobe; adherent to all surrounding structures; slight movement on swallowing. No toxic signs. Larynx normal. Slight displacement of trachea to right; no compression.

OF RIEDEL'S DISEASE

Diagnosis.	Operation.	Result.	Pathological Report.
	Mass was so firmly adherent to carotid sheaths that removal was impossible. Resection of wedge from right lobe for microscopical examination.	Discharged on 16th day after operation. Improved.	"Dense fibrous tissue undergoing marked hyaline degeneration and infiltration with leucocytes; only one small collection of epithelial cells seen. Muscle involved in the fibrous change."
	Removal of left lobe; infrahyoid muscles were firmly adherent to the mass; no involvement of carotid sheath, recurrent nerve, or trachea.	Discharged 19th day after operation. Patient free from recurrence of symptoms some years later.	"Riedel's disease."
? Slowly growing carcinoma. ? Riedel's disease.	Removal of whole of left lobe and lower part of right lobe; mass involved left recurrent nerve and was adherent to carotid sheath.	Disappearance of dyspnoea and dysphagia; some improvement in voice. Discharged 16th day after operation. Death 5½ years later; stridor, dyspnoea and dysphagia had recurred with loss of weight, tachycardia, and auricular fibrillation.	"Riedel's disease."
(Provisional) Malignant disease.	Removal of mass, which was very adherent to the underlying structures, especially trachea.	Wound healed by first intention. Discharged 16th day after admission. Improved.	"Resembles Riedel's struma."
	Three-quarters of each lobe resected, with portions of adherent infrahyoid muscles.	Discharged 19th day after admission. Improved.	"Chronic inflammatory condition characteristic of Riedel's disease."
	Removal of mass size of tangerine orange, adherent to trachea and surrounding muscles and to right internal jugular vein, which had to be divided.	Satisfactory healing of wound. Discharged 12 days after admission. Perfectly well 12 months later; no tumour, no pressure symptoms, no hypothyroidism.	"Condition resembles Riedel's struma."
Riedel's disease.	Removal of right lobe, containing hard mass 1in. by 1 in., adherent to infrahyoid muscles and carotid sheath.	Good recovery. Discharged 11th day after operation. Patient well 14 months later.	"Riedel's disease."
	Whole left lobe and portion of right lobe removed; left lobe infiltrated with firm, fibrous-looking mass.	Good recovery. Discharged 6th day after operation. Quite well 12 months later.	"Typical Riedel's disease."

invariably get well if left alone, and that hypothyroid symptoms do not follow.

Our own experience is strongly in favour of resection of a sufficient portion of the involved gland, including the isthmus, to relieve pressure on the trachea. The infrahyoid muscles should be directly sutured to the raw cut surfaces of the lobe remnants, to prevent regeneration of fibrous tissue over the front of the trachea.

Deep-seated adult fibrous tissue is not easily influenced by radium treatment or by X-rays. It is not, therefore, a promising method in Riedel's disease. Crile (1948) found it quite ineffective in the three cases in which it was used. Our opinion is that in Riedel's disease proper, as distinguished from other forms of chronic thyroiditis and lymphadenoid goitre, there is neither theoretical nor practical basis for belief in the value of treatment by X-ray therapy or by radium. Indeed we agree with Marshall *et al.* (1948) that it is likely to result in additional fibrosis, leading to myxoedema and further tracheal constriction.

III. Subacute Thyroiditis*

By GEORGE CRILE, JR., M.D.

Incidence — Aetiology — Symptoms and Signs — Laboratory Findings — Clinical Course — Pathology — Treatment — Summary.

Subacute thyroiditis has been variously named tuberculosis of the thyroid, pseudotuberculous thyroiditis, giant-cell thyroiditis, and granulomatous thyroiditis. Histologically it resembles tuberculosis, but tubercle bacilli cannot be demonstrated. Cultures of the thyroid are sterile. The pseudotubercle or giant-cell reaction represents a reaction of wandering cells to colloid which they appear to be phagocytizing.

Incidence. Subacute thyroiditis either has increased in frequency or is being recognized more often. In the past two years more cases of this disease have been recognized at the Cleveland Clinic than in all the preceding twenty years.

Women are affected six times as often as men, and the disease is most common in the mid-forties.

Aetiology. Although the aetiology of subacute thyroiditis has not been proven, it seems likely that it is initiated by a virus infection. The acute onset with fever, pain, tenderness, and prostration, and the frequent history of an influenza-like illness preceding the localization in the thyroid favour this hypothesis.

The fact that the thyroiditis sometimes persists for as long as a year can best be explained by assuming that the thyroid epithelium is so damaged by the acute virus infection that either the follicles are disrupted allowing the colloid to escape into tissue spaces or the colloid is changed so that it acts as a foreign body and provokes a granulomatous reaction. Histiocytes

* From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

attempt to phagocytize the displaced or abnormal colloid and this perpetuates the local symptoms until the colloid has been absorbed. This reaction can be shortened either by röntgen-ray therapy, which presumably destroys the wandering cells, or by giving thiouracil, which presumably stops the formation of colloid.

Symptoms and signs. Most cases of subacute thyroiditis are mild and manifest themselves merely by slight pain and tenderness of the thyroid, fatigue and a low-grade fever. In others, however, the disease may be severe and fulminating, with intense pain radiating up to the ear, exquisite tenderness of the thyroid, an elevation of the temperature to 104° F., chills, sweats, and prostration. Occasionally the chief complaint is a neuralgic type of headache referred to the sides of the head that may be so severe as to interfere with sleep.

Pain on swallowing is a common complaint and in some cases the patient may complain of a sore throat. The physician immediately looks down the throat, examines the lateral cervical region for enlarged lymph nodes, and often fails to examine the thyroid. The diagnosis of thyroiditis may thus be missed and the patient treated for pharyngitis.

Usually the thyroid is not enlarged to more than twice its normal size and it may not be enlarged at all. Its consistency, however, is firm or hard and the entire gland usually is involved so that the poles, isthmus, and contour of the thyroid can be outlined. Occasionally only one lobe or one area of a lobe will be involved, but in these cases the disease tends to spread progressively to involve the entire gland (creeping thyroiditis).

At the onset of the disease the gland is exquisitely tender, so much so that often it is impossible to palpate it. This tenderness may persist, or may subside gradually, leaving a hard gland that is only slightly tender.

Laboratory findings. Although the basal metabolic rate is elevated above +15 per cent. in one third of the cases, basal metabolic rates above +25 per cent. are seen only occasionally. The systemic reaction is out of proportion to the elevation of the basal metabolism and the patients appear to be suffering from a toxaemia rather than from a true hyperthyroidism. Whereas patients with mild hyperthyroidism usually feel quite well, those with subacute thyroiditis are weak, prostrated, and feel sick. The pulse rate is elevated out of proportion to the fever and the basal metabolic rate and may be as high as 160, although the average is about 110.

In spite of the elevation of the basal metabolic rate, the thyroids of patients with subacute thyroiditis take up only very small amounts of radioactive iodine. Whereas patients with hyperthyroidism take up 50 to 85 per cent. of a tracer dose and patients with normal thyroids take up 30 to 50 per cent. of a tracer dose, those with subacute thyroiditis take up only 5 to 25 per cent. This indicates that the thyroid epithelium is not making as much thyroid hormone as it normally does and that any clinical evidence of hyperthyroidism must be the result of absorption of previously formed colloid. It would therefore appear that the thyroid cells are either so damaged by the infection that they are rendered temporarily incapable of functioning, or else the rapid

absorption of preformed colloid has removed the stimulus that normally causes the thyroid cells to make hormone. The finding of a low uptake of radioactive iodine is so constant a finding in subacute thyroiditis that it is of great value in establishing the diagnosis. In six cases in which tracer studies were made, the thyroids took up from 5 to 25 per cent. of the tracer dose, a finding which definitely excluded the possibility of hyperthyroidism.

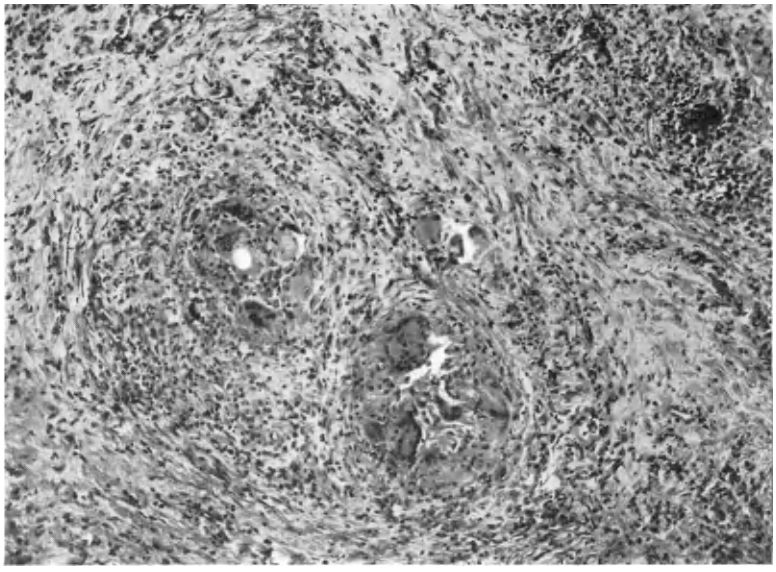

FIG. 117.—Biopsy of subacute or giant-cell thyroiditis. Prompt and complete resolution following X-ray treatment (× 30).

An elevation of the sedimentation rate is a constant finding in subacute thyroiditis. I have seen no case in which the rate was not elevated to figures at least two or three times the upper limit of normal. A normal sedimentation rate is strong evidence against the presence of subacute thyroiditis.

Clinical course. Even if no treatment is given, the natural course of the disease is towards spontaneous recovery. Without treatment, however, the patient may be incapacitated for weeks or months by the local symptoms and systemic reaction. Exhaustion and prostration are out of proportion to other manifestations of the disease.

Although spontaneous recovery takes place within a few weeks or months, the symptoms may persist for as long as a year. After recovery has taken place the function of the thyroid appears to be normal. Even in the most severe cases there has been no evidence of hypothyroidism.

Pathology. Subacute thyroiditis is characterized by a diffuse involvement of the entire thyroid in a subacute inflammatory process. There is

infiltration with leucocytes and numerous foreign-body giant cells are present (Fig. 117). The arrangement in formations somewhat resembling tubercles gives rise to the name pseudotuberculous thyroiditis. The foreign-body reaction is probably a response to the colloid in the degenerating follicles, and histiocytes can be seen phagocytizing this material.

The thyroid rarely contains adenomas. The thyroid gland is not enlarged to more than two or three times its normal size, and the enlargement tends to be symmetrical. The cut surface of the gland is white and avascular (Fig. 118). It is quite brittle and will not hold a haemostat. The capsule is

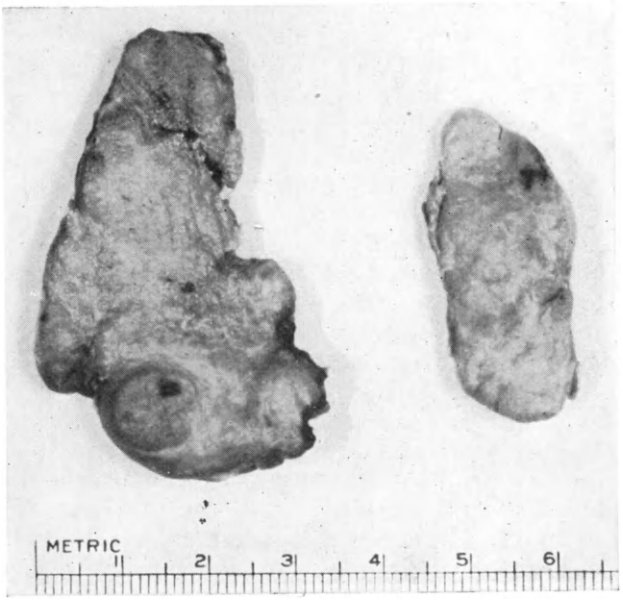

FIG. 118.—Gross appearance of subacute thyroiditis. The small adenoma isan unusual finding.

only very slightly adherent to surrounding structures, and there is no tendency to infiltration and fixation, as in Riedel's struma. Tubercle bacilli have not been identified in this lesion.

Treatment. Subacute thyroiditis responds promptly and completely to röntgen-ray therapy. Six hundred to 800 *r* usually suffice to effect resolution of the inflammatory process in two or three weeks. The pain and tenderness subside in a few days. The average time at which fifteen patients treated with röntgen-ray were considered to be entirely well was nineteen days after the start of treatment. By this time the thyroid is rarely either tender or palpably enlarged. In two of our cases, two or more courses of therapy over a period of three months were required before a complete cure was effected. Three patients considered themselves well in one week.

Thyroidectomy is a satisfactory means of controlling subacute thyroiditis, but since the disease is essentially self-limited and since röntgen-ray therapy effects such prompt and complete resolution, operation is not often indicated. Most of the patients reported here as having been subjected to operation were seen before we recognized the value of röntgen-ray therapy.

Thyroidectomy was performed on six patients; five of these are well and one has developed hypothyroidism.

A single lobe was removed in six cases. Three of these patients developed a recurrence or suffered from persistence of symptoms due to involvement of the remaining lobe. All eventually recovered.

Since röntgen-ray therapy has given such prompt and satisfactory results we have not often used thiouracil in the treatment of subacute thyroiditis as described by King and Rosellini (1945).

Five patients with subacute thyroiditis have had the diagnosis confirmed by biopsy of the thyroid and have then been treated with röntgen-rays. In all of these cases the biopsy showed the typical granulomatous reaction and in all the symptoms and signs of the disease subsided promptly after treatment. In one case biopsies were obtained by the Silverman liver biopsy needle both before and immediately after röntgen-ray treatment. The second biopsy showed no significant change in the histologic appearance except for an apparent diminution in the number of wandering cells. In spite of the absence of histologic change the patient had made striking clinical improvement and the size of the gland had diminished by one-third in the time between the two biopsies.

Relationship to other types of thyroiditis. The fact that subacute thyroiditis is almost always associated with pain and tenderness and that these symptoms only rarely occur in the other types argues against the possibility that subacute thyroiditis represents an early stage of the more chronic processes. The tendency to spontaneous recovery in subacute thyroiditis and its prompt and dramatic response to röntgen-ray treatment, however, argue against this possibility.

Summary. The clinical entity described as subacute thyroiditis has been proved by biopsy to be giant-cell or pseudotuberculous thyroiditis.

Although the aetiology of these diseases is unknown, it is possible that subacute thyroiditis is the result of a virus infection and that persistence of symptoms and evidence of inflammation in the thyroid are due to a foreign-body reaction to colloid.

Röntgen-ray therapy is the treatment of choice for subacute thyroiditis and thyroidectomy is rarely indicated. Thiouracil may be of value.

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CHAPTER XXII

MALIGNANT DISEASE OF THE THYROID GLAND

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Incidence — Age — Pathology — Iodine content of Malignant Goitre — Classification of Malignant Neoplasms — Papillary Carcinoma — Adenocarcinoma — Highly Malignant Forms — Lateral Aberrant Thyroid — Rare Forms — Metastatic Tumours to the Thyroid — Metastases from the Thyroid — Diagnosis of Malignant Tumours of the Thyroid — Differential Diagnosis — Prognosis — Treatment — Benign Neoplasms.

At the present day our knowledge of malignant disease of the thyroid gland is in a state of confusion. The criteria for its diagnosis are not uniformly interpreted by experienced pathologists even when they study the same sections. No widely accepted classification exists for the neoplasms encountered. Disagreement is evident as to the epithelial or mesothelial origin of certain tumours. The influence of thiourea and its derivatives as carcinogenic agents and the role of radioactive isotopes are other factors as yet unsettled. Nevertheless, we are on the threshold of a new epoch in knowledge and treatment of thyroid cancers. The use of radioactive iodine is clarifying immensely the pathology of these tumours. Soon we may hope for a satisfactory clinico-pathological classification and for earlier diagnosis and a combined attack by surgery and irradiation which is both rational and radical.

Incidence. It seems logical that malignant disease of the thyroid gland should occur with greater frequency in areas where goitre is more common. This view is supported by Wegelin (1938) who reported an incidence of one malignant tumour of the thyroid in each ninety-six autopsies in Berne, an area of high goitre endemicity. Vanderlaan (1947), on the other hand, could only find five cases of thyroid malignancy in 18,668 autopsies in three Boston hospitals, a non-endemic area. In the State of New York where cancer is a notifiable disease, malignant lesions of the thyroid occurred 0·47 times in men and 1·74 times in women per 100,000 population during the years 1942–44. Watson and Pool (1940) stated that cancer of the thyroid occurred in 0·43 per cent. of the admissions to Memorial Hospital in New York (a cancer clinic).

It seems reasonable in the face of these conflicting observations to suggest that the incidence of malignant disease of the thyroid be estimated from study of surgically excised nodular goitres. Microscopic examination of excised tissue affords the most accurate method possible and the relatively high incidence of cancer so found, namely about 5 per cent., emphasizes the

importance of nodular goitre as a premalignant lesion. Thus, Horn *et al.* (1947) found malignant disease in 5·5 per cent. of 1,135 nodular goitres. Smith *et al.* (1934), in a study of 855 thyroid tumours, found cancer in 4·7 per cent. Pemberton (1938) reported an increasing frequency of malignant thyroid tumours from 2 per cent. in 1919 to 4·9 per cent. in 1938. During the past few years the frequency of carcinoma in single thyroid nodules has been much studied. Thus Cole *et al.* (1945) found that 24 per cent. of ninety-two cases of single non-toxic nodules of the thyroid were malignant. Ward (1947) reported 14 per cent. of a hundred solitary non-toxic nodular goitres were definitely malignant. McClintock and Farrell (1948), in a review of 382 single tumours of the thyroid, reported that 11·25 per cent. were malignant. Anglem and Bradford (1948) found 9 per cent. of 363 single non-toxic adenomas to be malignant (cf. Chapter VII).

This increase in the frequency with which malignant disease of the thyroid is diagnosed requires explanation. As Pemberton (1938) emphasized it depends on the increased ability of pathologists to differentiate accurately between benign and early malignant lesions. The increased incidence of carcinoma is thus more apparent than real.

There is much evidence that malignant disease of the thyroid gland occurs most commonly in those who have been goitre bearers for several years. Thus Coller (1929) found histologic evidence of pre-existing goitre in 98 per cent. of his cases even though only 76 per cent. of the patients were aware of pre-operative enlargement. Portmann (1941) noted a history of goitre in 80 per cent. of his cases. Welti (1939), however, considered that only thirty-eight patients gave a satisfactory history of pre-existing goitre out of a series of eighty-eight. Pemberton (1938) stated that an accurate determination of the incidence of cancer developing in a pre-existing goitre is not possible from a review of the records. Even though it may not be possible to differentiate between those tumours that become malignant after many years and those that are very low-grade malignant tumours from the outset, it is still widely accepted that nodular goitre predisposes to malignant disease.

The sex incidence for malignant disease of the thyroid averages three females to one male. In Pemberton's 774 cases of cancer of the thyroid the ratio was 1·74 to 1, while during the same period the male-female ratio for benign tumours was 1 to 5·07. In my own series of 125 malignant thyroid lesions 112 were females and 13 males.

Age. The disease occurs at all ages. The majority of cases occur between forty and sixty years of age but the extremes of life are not immune. Of importance is the fact that tumours in childhood are more apt to be malignant than corresponding lesions in adult life. Ward (1947) reports that 40 per cent. of ten children under fifteen years of age were found to have malignant disease of the thyroid. Hare (1937) and Kennedy (1935) recorded a total of fourteen cases under fourteen years of age.

The relationship of thiourea and its compounds to the development of carcinoma in the thyroid gland is a moot question. Purves and Griesbach (1946–47) report the formation of adenomata and adenocarcinoma in the

thyroids of rats given thiourea. Money (1946) reported that 100 per cent. of white rats given thiouracil developed adenomata in their thyroid glands. In spite of these indications from the laboratory, no conclusive case of carcinoma arising in humans as the result of the administration of thiouracil or its derivatives has been reported. It is anticipated that such reports will appear and they should be subjected to very close scrutiny.

Pathology. The exact pathological relationship between the various types of malignant growths found in the thyroid gland is still in dispute. The criteria for the histologic diagnosis of malignancy accepted by pathologists are not uniform. Even when the same microscopic slides are examined by a small group of pathologists experienced in thyroid disease, opinion regarding benignancy and malignancy differs in a significant percentage of the cases. An unusual feature of malignant tumours of the thyroid, distinguishing them from malignant tumours of other glands, is their capacity under certain conditions to carry on the specific function of the gland. Colloid storage may be observed in certain early adenocarcinomas and, in von Eiselsberg's famous case (1894), a metastasis in the sternum served to relieve myxoedematous symptoms which followed the removal of the original tumour, but the hypothyroid phenomena recurred when the metastasis itself was excised.

Iodine content of malignant goitre. The iodine content of malignant goitre varies. Branovacky-Pelch (1926) found appreciable quantities of iodine in three cases of adenocarcinoma.

Miles (1934) presented evidence that there exists in the metastases from tumours of the thyroid a principle that accelerates the growth and maturation of tadpoles. Engelstad (1936) reported two cases of metastatic carcinoma from thyroid tumours that gave positive reactions to the acetonitrile test in mice.

The development of radioactive isotopes of iodine has made it possible to obtain more information about the iodine content of malignant goitre and its metastases. Hamilton and his associates (1940–42) showed that no significant uptake of radio-iodine occurred in the carcinomatous tissue. Keston *et al.* (1942) reported absorption of radio-iodine by several metastases from a thyroid tumour. Since these early reports, our knowledge of iodine metabolism in relation to malignant thyroid disease has advanced tremendously and is constantly being increased by greater experience and new evidence. Using the technique of radioautography, Marinelli *et al.* (1947) reported studies on nineteen patients with carcinoma of the thyroid. They state that the structural type of the tumour is an important factor in determining the tumour's ability to accumulate radioactive iodine. In both metastatic and primary tumours an orderly arrangement of cells in follicular pattern with the presence of colloid-like material is the most conducive to uptake of radioactive iodine.

Classification of malignant neoplasms. Dunhill stated (1931): "The classification of carcinoma of the thyroid varies in every country, and with every author I have read." For the present, the following method is suggested because of its simplicity and the fact that it distinguishes between those tumours that are least likely to be fatal and those that nearly always result

in death. This clinico-pathologic method thus helps the surgeon to formulate his prognosis.

I. Papillary Carcinoma.
II. Adenocarcinoma.
  (a) Solid cord type.
  (b) Foetal type.
  (c) Alveolar carcinoma.
III. Highly Malignant Types.
  (a) Epidermoid carcinoma.
  (b) Giant-cell carcinoma.
  (c) Fibrosarcoma.
  (d) Reticulum-cell sarcoma.

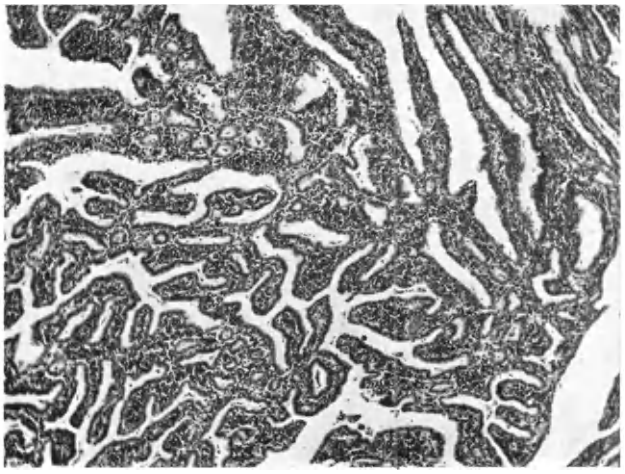


FIG. 119.—Papillary carcinoma. (× 120.)

IV. Lateral Aberrant Tumours.
V. Rare Forms.
VI. Metastases to the Thyroid.

Frazell and Foote (1949) have recently contributed a valuable account of the natural history of the various types of thyroid cancer.

There is no unanimity of opinion concerning the mesothelial or epithelial origin of some of these tumours. Experienced pathologists differ in their interpretation of spindle-cell carcinomas as opposed to fibrosarcoma, and small-cell carcinoma in contrast to reticulum-cell sarcoma. The percentage of sarcomatous lesions as compared with carcinomatous will vary with the authority quoted.

1. Papillary carcinoma. In Pemberton's (1938) series of 517 graded cases, papillary tumours accounted for 30 per cent. Foote (1948) reported a series

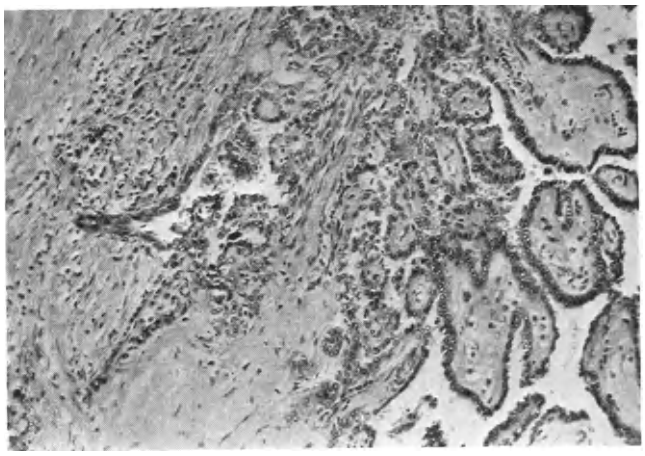


FIG. 120.—Case No. 7. Papillary carcinoma metastatic in cervical lymph node. So-called Lateral Aberrant Thyroid. (× 225.)

of 210 thyroid cancers, 104 of which were of the papillary type. In a group of 318 cases of cancer or suspected cancer, papillary tumours were present in

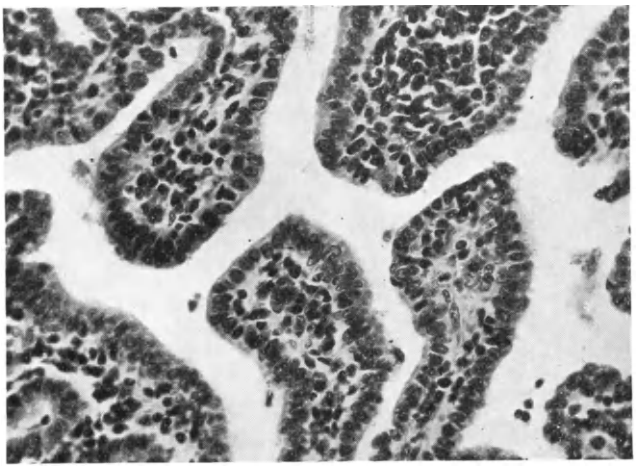


FIG. 121.—Papillary carcinoma. (× 625.)

27·3 per cent. (Klink, 1948). The female sex was affected eighty times while only seven males had papillary tumours in this series of eighty-seven cases reported by Klink. The average age is younger than that for other types of

thyroid cancer. Black (1948) reported a male-female ratio of 1:2·6 in 112 cases. The mean age in his series was 43·4 years. It has the best prognosis of all thyroid cancers.

Macroscopically, if the tumour is small, there may be no feature to separate this tumour from other types of adenoma. Large tumours with cystic areas may present papilliferous projection into the tumour cavity. Cyst formation and haemorrhage should suggest the possibility in tumours of moderate size.

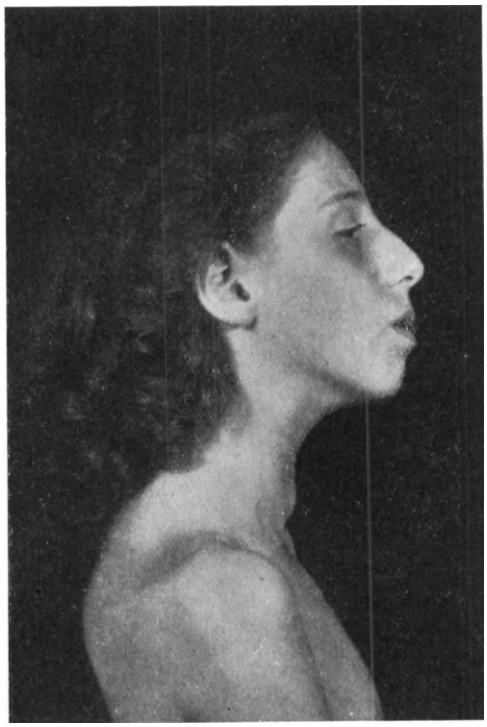


FIG. 122.—Case No. 1. Girl, aged 11. Lump noticed six months.

Microscopically, all degrees of papillary formation may be noted in a series of tumours, from papilloma without cystic change to large cystic spaces and branching papillary projections. The stroma of such papillae may be delicate or abundant and show all manner of degenerative change, oedema, fibrosis, lymphocytic infiltration or even psammoma bodies (Figs. 119–121). In some there are definite acini in the stroma of the papillae. The epithelium is usually cuboidal or tall columnar in character, rarely is it stratified. In more malignant forms the epithelium may grow in solid sheets, and the cells show greater degrees of anaplasia. Invasion of capsule and lymphatics occurs more frequently than does blood-vessel invasion.

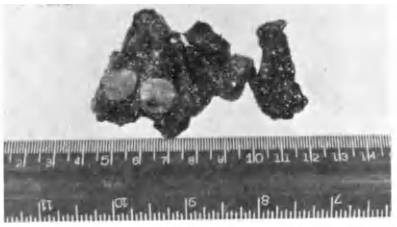


FIG. 123.—Adenocarcinoma of thyroid gland—right lobe.

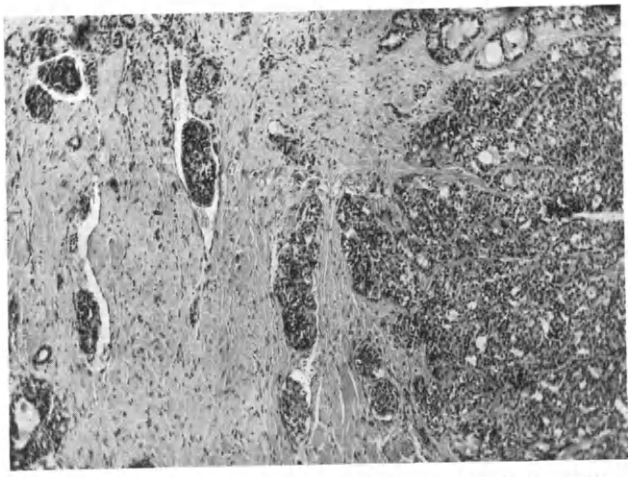


FIG. 124.—Adenocarcinoma from case No. 1. (× 120.)

FIG. 125.—Extension of thyroid nodule through its capsule. Evidence of malignant growth. (× 225.)

About 60 per cent. of patients show involvement of the cervical lymph nodes on admission to hospital (Frazell and Foote, 1949). Nevertheless, the subsequent clinical course is very prolonged, most patients living for at least five years after the diagnosis is established. Ten to twenty-five year survivals are by no means rare, even when treatment has been clearly ineffectual. Death is eventually due in many instances to invasion of the larynx, trachea or oesophagus.

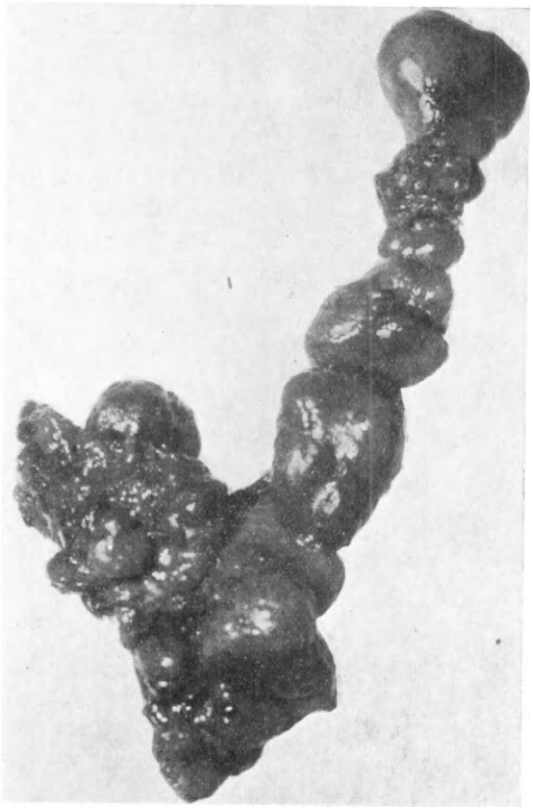


FIG. 126.—Case No. 2. Gross specimen, left lobe and cervical lymph nodes.

II. Adenocarcinoma. In this category are placed all those lesions formerly called " benign metastasizing goitre," malignant adenoma, or adenoma with blood-vessel invasion. The so-called Hürthle cell tumour, separated by some authors, is included in this group (Fig. 130).

In Frazell and Foote's series (1949) two-thirds of this group of patients had a previous history of goitre and about half already presented evidence of lymph glandular or osseous metastasis on admission. The clinical course

was not rapid and one of their patients was alive and asymptomatic twenty-two years after her thyroidectomy and thirteen years after the onset of her bone lesions.

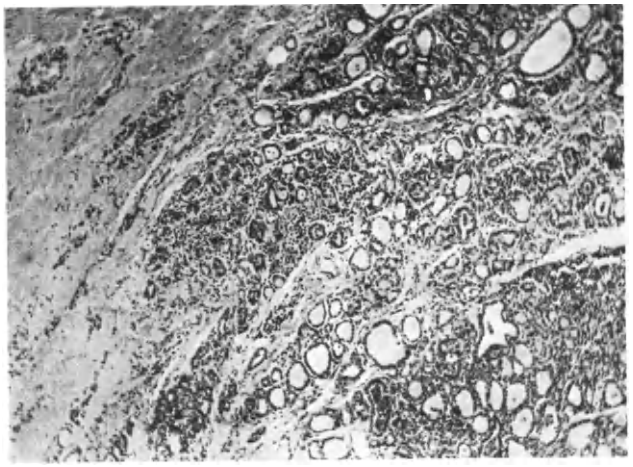


FIG. 127.—Case No. 2. Adenocarcinoma of thyroid gland. (× 120.)

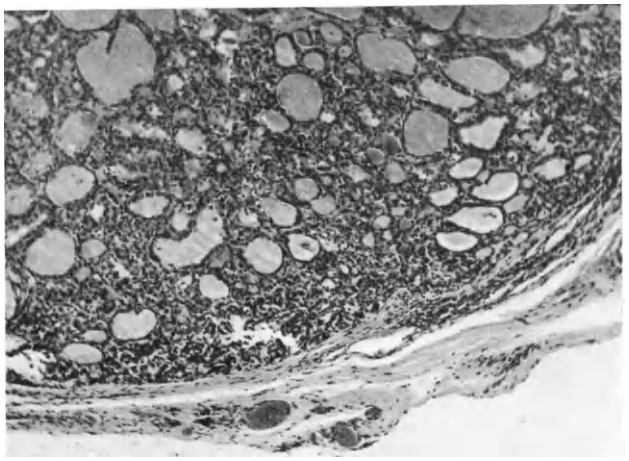


FIG. 128.—Case No. 2. Section of cervical lymph node containing metastatic adenocarcinoma of thyroid. (× 225.)

(a) Solid Cord Type: This descriptive term is used to distinguish a variation in the histology as observed microscopically. So far as is now known this variety has the same significance as the foetal type. In fact, these two forms are frequently combined with one type predominating.

Microscopically, the solid cord form is composed of closely packed cords or plates of cells. Between such cords there is only sufficient connective tissue stroma to support the cells (Fig. 131).

(b) Foetal Type: In typical examples the tissue is composed of small, closely packed acini usually without colloid although in some areas of such

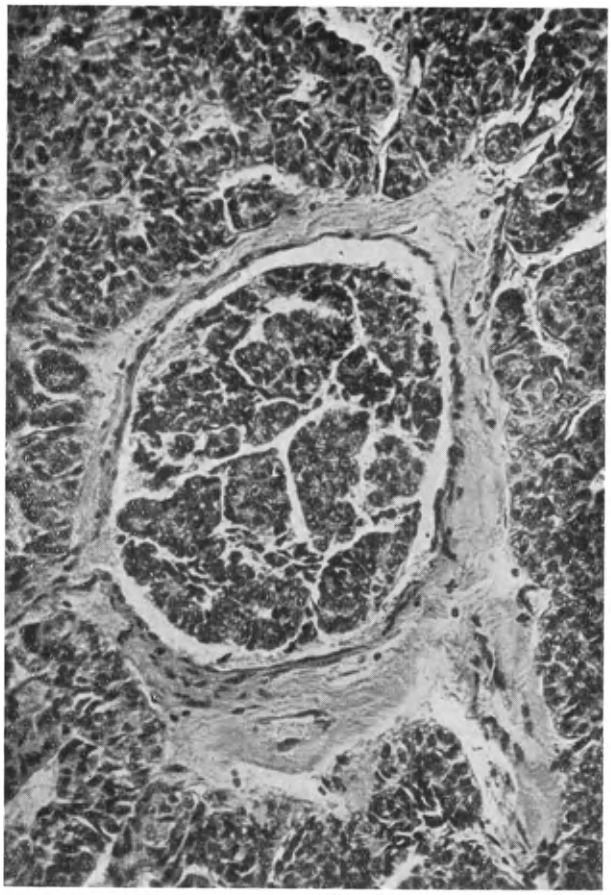


FIG. 129.—Case No. 5. Tumour thrombus in blood vessel. Accepted as evidence of blood vessel invasion. (× 225.)

a tumour, acini with colloid may be observed (Fig. 132). Stroma is usually small in amount. There may be fibrous trabeculations throughout the tumour especially if it is of long standing. In such cases the central part of the adenoma may show oedema, haemorrhage, cystic degeneration, fibrosis, and in very long-standing tumours, calcification.

These two forms of adenocarcinoma may occur at any age, though the incidence peak is reached between forty and sixty years. These tumours are of comparatively low-grade malignancy and the five-year survivals average

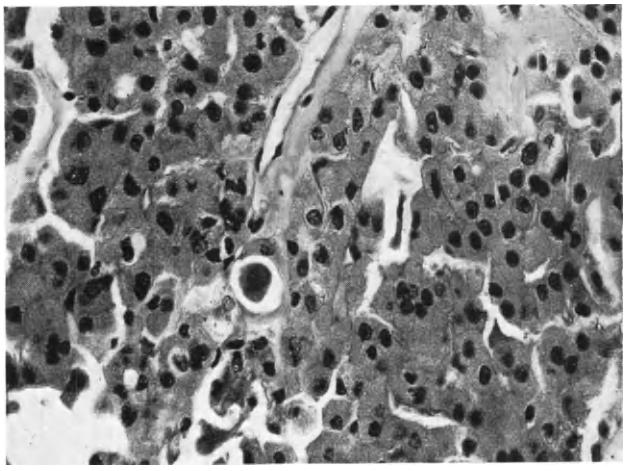


FIG. 130.—Adenocarcinoma of thyroid gland. So-called Hürthle cell type. (× 625.)

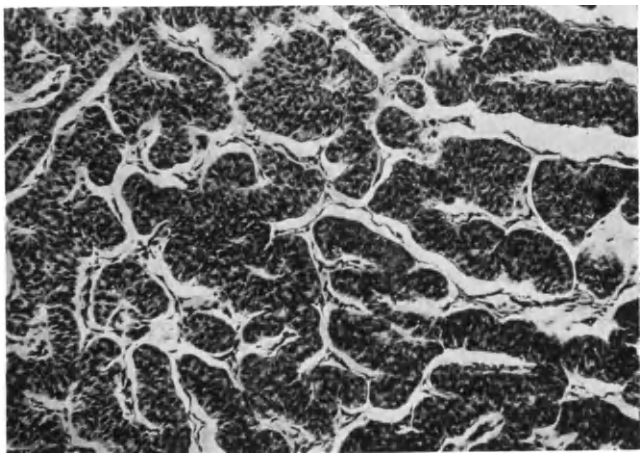


FIG. 131.—Case No. 5. Adenocarcinoma of the thyroid gland. So-called solid cord type. (× 225.)

70 per cent. in the cases reported. These lesions are found four times more often in the female than in the male.

Grossly, these tumours are well encapsulated, and occur singly in the thyroid gland or in conjunction with multiple colloid adenomata. Late in

their course the capsule is penetrated and local infiltration of surrounding tissues occurs with fixation of the tumour.

The surface of such tumours may be bosselated and present variations in colour from greyish-white to dark red. Vascularity is increased. On the cut surface the appearance is usually uniformly cellular, greyish-white or yellowish in colour. Haemorrhagic areas may be scattered throughout or the central portion may be replaced by an extensive area of haemorrhagic and cystic degeneration. A stellate hyaline scar may be observed near the centre of the substance of the nodule.

A peculiarity of these lesions is that vein penetration may take place before the capsule is perforated and widespread dissemination of the tumour can

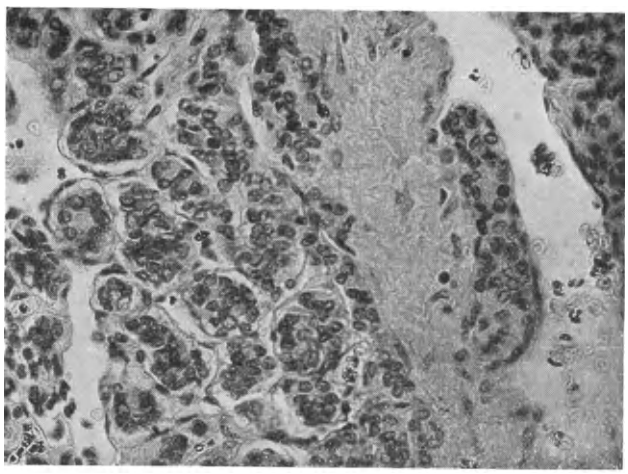


FIG. 132.—Case No. 10. Adenocarcinoma. So-called foetal type. (× 625.)

thus occur from a small, apparently benign, nodule. Holt (1934), Jacobs and Seltzer (1936) and Ross (1941) have all described tumour tissue growing through the thyroid veins to the internal jugular and even into the heart. This property of vein invasion makes it necessary to excise all venous channels from the thyroid gland in radical operations for removal of this form of thyroid cancer.

The fact that some of these tumours have a benign appearance histologically, makes accurate separation of benign from malignant neoplasms most difficult. The criteria commonly relied upon for this differentiation are invasion of blood vessels, tumour capsule or adjacent normal thyroid or the finding of metastatic tumour deposits. The acceptance of these criteria for a malignant diagnosis is not universal and several pathologists experienced in the field of thyroid disease may disagree on the interpretation of the same microscopic sections.

(c) Alveolar carcinoma; medullary carcinoma: The presence of broad sheets of neoplastic cells is a feature of these types and such anaplasia indicates a higher degree of malignancy (Fig. 133). Prognostically, such tumours have a much lower five-year survival rate (about 30 per cent.) than the two less malignant forms just described. The age and sex distribution, however, are similar.

Macroscopically, these tumours vary widely in appearance and consistency. Local extension is not uncommon. Areas of cystic degeneration, haemorrhage or fibrosis may be observed throughout. Apparently normal thyroid tissue may be present.

Microscopically, normal acinar development may be observed in some areas. Scattered throughout the tumour are areas of neoplastic cells that have

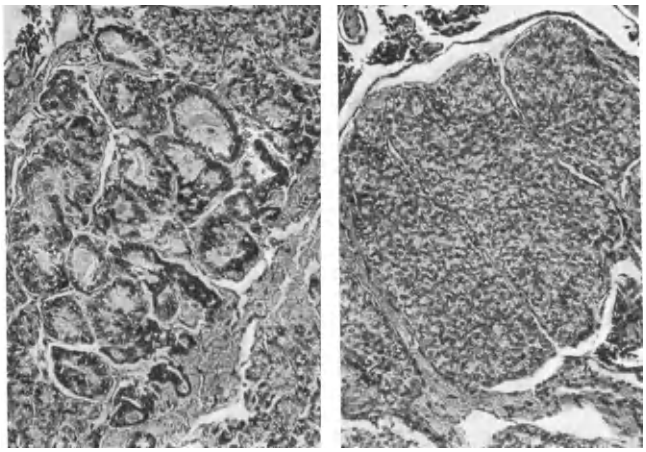


FIG. 133.—Case No. 9. Adenocarcinoma with foci of neoplastic cells growing in sheets. (× 225.)

no tendency to form acini and appear as sheets with but little supporting stroma. Metastases from such lesions may present apparently normal thyroid acini.

Graham (1927) described a form of carcinoma that spreads by infiltration of the surrounding thyroid tissue from a small focus of origin which is not an adenoma. He has stated that total extirpation of such lesions always results in cure.

III. Highly malignant forms. This group contains tumours of widely different histologic types. Universal agreement does not exist as to the mesothelial or epithelial origin of some of the tumours so that such names as carcino-sarcoma are found in the literature. Regardless of these discrepancies all members of the group are highly malignant, usually radioresistant, and are rapidly fatal. Lahey, Hare and Warren (1940) have indicated that the

five-year survival in this group should be improved but few other writers have reported any success in treatment.

(a) Epidermoid carcinoma: The inclusion of squamous-cell rests in the thyroid parenchyma is philogenetically possible. In addition, Jaffé (1937) considered epithelial metaplasia as the source of squamous-cell carcinoma. Whichever concept is accepted, primary squamous-cell carcinoma of the thyroid does occur, though it is rare.

The macroscopic appearance of squamous tumours gives no clue as to their type. In an advanced lesion fibrosis may make differentiation from chronic thyroiditis difficult. When the tumour has invaded surrounding structures, fixation and hardness are present but are not characteristic.

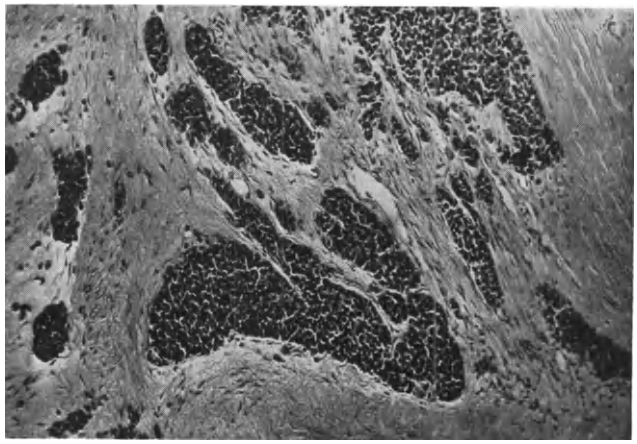


FIG. 134.—Case No. 6. Epidermoid carcinoma arising in thyroid gland. (× 225.)

Microscopically, islands of squamous cells are found with or without definite pearl formation (Fig. 134). Intercellular bridges can sometimes be demonstrated. Usually marked fibrosis is present but it is not a necessary feature.

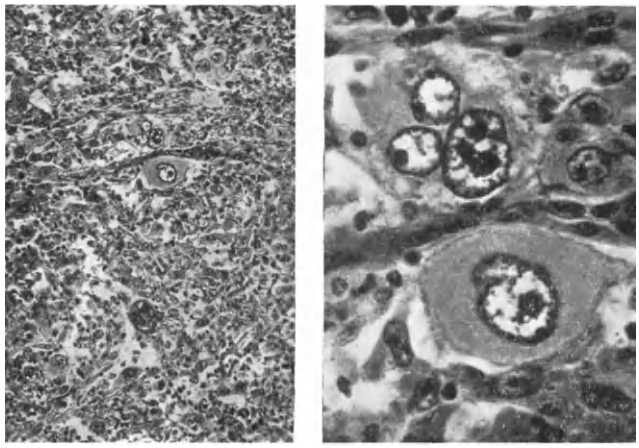
(b) Giant-cell carcinoma, large-cell carcinoma, spindle-cell carcinoma: This is one of the most highly malignant of all thyroid tumours with an incidence that reaches a peak in the seventh decade. A history of long-standing goitre may be obtained. The tumour is bulky and gives the patient a " bull-necked " appearance. Involvement of the cervical lymph nodes and infiltration of the trachea, larynx and oesophagus rapidly occur. No treatment has yet proved effective and, as Frazell and Foote remark, in no other form of human cancer is a lethal outcome so inevitable.

Macroscopically, the tumour frequently presents obvious extension outside the capsule of a pre-existing adenoma. The central portion is often necrotic and haemorrhagic. The highly vascular, rapidly growing tissue may outstrip

its supporting connective tissue and greyish-red, semi-liquid material is discovered in the mass. In the spindle-cell form, increase in connective tissue may be noted but is not characteristic.

Microscopically, highly anaplastic, large irregular or elongated spindle cells are seen (Fig. 135). Mitotic figures are abundant. Hebbel (1940), in reporting a case of giant-cell carcinoma, states that the presence of collagen is not proof of a sarcoma. Acini, if present, are irregularly shaped and incompletely formed. Stroma in the large-cell variety is scanty but may be abundant in the spindle-cell type. The spindle form has been called sarcoma or carcino-sarcoma. Until more evidence is available it seems best to suspend judgment as to its mesothelial or epithelial origin.

(c) Fibrosarcoma (Fig. 136). Very little has appeared in the literature concerning this tumour during the past decade. Most American authors



(× 225) (× 500)

FIG. 135.—Giant-cell carcinoma of thyroid gland.

refer only to the spindle-cell carcinoma without attempting to differentiate the fibrosarcoma. Although criteria are available to distinguish mesothelial from epithelial tumours with spindle-cell architecture, it seems certain that more reports will refer to fibrosarcoma in the future.

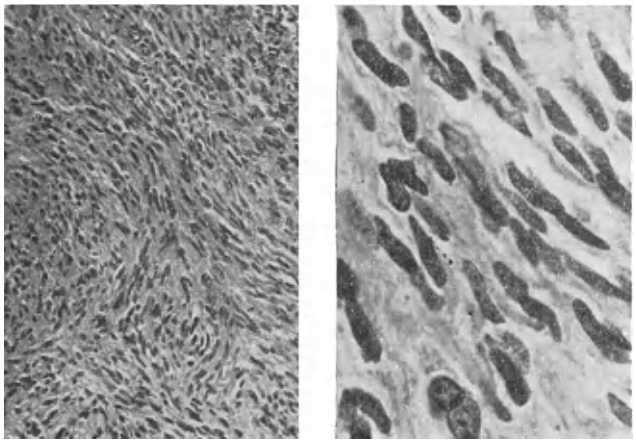
(d) Reticulum-cell sarcoma: This tumour is frequently referred to in the American literature as small-cell carcinoma. No clear-cut differentiation between an epithelial or mesothelial origin for these cancers has been established. Graham (1938) feels that most of them are sarcomata. Other members of the lymphoblastoma group are the rare lymphosarcomata of the thyroid (Dinsmore *et al.*, 1949). Males and females are affected about equally. Cases have been reported in young patients but the majority occur in the fifth and sixth decades.

Macroscopically, the tumour infiltrates the surrounding tissues and is hard. The appearance, on cut section, is greyish-white or yellowish. Areas of

necrosis and haemorrhage may occur but are less common than in the giant-cell group. Except for extensive extra-capsular extension the appearance is that of struma lymphomatosa.

Microscopically, some acini may be observed and rarely colloid is found. The cells may resemble lymphoblasts or contain small, dark nuclei with abundant cytoplasm. Anaplastic tumour cells grow diffusely throughout the tissue and are supported by a delicate fibrous stroma (Fig. 137).

IV. Lateral aberrant. This descriptive term is applied to a group of tumours characterized by masses of thyroid tissue that are found in the lateral regions of the neck. The vast majority of these tumours are papillary in character and more properly belong in the discussion of papillary tumours. They are set aside here because of the controversy that has raged concerning



(× 65) (× 500)

FIG. 136.—Anaplastic, highly malignant thyroid tumour. Said by some to be spindle-cell carcinoma, termed by others fibrosarcoma.

them but the evidence now indicates clearly that they are metastatic lesions in the regional lymph nodes.

Many have adhered to the belief that these lesions resulted from abnormalities of the lateral thyroid anlage. Leech, Smith and Clute (1928) were then of this opinion. Dunhill (1931) does not take any side in the controversy but states that the presence of these " misplaced bits of tissue . . . foredoom the host to carcinoma from before the day of birth ". Crile (1939) felt that these tumours were multiple benign lesions, but in 1947 he stated, "It is thought that the lateral cervical nodules are probably metastases from a tumour of the thyroid . . . ." King and Pemberton (1942) emphasized the metastatic nature of these tumours. Black (1948) found lymph-nodes involved in 44 of 112 cases of papillary thyroid tumours and feels that these represented metastases.

Just why a few adenomatous tumours should behave as papillary ones and metastasize to the cervical nodes is not clear. Moritz and Bayless (1932), Cohn and Stewart (1940), and Ward (1940), in reviewing the subject noted the presence of adenomatous lesions in lateral aberrant thyroid tumours. Examples of this type are shown in cases 1 and 2.

Macroscopically, multiple, discrete nodules are found surrounding the vascular sheath from the angle of the jaw to the sterno-clavicular joint. They are usually well encapsulated and bluish-brown or grey in colour. Microscopically, they present the features of papillary adenocarcinoma of the thyroid.

It is of importance to scrutinize the homolateral thyroid lobe but even where no definite nodule is visible or palpable, a total lobectomy should be

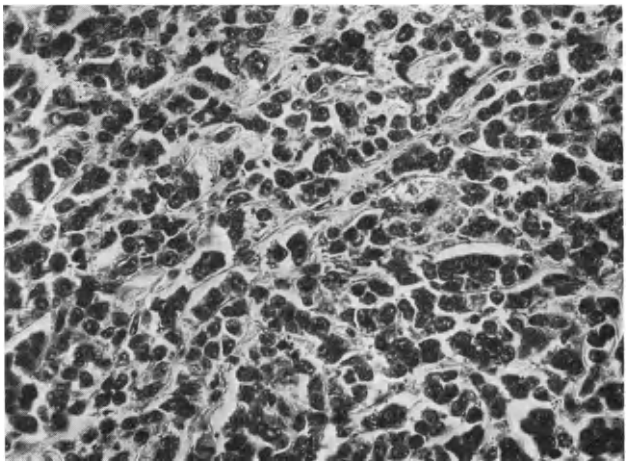


FIG. 137.—Reticulum-cell sarcoma arising in the thyroid gland. (× 625.)

done. Microscopic examination of sections in multiple planes has revealed a primary tumour of like histology in the homolateral lobe in every case where adequate search has been made.

V. Rare forms. (a) Endothelioma: Writers in the last twenty years have failed to recognize and record this rare tumour.

(b) Haemangio-endothelioma: Bosse (1943) recorded a case he considered to be of this type. Rice (1931) reported a case in a fifty-year-old female in which surgery was unsuccessful but the patient was alive and free from disease a year following post-operative radiation therapy. Simon (1939) collected twenty-one cases from the literature and added one case of his own seen in Switzerland. It is of interest to speculate on the reason why only two cases have been reported from North America and all of the remainder from Europe. The disease invades early, is extremely vascular, and frequently causes death from haemorrhage.

Another rare tumour of the thyroid was recorded by Batts (1940), namely, osteogenic sarcoma of the thyroid gland. He collected six cases from the literature and recorded one of his own.

(c) Teratomas: Potter (1938) recorded a tumour that replaced the right lobe of the thyroid gland in a stillborn infant. It was found to contain many cell and tissue types including cartilage, connective tissue, and thyroid acini. He felt there was evidence to indicate attempts at the formation of kidney, gastrointestinal, lung and brain tissue. Pusch and Nelson (1935) collected forty-three cases from the literature. In this series of cases nearly every tissue, and many organs, were represented by cell types or attempted organ formation.

Smooth and striated muscle, cartilage, connective tissues, hair, bone, teeth and many types of glandular tissue have been noted in these teratomas.

Struma ovarii probably occurs with greater frequency than is indicated in published reports. Goodall (1941) stated in Nelson's Loose-Leaf Surgery, " The less malignant types may supplement the thyroid secretion (Trapl) and iodine has been demonstrated in the tissues (Meyer)."

Thyroid tissue can frequently be found in ovarian teratoma but a tumour composed largely of thyroid gland elements is rare.

IV. Metastatic tumours in the thyroid. The thyroid gland may be invaded directly by malignant growths arising in adjacent organs. In addition, new growths in distant parts of the body may be associated with metastatic deposits in the thyroid. Boys (1947) collected from the literature fifteen cases of hypernephroma which metastasized in the thyroid and he added one of his own. Denton and McClintock (1948) tabulated twenty-one similar cases. Rice (1934) found five macroscopic and four microscopic lesions in the thyroid which proved to be metastatic from malignant disease elsewhere in the body. These nine cases were found in eighty-nine necropsies and Rice concludes that more careful examination of the thyroid will reveal a higher incidence than is now recorded. Willis (1934) found 4·6 per cent. of 323 autopsies showed secondary deposits of carcinoma in the thyroid. Malignant melanoma, tumours of the kidney, lung, and breast have metastatic lesions in the thyroid more commonly than do tumours of other organs. A sarcoma of the ilium with metastasis in the thyroid is included in the museum of the Cancer Hospital, London.

Metastases from the thyroid. Reference has been made to direct extension of adenocarcinomas into the veins of the neck and superior vena cava. In addition, the heart may be involved by metastatic implants as reported by Grosjean and Snyder (1941). Another rare location for metastatic cancer of the thyroid is in the ciliary body, reported by Campbell Orr and Johnstone (1935). Pulsating tumours of the sternum and skull from malignant thyroid tumours have been recorded by Molle (1943) and Albright (1944). Tumours of the thyroid gland and carcinoma of the kidney (hypernephroma) account for all pulsating malignant tumours of the sternum according to Albright. Thyroid cancer is one of the few diseases that frequently metastasizes to long bones according to the reports of Pemberton (1938), Haas (1937), Simpson (1926),

Crotti (1917), Binnie (1918), McClellan (1935), Maver (1933), and Finsterbusch (1936). By far the highest incidence of metastasis is found in the cervical lymph nodes in all types of thyroid cancer. Next in frequency are the lungs; hypertrophic pulmonary osteoarthropathy may then develop (Hoddle, 1949). The mediastinum, closely followed by the spine, has the next greatest number of metastatic lesions. In approximate order of frequency the skull, liver, pelvis, sternum, long bones, rib, clavicle, scapula, and mandible then share in receiving these metastatic deposits. There are some slight variations in the predominant location of the metastases in accordance with the type of primary lesion. No tissue and no organ of the body is immune and it seems to be only a question of the " proper soil to grow the seed " that determines where the lesions will be found in any single case.

Diagnosis of malignant tumours of thyroid. An accurate pre-operative diagnosis of these tumours is extremely difficult, even for the experienced surgeon. In a review of 774 cases Pemberton (1938) reported that the diagnosis was not suspected in 60 per cent., was definitely made in 23 per cent., and only suspected in the remainder. Graham (1937) reported a series of twenty cases in which the diagnosis was made clinically in eighteen. Other authors, Troell (1946), Rankin and Donald (1933), and Tinker (1934), indicate that a benign lesion was diagnosed clinically in 42–60 per cent. With earlier removal of single tumours and greater experience in their histologic interpretation, it is to be expected that a higher percentage of benign diagnoses will be made pre-operatively. It is of importance, however, to note that the presenting symptoms may depend on metastases from a nodule so small as to escape casual examination. From these observations it is clear that all tumours of the thyroid should be viewed with suspicion.

The diagnosis of malignancy may be suspected when there has been a history of recent rapid growth, a recent change in voice, or a change in consistency with increasing hardness on palpation. It is to be remembered that a sudden increase in size over a few hours or days may be caused by haemorrhage into a pre-existing adenoma. This rapid increase should be contrasted with the steady enlargement over weeks or months in malignant goitre. Pressure symptoms are common with haemorrhagic cysts; there is local tenderness, but toxic symptoms are not found.

1. Consistency and Mobility: When the nodule is fixed the diagnosis of malignancy is probable. A hard, irregular nodule likewise strongly suggests cancer though extensive calcification may simulate it. Fixation to the trachea should arouse suspicion but is not necessarily pathognomonic of carcinoma.

2. Pressure Symptoms: (a) Dysphagia is not a common symptom and when present occurs late in the course of malignant disease of the thyroid. It usually indicates extension of the tumour into the oesophageal wall. The converse may apply, namely, that an oesophageal carcinoma is spreading into the thyroid gland. Large goitres, benign or malignant, may from pressure alone cause difficulty in swallowing. (b) Dyspnoea is a symptom common to both benign and malignant tumours and is not necessarily more severe with one than with the other form of adenoma. Flattening of the trachea occurs

when it is compressed against a nodule in the opposite lobe, or from in front against the unyielding spine. Direct extension of cancer into the tracheal or laryngeal wall will cause persistent dyspnoea that is not relieved by change in position. Under such circumstances dyspnoea tends to become progressively more severe. (c) Cough and expectoration occur from irritation or invasion of the trachea or the stimulation of the laryngeal nerves. (d) Displacement of the larynx is occasionally seen in malignant disease but the most extensive displacements are associated with benign tumours.

3. Involvement of Lymph Nodes: This is common. Careful scrutiny of all the cervical, axillary and accessible groups of lymph glands is essential and may, in otherwise doubtful cases, make the diagnosis clear. Cope *et al.* (1949) have emphasized that enlargement of the lymph glands in relation to the thyroid isthmus may be an early and valuable clinical sign.

4. Involvement of Vessels: Pressure on the internal jugular or innominate vein or their direct invasion by the growth may lead to obstruction of the veins of the head and neck and sometimes of the brachial, thoracic, or abdominal veins. The pulsation of the carotid arteries may be obscured by malignant thyroid growths. Oedema of the head and neck, and sometimes of the upper limbs, may follow complete occlusion of the superior vena cava by the growth.

5. Involvement of Nerves: Involvement of the recurrent laryngeal nerve, which is often an early phenomenon, is indicated by an alteration in the voice and sometimes by troublesome stridor, with a brassy cough. Laryngoscopy may reveal weakness or complete paralysis of one vocal cord without change in voice. Vocal-cord paralysis is associated with a benign tumour in a small number of cases. Pressure on the cervical sympathetic chain may occur with the characteristic contraction of the corresponding pupil and narrowing of the palpebral fissure.

Rarely, the vagus may be damaged as indicated by bradycardia. Pain from involvement of sensory nerves may occur. Such pain may be referred to the corresponding ear, jaw, mastoid area, back of neck, the upper part of the chest, shoulder and arm. It results from involvement of branches of the superficial cervical plexus.

6. Associated Hyperthyroidism: Hyperthyroidism may be associated with malignant thyroid disease. Goetsch (1940) has described eight cases of incipient carcinoma arising in hyperplastic goitre. He concludes that cancer rarely, if ever, occurs primarily in such glands but arises from minute, pre-existing adenomas. Crile (1936) concludes that in no case of a series of 249 malignant tumours of the thyroid was there unequivocal evidence of hyperthyroidism. Horn *et al.* (1947) found two patients with definite hyperthyroidism in a series of seventy-one patients with thyroid cancer. Pemberton and Black (1948) stated that an associated malignancy was found in 0·4 per cent. of all exophthalmic goitres operated upon at the Mayo Clinic.

Seidlin *et al.* (1946) have recorded a case that developed multiple metastases together with symptoms of hyperthyroidism fifteen years after excision of the primary thyroid cancer. The hyperthyroidism was controllable with thiouracil.

Thus, malignant disease is occasionally associated with true hyperthyroidism and conversely. Some malignant lesions have the ability to function and *in toto* produce an excess of thyroid secretion.

Differential diagnosis. The conditions most frequently confused with malignant disease are subacute and chronic thyroiditis and calcification of an adenoma. The latter condition presents a very hard, irregular mass that often has a well-defined margin. Occasionally the entire capsule will have a thin, smooth shell of calcification. X-ray examination will reveal the character of such masses, but it should be remembered that carcinoma may develop in such a tumour.

Clinically the hardness of a tumour may suggest Riedel's disease (Ward *et al.*, 1950). Riedel's struma, a form of chronic thyroiditis, occurs at any age, may be unilateral, and is frequently associated with a pre-existing adenoma. It is characterized by fibrous tissue overgrowth that can lead to fixation and irregular, woody, hardness. The gross appearance is that of excessive connective tissue overgrowth and little vascularity. A small amount of normal thyroid tissue may occur in scattered islands. The tissue cuts with a gritty resistance. Final diagnosis depends upon microscopic examination.

Non-specific chronic thyroiditis, subacute sclerosing thyroiditis, and pseudo-tuberculous thyroiditis are terms applied to a group of chronic or subacute inflammatory lesions of the thyroid. They usually develop in a younger age group, 25–40, and affect the sexes without distinction. The process may start following an acute upper respiratory infection. The history frequently indicates that the disease began in one lobe to extend across the isthmus into the opposite side. Pain, tenderness, dysphagia, and fever help to differentiate these hard, smooth enlargements.

Struma lymphomatosa of Hashimoto occurs in older women. The process is bilateral and the thyroid is diffusely and smoothly enlarged. Pressure and mild hypothyroid symptoms are not infrequent.

Grossly, the gland presents a uniform greyish-white appearance. Fibrous septa usually divide the cut surface of the gland. The degree of enlargement and the firmness of the goitre have misled many surgeons who have done a total thyroidectomy in the belief that the condition was malignant. Lack of extrathyroidal involvement is a distinguishing feature.

Rawson (1948) has commented on two cases of squamous carcinoma the onset and symptoms of which led to the clinical diagnosis of an inflammatory lesion. It is thus clear that histologic examination of excised tissue is essential for an accurate diagnosis.

Specific inflammatory lesions of the thyroid, including syphilis, tuberculosis, actinomycosis, occur so rarely that they need not be a cause for concern in the differential diagnosis of malignant disease. Positive serology or the demonstration of the causative organism helps to establish the diagnosis.

Prognosis. More widespread removal of nodular goitres and better pathologic interpretation of the tissue removed are increasing the number of early thyroid cancers being recognized. This increase in our knowledge is

reflected in improvement of the overall mortality statistics for thyroid cancer. Nevertheless, we rarely speak now of "cures" obtained in malignant disease of the thyroid, "survival rate" is a much more accurate expression.

Such rates are compiled in many different ways and the prognosis varies accordingly.

Portmann (1941) groups his cases in the following manner; Group I: Malignancy only recognized microscopically; Group II: Cases previously suspected of being malignant but cancer confined within its capsule; Group III: Clinically recognizable malignancies with extension beyond the capsule; Group IV: Evident cancer with clinical or X-ray evidence of metastases. Horn *et al.* (1947) reported, in a total of forty-four patients, 86 per cent. survived five years in Group I, 67 per cent. in Group II, 41 per cent. in Group III, and 22 per cent. in Group IV.

Clute and Warren (1931) arranged tumours of the thyroid so that three major groups resulted: Group I of low or potential malignancy. Group II, moderate malignancy. Group III, high malignancy. Using this arrangement, Cattell (1946), in a series of 487 cases has reported unusually favourable five-year follow-up results:

Group I	Adenoma with blood-vessel invasion	71 per cent.
	Papillary cystadenoma (malignant)	62 per cent.
Group II	Papillary adenocarcinoma	80 per cent.
	Alveolar adenocarcinoma	27 per cent.
Group III	Small-cell carcinoma	22 per cent.
	Giant-cell carcinoma	17 per cent.
	Fibrosarcoma	33 per cent.

Less hopeful are the results of five-year survivals reported by Foote and Frazell (1948) using their own method of classification:

Papillary carcinoma	50 per cent.
Follicular and alveolar carcinoma	30 per cent.
Hürthle-cell carcinoma	30 per cent.
Solid type	16 per cent.
Giant-cell type	0 per cent.

In those cases operated upon by the present author during or before 1943, the following five-year survival rates have been found:

Papillary carcinoma	55·1 per cent.
Adenocarcinoma	48·7 per cent.
Epidermoid carcinoma	0 per cent.
Giant-cell carcinoma	0 per cent.
Fibrosarcoma	0 per cent.
Reticulum-cell sarcoma	25 per cent.

Treatment. Complete excision or destruction of all malignant cells is the ideal therapy. The experience and ability of the surgeon affect the amount of tumour that is excised. Too often inadequate operations are done, but on the other hand it does not seem justifiable to remove large portions of the trachea or oesophagus.

Crile and Crile (1937) described their radical operation for these tumours emphasizing the need of including all veins even the internal jugular. Watson and Pool (1940) have reported a slightly different approach to radical resection. All procedures are designed to remove the venous channels together with overlying muscles, lymph nodes, and thyroid. Arteries and nerves are sacrificed on one side if necessary.

The papillary group of tumours tends to invade lymph channels and may remain localized in the neck for many years. This fact enables the surgeon to obtain a high percentage of long-term survivals by excision of all involved glands, the homolateral lobe and the overlying muscles. It is important always to remove the whole of the homolateral thyroid lobe in cases of lateral aberrant tumours. Careful search, including serial sections, of the lobe has revealed a primary tumour in every case.

The more highly malignant tumours of the thyroid are usually unsuitable for surgical treatment. This fact should not deter the surgeon from an attempt to excise the disease. Radical operation with removal of as much of the tumour mass as possible enhances the effectiveness of radiotherapy. Recent statistics, indicating more five-year survivals, warrant the wider trial of surgery in this group.

Bilateral total thyroidectomy is indicated for early cancer near the midline. For extensive bilateral growths, radical removal in two stages is preferable. Both internal jugular veins may if necessary be sacrificed if the procedure is divided into stages. Great care must be exercised to preserve parathyroid function, and the laryngeal nerves.

Radium and X-ray Treatment: All the available data indicate that surgery combined with radiotherapy offers the best hope of recovery. Even where surgery has been refused or was impossible, irradiation has enabled patients to survive for long periods.

Some surgeons implant radon seeds at 1 cm. intervals in tumour tissue that cannot be excised. Implantations of radium needles or the use of capsules in rubber drainage tubes may be used. External application of radium by plaque, collar, or " bomb " still has a few advocates.

The majority of therapists to-day favour administration of external X-ray therapy. Multiple ports and a cross-fire technique are used. Total dosage will depend on the tolerance of the patient but should reach 6,000 röntgens. Treatment can be started as soon as the patient is ambulatory since it has been found that radiation therapy will not significantly retard wound healing. Hare (1941) has given the technique of administration and the five-year results obtained; these are distinctly encouraging. X-ray treatment of metastases should be carried out.

Malignant disease of the thyroid gland varies greatly in its response to radiation therapy. Since papillary tumours may remain localized in the neck for many years without any treatment the efficacy of irradiation has not been established. These tumours are, however, generally said to be radiosensitive. On the other hand, the response of adenocarcinomas to radiation therapy is usually not good. Some temporary reduction in the size of the goitre may

occur, but whether this is due to capillary occlusion as suggested by Portmann (1935) is not clear. Highly malignant thyroid tumours are more radioresistant than are the less malignant lesions. Reticulum-cell sarcoma may nevertheless respond favourably to deep X-ray treatment and the writer has had at least one seven-year survival in this group. Even though there are few cures from the use of deep X-ray therapy, more five-year survivals are obtained than with surgery alone. X-radiation is considered an essential part of the treatment of thyroid cancer in spite of its limitations.

Radioactive isotopes. Hertz, Roberts, Means and Evans (1938) first demonstrated the value of radioactive iodine in the study of thyroid physiology. Hamilton and Soley (1939–40) reported the use of this substance in clinical studies of iodine metabolism and later studies were summarized by Rawson and McArthur (1947). Keston *et al.* (1942) and Frantz *et al.* (1944) reported uptake of radio-iodine by metastases from thyroid cancers. Marinelli *et al.* (1947) reviewed their results in treating nineteen patients with thyroid carcinoma using radio-iodine. They state that: " Pick-up of radioactive material is closely linked with structural qualities which include orderly cell arrangement in follicular pattern and the presence of colloid-like material."

In valuable studies correlating structure with function, Fitzgerald and Foote (1949) have shown that the commonest type of thyroid cancer, the papillary type, unfortunately does not concentrate radioactive iodine, nor do the predominantly solid-cord, Hürthle cell and reticulum-cell cancers. Only the adenocarcinomas or those tumours with a fair admixture of follicular elements show much " pick-up " of radio-iodine.

The amount of radio-iodine picked up by the metastases may however be increased by the following means (Trunnell *et al.*, 1949).

(i) Total thyroidectomy. All *normal* thyroid tissue, as well as the primary growth, should be extirpated or destroyed because it competes with the metastases for administered radio-iodine and can indeed pick it up more effectively (Fitzgerald and Foote, 1949).

(ii) The injection of pituitary thyrotropic hormone.

(iii) Prolonged thiouracil therapy.

It should also be remembered that the histological pattern varies from section to section in many thyroid cancers and as between the primary growth and the metastases. Usually, in some areas there are attempts at follicular differentiation. Thus of 100 consecutive cases studied by Fitzgerald and Foote (1949), forty-six gave radio-autographic evidence of concentration of the isotope.

Brilliant results may be obtained as shown by the six-year progress report of one of the earliest cases treated (Seidlin *et al.*, 1949). This patient had presented with severe thyrotoxicosis due to excess hormone production by metastases, the thyroid with the primary growth having been removed eighteen years previously. Biopsy of a metastasis showed a highly cellular well-differentiated adenocarcinoma. Radioactive iodine (111 millicuries over a six-year period) changed his clinical state to one of hypothyroidism and a

TABLE XXVII. CASES OF MALIGNANT DISEASE OF THE THYROID.

Case	Sex	Age	Previous Goitre	History	Clinical Details	Treatment	Subsequent Progress	Pathology Report	Result
1	F	11	4 mths.	Swelling in midline 4 months. Recently increasing hoarseness.	Irregular mass attached to trachea below thyroid cartilage; small; firm, left thyroid lobe 2 × normal size; somewhat fixed. Located behind left sternocleidomastoid muscle, along posterior border of sternomastoid muscles, either side, chain of lima bean-sized, fixed lymph nodes. Ad 6–11–47 to 15–11–47	Rt. radical resection—internal jugular vein and muscles. Inoperable—extends into chest over to left side. Biopsy, lymph node.	Removal of thyroid tissue left neck and radioactive iodine given Jan. 1948.	1. Adenoca. thy. gland metastatic to lymph node. 2. Adenoca.	Alive Nov. 1948, under treatment, gr. 2 thyroid extract. Well 1951.
2	F	27	18 yrs.	Lump in neck noted at 9. Thyroidectomy attempted Dec. 1946 elsewhere, incomplete because of haemorrhage. Wt. loss, cough, nervousness 6 months.	Behind or intwined in lt. sternomastoid muscle and in post. triangle there are 6 shotty masses bean-shaped; large superior one about 3 cm. Ad 13–7–47 to 23–7–47	Radical left hemithyroidectomy with removal of sternohyoid and sternothyroid muscles, portion internal jugular vein, lymphatic tissue angle of jaw down into superior mediastinum. X-ray therapy: 800 r to rt. thy. 800 r to lt. thy.	Large lymph node removed 6–3–48. Right lobectomy and pyramidal lobe removed 9–3–48. Postop. parathyroid tetany. X-ray therapy: 800 r rt. thyroid 800 r lt. thyroid Oct. 1948, metastases left frontal parietal bones. Radioactive iodine therapy.	July 1947—Early adenoca of thyroid gland. March 3, 1948—Adenoca gr. 2 of thy. gl. origin. March 9, 1948—Adenoca involving portion of thyroid gland.	Alive Nov. 1948, under treatment. Well 1951.

CASES OF MALIGNANT DISEASE OF THE THYROID.

Case	Sex	Age	Previous Goitre	History	Clinical Details	Treatment	Subsequent Progress	Pathology Report	Results
3	F	61	12 yrs.	Swelling of neck noticed 12 yrs. ago—increasing 4 months, also nervousness. Wt. loss.	Left thyroid lobe enlarged, hard, firmly fixed.	Left lobectomy.	Temporary improvement. Died 4 months post-operatively.	Anaplastic thyroid cancer.	Dead.
4	F	56	6 mths.	Swelling neck and nervousness 6 mths.	Huge adenoma left and median lobes; fixed. Ad 21–7–38 to 30–7–38.	Bilateral subtotal thyroidectomy. X-ray therapy.	Died 16 months after operation.	Spindle-cell cancer of thyroid gland.	Dead.
5	F	35	12 yrs.	" Lump in throat 12 yrs. ago ", 9 mths. ago visible enlargement, nervousness. X-ray treatment.	Nodule size of large plum, right lobe, inferior pole. Ad 29–3–35 to 6–4–35	Right subtotal resection.	Recurrence 6 yrs. later—left lobectomy.	29–3–35—Carcinoma of thyroid gland. 1941—Carcinoma of thyroid gland.	Alive and well, 1948.
6	F	25	2 yrs.	Mass 2 yrs., rapid increase in size 4 mths.	Thyroid large, firm, nodular. Fixed to trachea. Ad 2–5–46 to 10–5–46	Incomplete right lobectomy. X-ray therapy.	Recrudescence 4–47 Laryngectomy 4–48	Anaplastic epidermoid carcinoma of thyroid gland.	Alive Oct. 48, with persistent tumour.
7	F	32	18 yrs.	Swelling in neck 18 yrs., gradual increase in size. Occ. choky feeling.	Firm, hard, freely movable mass, size of egg in left side of neck. Smaller mass ant. to large one.	All muscles, internal jugular vein, lymphoid tissue and left lobe of thyroid were excised *en bloc* from level of first rib up to the superior border of the thyroid cartilage.	Continued improvement.	Pap. adenoca. of thy. gl. Tumour has metastasized to regional lymph nodes.	Alive and well, Jan. 48.

CASES OF MALIGNANT DISEASE OF THE THYROID.

Case	Sex	Age	Previous Goitre	History	Clinical Details	Treatment	Subsequent Progress	Pathology Report	Result
8	M	18	10 yrs.	Swelling in neck bilaterally 10 yrs. ago. 2 weeks rapid increase in size.	Thyroid diffusely swollen above clavicle. On right, behind sternomastoid is mass of lymph nodes, stony hard. Also smaller similar mass of nodes without calcification, left. Ad Aug. 30, 1948 to Sept. 6, 1948. X-ray shows metastases to lungs.	Node, superior pole rt. thyroid dissected. Isthmus excised.	Radioactive iodine, tracer dose Sept. 23, 1948. Right radical hemithyroidectomy, dissection glands of neck, Sept. 25, 1948. Tracer dose radioactive iodine October 28, 1948. Left thyroid lobectomy and dissection lymph nodes Oct. 30, 1948.	8–48—Adenoca gr. 2 of thy. gl. In some sections the tumour is seen in lymphatic channels and invade lymph nodes. 9–25–48—Adenocarcinoma of thyroid gland. October 30, 1948—Adenoca. of thyroid gland metastatic to lymph node.	Alive 1951, under treatment with R.A.I.
9	F	43	12 yrs.	Swelling in neck 12 yrs., rapid increase in size 3 yrs. Easy fatiguability and irritability.	Large grapefruit-sized adenoma right lobe thyroid gland. Ad 4–5–36.	Bilateral subtotal thyroidectomy.	Recurrence 4 yrs. later, 23–4–40—partial rt. lobectomy. 4,125 r units röntgen therapy to rt., lt. and ant. regions of thyroid. Recurr. 1944, nodule removed anterior medially to and over larynx. 1947—radical thyroidectomy including sternal head of rt. sternocleidomastoid muscle, rt. int. jug., vagus nerve and lymph tissue on rt. 2,000 r rt. and lt. thy.	5–5–36—lg. cellular ad. which produces atypical acini containing no colloid and showing evidence of blood vessel invasion. Must be considered malignant. 23–4–40—ca. of thy. 5–1–47—adenoca. gr. 1 of thyroid.	Alive 1951. No pick-up of R.A.I but disease assumed present.

CASES OF MALIGNANT DISEASE OF THE THYROID

Case	Sex	Age	Previous Goitre	History	Clinical Details	Treatment	Subsequent Progress	Pathology Report	Result
10	F	16	2 yrs.	Suspicious multiple adenomata removed July 1935. Swelling in neck 2 yrs. ago and inc. pressure symptoms.	Lt. lobe large, hard, fixed mass in region of lt. stump extends to midline anteriorly. Small hard lymph nodes in post. chain behind sternocleidomastoid muscle. Ad 12–1–39 to 20–1–39.	Lt. lobectomy 12–1–39. 2,550 r units röntgen therapy to thy., ant.	Recurrence 1946. Complete right lobectomy 3–6–46. 5,600 r units röntgen therapy.	39—malig. ad. of thyroid gland. 46—recurrent malig. ad. of thy. gl.	Alive and well, Oct. 48.

recently excised skull metastasis showed complete necrosis of tumour tissue; radioactivity could be detected in the necrotic debris.

Harmful side-effects of such heavy dosage include an exacerbation of hyperthyroidism while the tumour tissue is undergoing necrosis, amenorrhoea and a depression of haemopoiesis, which may progress to a fatal pancytopenia, as in a case reported by Trunnell *et al.* (1949).

Benign neoplasms. 1. Papillary Adenocystoma: Papillary tumours that do not exhibit the criteria of malignancy must be placed in this group even though some authorities consider all such tumours as slightly or potentially malignant. Local recurrence or metastases may occur long after initial removal so that follow-up examinations should be continued for long periods (ten to twenty years).

2. Dermoid cysts of the thyroid are rare (Greene, 1925; Crotti, 1917). No example of this lesion has been reported during the last twenty years.

3. Mediastinal aberrant goitres; Fourteen cases were collected from the literature by Rives (1947) who added three of his own. He emphasized the fact that these adenomata do not derive their blood supply from the thyroid arteries and are hence best approached surgically through a trans-pleural route.

4. Tumours of the Parathyroid Glands: Mandl (1925) first drew attention to the ability of surgeons to relieve symptoms of osteitis fibrosa generalisata by the surgical removal of a parathyroid adenoma. A great many reports followed his description of the pathology, surgical treatment, chemistry and symptoms of hyperparathyroidism.

Castleman and Mallory (1935) summarized the pathologic types found in twenty-five cases of their own and correlated the findings in 160 cases from the literature. They recognized hyperplasia and neoplasia of the parathyroid glands. They point out the variability of the histology of these nodules indicating that chief cells, wasserhelle cells, transitional oxyphil cells or any combination may co-exist in a single tumour. More than one parathyroid gland may contain a nodule though a single tumour is the more common finding.

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CHAPTER XXIII

HYDATID (ECHINOCOCCUS) DISEASE OF THE THYROID GLAND

Pathology — Clinical Features — Prognosis — Treatment.

Echinococcus disease of the thyroid gland is rare; even among sufferers from hydatids its incidence has been stated to be only 1–2 per cent. (Dew, 1928; Blum *et al.* 1939). Landiver (1913) collected thirty-one cases recorded up to 1915, and the total of proven cases is still under fifty. In the U.K. the condition is almost unknown, but Watson Cheyne (1895) described one case, and daughter-cysts from another are preserved in Charing Cross Hospital Museum (Specimen 1393):

Hydatid vesicles removed from a cyst of the thyroid. Amos S., aged 28, stone-mason. Admitted June 16th, 1897; discharged August 10th, 1897.

Swelling on the right side of the neck noticed 14 years previously, about 1 in. above the clavicle. For about three months prior to admission the voice had altered and had become husky and rough, and some difficulty in breathing was experienced. *On examination* a cystic swelling moving on deglutition was found in the right lower lobe of the thyroid, extending under the right sternomastoid to the supraclavicular fossa and a little across the middle line to the left side. The trachea was not displaced, but there was slight stridor. *Operation*, June 19th, 1897: a yellowish-white, loculated cyst was found. It was opened; thick cheesy pus escaped, followed by a large number of daughter-cysts. The cavity was found to extend as high as the right cornu of the thyroid cartilage and as low down as the sternum. The wall of the cyst in parts cut like cartilage.

Watson Cheyne's patient was a female, aged twenty, a Londoner. Seven weeks before admission she had noticed a swelling the size of a nut on the right side of the neck. The lump grew larger, extended downwards and forwards, and became painful; for five weeks there had been alteration in the voice and dyspnoea. A hard swelling, the size of a pigeon's egg, was felt in the right lobe of the thyroid. During removal the cyst ruptured and daughter-cysts escaped.

Vitrac (1897) described a case in a male, aged thirty-four, who had had repeated attacks of urticaria, associated with abrupt variations in the size of the cyst. The combination of symptoms enabled Lannelongue to make a correct diagnosis.

Patel (1903) reported a case of Jaboulay's, the cyst containing half a glassful of clear fluid in which numerous hooklets were found. The patient had noticed the swelling during pregnancy, and had had slight dysphagia, but no urticaria. The cyst was extirpated, with its surrounding pseudocyst, the operation being a little more difficult than for an ordinary thyroid cyst.

Ultzmann (1909) reported two interesting cases. In both the trachea was compressed by the cyst, and in one, the right vocal cord was also paralysed.

Ferrer's (1909) patient was an Arab male, aged sixteen, who had always associated with numerous dogs. For a year he had noticed a swelling in the neck, considerable pain, and dyspnoea. The tumour was smooth, regular in outline, and the size of a tangerine, the skin over it movable. No affection of the voice or thyrotoxic phenomena were present. The cyst was excised with a portion of the surrounding gland tissue, though during the process it ruptured, clear fluid escaped, and typical laminated membrane was revealed.

Gatti's patient (1913) was only four years old. He had had a swelling of the neck for twenty months, associated with slight dyspnoea. The tumour was bilobed, smooth and the size of a turkey's egg. It was resected and proved to be a typical hydatid cyst with clear fluid contents. The patient was quite well when seen more than three years later.

Pathology. Infestation occurs through the gastro-intestinal mucosa and the parasite passes into the portal blood to the liver. Before it can infest the systemic blood stream, it must first negotiate the hepatic and pulmonary capillaries. According to Dew about 90 per cent. of parasites are blocked by these filters. The remainder are scattered far and wide and occasionally one lodges in the thyroid gland. In many of the cases reported including those of Blum *et al.* (1939) and Shaw (1946) there is complete absence of associated infestation of the liver and lungs. As a rule, the cyst is unilocular, but a large number of daughter-cysts may be found (as in the Charing Cross Hospital specimen described above). The fluid content is almost invariably clear; occasionally hooklets have been detected. All the typical features were present in Reddy and Thangavelu's well-documented case (1946). Suppuration in the cyst has occurred in a few instances, and calcification in its wall has been noted (Chavier, 1897; Dew, 1928).

A more usual complication is for the cyst to erode surrounding structures including the trachea, when the patient may inhale or cough up part of its contents (Martini Herrera, 1944).

Clinical features. Usually young adults are affected but owing to the slow development of the disease infestation probably considerably antedates the appearance of the swelling. Ramsay's patient (1913) was sixty-six and Gatti's four years old. There is no special evidence of a sex preponderance, though in records of both Henle (1895) and Vitrac (1897) about two-thirds of the cases were females.

Study of recorded cases suggests that it is not unusual for the cyst to remain quiescent, or to grow very slowly for a time, and later to increase rapidly in size. The cyst may have been present for six months to forty years before producing symptoms. In Creyssel and Hutinel's case (1940) a thyroid swelling had been present since the age of three but resection was not done until the patient was forty-two.

Pressure effects are usual. Dyspnoea is commonest, and may be severe; deaths from suffocation have been recorded. Paralysis of one vocal cord has been noted in several cases. Dew's patient exhibited slight paralysis of the

cervical sympathetic nerve. The trachea is usually displaced to one side, or its wall may be deeply grooved. In Ramsay's patient the cyst nearly surrounded the trachea and had eroded its rings and hollowed its lateral walls. Perforation of the tracheal wall by the cyst, with sharp reduction in size of the goitre, may end fatally, but if leakage is slow, the contents may be expectorated and the cyst subsequently excised with recovery, as in Martini Herrera's case (1944). Intracystic suppuration or haemorrhage may occur; in either event aggravation of symptoms follows. Hydatid fremitus is a very unusual sign, owing to the small size of such cysts in the thyroid, but when detected it has its diagnostic value.

The intradermal reaction of Casoni (1911) is positive in from 90 to 95 per cent. of cases (Dew, 1928).

Lannelongue appears to have based his correct diagnosis on the abrupt variations in the size of the cyst in association with outbreaks of urticaria.

Prognosis. Gatti states that three out of four patients treated expectantly die. Spontaneous cure may follow calcification of the cyst wall.

Treatment. Resection of the cyst, together with a small amount of the surrounding thyroid tissue, is the operation of choice, since by permitting removal of the cyst entire, without danger of rupture in the process, it minimizes the risk of recurrence.

Recurrence of hydatid disease locally, due to imperfect removal of all the involved tissue, is exemplified by Creyssel and Hutinel's case (1939)

Botto-Micca (1928) and others have referred to the difficulty experienced in extirpating these cysts, owing to adhesions to the trachea and other structures. The oesophagus was injured during the removal of the cyst referred to in the Charing Cross Hospital Museum, but it was successfully sutured. Attempts at enucleation have often failed because the plane of cleavage which is most likely to be entered is that between pseudocyst and ectocyst, rupture of the latter being avoided with difficulty. If, however, the plane of enucleation is maintained strictly outside the pseudocyst, success may be expected. Some surgeons have resected the more prominent portion of the cyst and have then " marsupialized " the remainder. This method is fraught with the risk of a persistent sinus, and has little to recommend it except in cases where the deeper part of the cyst is firmly adherent to vital structures.

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CHAPTER XXIV

AMYLOID GOITRE

There are some sixty cases on record in which extensive amyloid infiltration of the thyroid gland has occurred. Usually the condition is widespread in the body tissues and involvement of the thyroid is incidental. Nevertheless, amyloid infiltration of the thyroid deserves brief description because, not infrequently, it leads to well-marked enlargement of the gland, amyloid goitre. The pathology of amyloid goitre is well described by Wegelin (1926) and its clinical features are illustrated in cases described by Walker (1942) and Kranes (1947).

Classification of amyloidosis. Reimann, Koucky and Eklund's classification (1935) includes four groups, primary amyloidosis, secondary amyloidosis, tumour-forming amyloid disease and amyloidosis with multiple myeloma. Amyloidosis of the thyroid is usually of the secondary type and in many cases has complicated pulmonary tuberculosis and suppurative lung lesions.

Amyloid goitre may however be part of a primary amyloidosis and there are even cases on record (Schilder, 1909; Oberling, 1927) where amyloid degeneration has been confined to the thyroid gland.

In one of Walker's cases, the amyloid goitre weighed 280 gm. but in about half the cases recorded the gland is not clearly enlarged. When enlargement occurs, it is diffuse and firm in consistency. The trachea may be pressed on and its lumen narrowed at the level of the gland. Softening of the affected tracheal rings has been noted.

Microscopically, the thyroid follicles are degenerate and even absent over wide areas of the gland. The bulk of the section consists of masses of amyloid material which gives the characteristic staining reaction with congo red and methyl violet. In some areas the amyloid material appears to have a fibrillar structure, resembling hyaline fibrous tissue. A noteworthy and frequent feature is that large amounts of ordinary adipose tissue, with mature fat cells, giving the characteristic staining reaction with sudan III, are seen in microscopic sections.

Though amyloidosis of the thyroid is usually subsidiary to some severe general disease, there are many cases on record where the latter has not been apparent, or the secondary nature of the goitre has not been appreciated, and thyroidectomy has been done, usually with highly unsatisfactory consequences in that the primary condition has pursued a more rapidly downhill course afterwards. Amyloid goitre is not associated with hyper- or hypothyroidism. It has most often been confused with malignancy of the gland or struma lymphomatosa.

There is nothing specific in the character of the thyroid enlargement, and diagnosis must depend on recognition of the general disorder. In cases of doubt special investigations including the congo-red retention test and biopsy of the thyroid will establish the diagnosis. Thyroidectomy is contra-indicated.

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CHAPTER XXV

ANAESTHESIA FOR GOITRE OPERATIONS

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Introduction — Examination of Patient; Operative Risk — Premedication — Stealing the Thyroid — Local Anaesthesia — Infiltration — Cervical Plexus Block — General Anaesthesia — Intubation.

Introduction. It is twenty years since this chapter was written for the first edition. During this period great changes have taken place in the progressive science of anaesthesia; but they have been less sweeping in the field of goitre surgery than in many others. Heavy premedication or basal narcosis is still necessary for the thyrotoxic, and though we have a preference for chloral and omnopon, one large clinic[1] has reverted to rectal paraldehyde, which we used in 1931. Most anaesthetists agree that they are not happy with avertin in the thyrotoxic on account of the frequent occurrence of both tachycardia and restlessness.

We now employ endotracheal anaesthesia for all types of case, albeit its use is not entirely universal. It is interesting to note that single large tube intubation,[2] which was suggested in the first edition as an alternative to insufflation, has now entirely replaced that method.

Local anaesthesia, we believe, is an aid to the surgeon both in relaxing the infra-hyoid muscles and in producing haemostasis, to the anaesthetist in allowing him to run the patient in the very lightest plane of anaesthesia without risk of movement, and to the patient in protecting him from the ill effects of pain during operation and to a great extent from pain immediately afterwards. We like to combine local with general anaesthesia but are aware that many surgeons find local anaesthesia alone to be highly satisfactory. In our experience thyrotoxic patients are greatly disturbed by the procedure; the operation takes longer and requires to be done with great gentleness. In many patients the pulse rate rises, they are restless during operation and appear exhausted afterwards. Crisis may be precipitated.

Lastly a change has taken place in many of the patients with whom the anaesthetist has to deal. Owing to the profound effect of propyl-thiouracil in countering thyrotoxicosis, the hazardous cases which at one time were common do not now come to operation until their condition has been controlled—it is, in fact, now rare to meet with a really toxic patient in the operating theatre.

Thyroidectomy is performed for widely different diseases of the thyroid gland, and the anaesthetist's problem varies considerably in the different

cases. From his point of view there are two big groups: the toxic and the obstructive.

The first comprises both primary and secondary thyrotoxic patients: the highly nervous case whose cardiovascular system, though subjected to severe strain, has not broken down; those with varying degrees of heart failure; and patients on whose cardiovascular system the disease has worked irretrievable damage, and in whom auricular fibrillation, hypertension, arteriosclerosis and coronary sclerosis may be present.

All such patients require careful handling. The methods and choice of anaesthetic may be varied; but there is one factor common to all—these patients stand oxygen deprivation badly and they must not be subjected to it.

In the majority of primary cases, thiouracil so effectively controls the thyrotoxicosis that the risks of anaesthesia and operation are few. The highly nervous, flushed and emaciated patient is seldom seen, and although the technique for " stealing the thyroid " is for the sake of completeness included in this chapter, we believe it is now seldom needed.

Secondary thyrotoxicosis occasionally responds more slowly to thiouracil than does the primary form, so that the operative risk is sometimes little reduced. After operation they invariably do well.

Nevertheless all the patients in this first group (both primary and secondary), have unstable nervous systems, and are better when they are prepared for operation by heavy premedication.

Local anaesthesia may be performed under basal narcosis quite painlessly and without the patient remembering anything about it, provided manipulations are gentle and sharp needles are used. We prefer to induce general anaesthesia with a small dose of pentothal, and then to continue with nitrous oxide + oxygen, always remembering that cyanosis must be assiduously avoided and that, if there is difficulty in keeping the patient quiet, it is better to add ether to the mixture than to give too large a dose of pentothal (a safe maximum total dose of pentothal for the thyrotoxic is 1 c.c. of 5 per cent. solution for each stone of body weight).

There are many cases of simple goitre not associated with toxic features and they present no special problems for the anaesthetist; but one sometimes meets patients where the stress of the operation may produce signs of hyperthyroidism for a day or two afterwards.

Colloid goitres may become very large and prolongations of the lateral lobes can surround the pharynx and oesophagus, pressing on these structures. These then come into our second group. In nodular goitres, adenomatous masses may extend behind the pharynx, oesophagus, or trachea. They are often large and an endotracheal tube is always necessary to ensure a clear airway during operation. Recurrent laryngeal nerve paresis may be present and may render difficult the passage of an endotracheal tube by the blind method.

Goitres which invade the chest may be partly or mainly intrathoracic. When such goitres grow large the structures in the upper part of the thoracic cavity are compressed; the trachea is narrowed and often so tethered that

movements of the larynx during deglutition are diminished. Veins are pressed upon and the recurrent laryngeal nerve may become involved. Dyspnoea is often severe and venous engorgement of the head and neck, with development of a collateral venous circulation, may occur. Mild symptoms of secondary thyrotoxicosis are often present.

These cases are some of the most difficult with which an anaesthetist may have to deal; endotracheal anaesthesia is essential and once the tube is past the obstruction, the improvement in the patient's condition may be dramatic.

Malignant disease may produce hyperthyroidism, or pressure on the trachea and on neighbouring vessels. Paralysis of the recurrent laryngeal nerve is often present. Local infiltration is contra-indicated. Compression of the trachea may call for intubation with a stiff tube; otherwise no special anaesthetic technique is needed.

Lastly, patients with hypothyroid conditions (cretinism with congenital or infantile goitre and Hashimoto's disease) are not often encountered by the anaesthetist but when they are it should be remembered that their vitality is low and that they require careful handling. Their low metabolic rate makes them especially sensitive to morphia. The heart is often dilated; atheroma and coronary artery disease may be present. Anaemia, which is usually present, will mask cyanosis.

Examination of patient. Operative risk. There are three important things an anaesthetist should do before undertaking an anaesthetic for thyroidectomy.

1. He should examine the patient.
2. He should assess the operative risk.
3. He should take part in the preparation for operation.

The first entails a knowledge of the pathology and symptomatology of diseases of the thyroid, a consideration of the patient's B.M.R., her cardiovascular system and exercise tolerance, and an X-ray of the chest.

Assessing the operative risk is always difficult; the degrees of loss of weight, myasthenia, excitability, cardiac damage, and the extent to which it is possible to control tachycardia, must all be considered. The following classification modified from Means's original book, *The Thyroid and its Diseases*,[3] has been of the greatest practical assistance over a number of years.

Operative risk

1. *Good Risks.* Non-toxic goitre and uncomplicated toxic goitre of very mild intensity.

2. *Fair Risks.* Ordinary cases of uncomplicated moderately severe toxic goitre. Very large non-toxic goitres. Intrathoracic goitres with little respiratory obstruction.

3. *Poor Risks.* Those patients who present any of the following criteria may not stand operation well:

(a) Poor or absent response to thiouracil and iodine therapy.
(b) Rising B.M.R.

(c) Presence of complications; chiefly cardiac failure and hyperpiesis.
(d) Extreme intoxication.
(e) Old age.
(f) Psychotic manifestations.
(g) Marked malnutrition.
(h) Marked myasthenia or muscle atrophy.
(i) Fat subjects, especially young primary cases.
(j) Severe respiratory obstruction.

Premedication. Premedication is an essential part of the anaesthesia: it calms the nervous patient, reduces the amount of anaesthetic necessary, and lessens its after-effects.

In secondary thyrotoxicosis associated with cardiac damage, the judicious use of sedative drugs is an undoubted aid to safe anaesthesia. The employment of deep basal narcosis, however, may produce depression of respiration. In such an event, the patient must be amply supplied with oxygen to counteract cyanosis.

In goitres which produce respiratory obstruction by pressure on the trachea in the neck or within the thorax, little or no premedication is indicated; a small dose of atropine and thorough preliminary oxygenation are advisable.

Thyrotoxic cases tolerate cyanosis badly; because of their high metabolic level they quickly throw off the effect of any given drug and correspondingly higher doses are, therefore, often prescribed. To give morphine or the barbiturates in amounts sufficient to control the nervous symptoms usually requires a dose that is too large to be safe; respiratory depression and consequent cyanosis will often follow. Premedication can be achieved more easily and safely by a combination of drugs, each in a small dose, than by the use of large amounts of one drug only.

The anaesthetic procedure should be varied according to the needs of the case; for each there is an optimum combination, sedative, basal, and operative anaesthetic.

Paraldehyde[4] by the rectum (1 drachm per stone of body weight) has been much used. The addition of small doses of morphine (gr. 1/40 per stone of body weight) is almost always required to produce unconsciousness in hyperthyroid patients. This combination is safe and does not depress respiration.

Avertin has many advocates. Doses varying from 0·1 to 0·15 gm. per kgm. are necessary in hyperthyroid cases. It has, however, the great drawback that many patients become excited during recovery and it often happens that the pulse rate is sometimes considerably raised above its pre-operative level, even when the patient is unconscious; but it cannot be denied that many workers have found it highly satisfactory. Premedication with a combination of morphine and luminal has been used by F. B. Bannister; the patients are not deeply unconscious, but very sleepy, co-operative, and undisturbed. Large doses of both drugs are, however, necessary.

Stealing the thyroid. Before it was possible to control hyperthyroidism the procedure of " stealing the thyroid " was frequently employed and had

undoubted advantages. At the present time, however, it is seldom necessary. The method is as follows:

Permission for operation having been obtained, the patient is not told on which day it will take place—any of the usual drugs may be used.

Daily routine for 3 days prior to operation.		On day of operation.
Injection of sterile water.	1½ hr.	Injection of morphine.
Draw curtains or screen.		Draw curtains or screen.
Plain suppository.	¾ hr.	Suppository chloretone gr. x.
Insert rectal tube.		Insert rectal tube.
Rectal saline 6 oz.	½ hr.	Avertin p.r.
Awaken.	0	To theatre.

The chloretone suppository aids retention of the enema by partially anaesthetizing the rectal mucosa. Meals must be arranged to fit in with the scheme.

Paraldehyde is preferred by some anaesthetists; when used it is advisable to put one drachm into the rectal saline each day, so that the patient will become used to the smell of the drug.

The barbiturates may also be given by rectum. The result is very similar to that obtained with avertin. Boston and James[5] describe a method of using hexobarbitone-soluble by rectum. The dose is calculated by multiplying the patient's weight in pounds by 0·02 the resulting figure being the number of grammes of hexobarbitone-soluble to be administered in about 10 c.c. of water. When additional premedication is given the factor used is 0·01 to 0·015. The larger figure of 0·02 would appear necessary for thyrotoxic cases. The solution is given an hour before operation and the effect lasts for some hours. Restlessness sometimes occurs and in one case in which we used the drug, the pulse became very rapid.

Another method which involves less trouble and has proved equally successful in some of our cases, is the use of intravenous hexobarbitone or thiopentone. The patient usually receives a dose of normal saline intravenously each day at the time on which she will be given hexobarbitone on the day of operation. The injection is most appropriately given by her doctor or the house surgeon. The barbiturate should be given in minimal dose, but fairly quickly. The trolley should be ready outside the ward and the anaesthetist waiting to carry on with gas and oxygen anaesthesia immediately the patient arrives in the anaesthetic room. The skin is not prepared until the patient is asleep.

Morphine. It has been our experience that dosage with morphine by body weight has many advantages and appears more likely than any other method to produce consistent results in a large number of cases. A usual dose is morphine tartrate gr. 1/40 or omnopon gr. 1/30 per stone of body weight.

Hyoscine. Hyoscine is a valuable sedative for most patients, it dries the secretions and is preferable to atropine, which tends both to counteract the

sedative effect of morphine and to produce a viscid tenacious sputum which is hard to cough up.

In some thyroid patients, however, hysteria follows the use of this drug. It was at one time the practice to test the reaction of the patient to hyoscine hydrobromide some days before operation, but now thyrotoxicosis is so well controlled before operation that such reactions rarely occur.

A useful solution is:

Omnopon gr. 1/30
Hyoscine hydrobromide gr. 1/1000 } in 1 minim,

put up in a rubber-capped vaccine bottle. With this solution the dose can be varied at will and heavier or lighter premedication achieved appropriate to individual cases.

Paraldehyde. Paraldehyde $(CH_3CHO)_3$ is a safe drug, having little effect on respiration or blood pressure. Toxic effects are rare.

It has been employed extensively for thyroidectomy and appears to be much favoured. In the doses usually administered per rectum[4] (*vide infra*) it will not produce complete unconsciousness in healthy adults without the help of some other drug such as morphine. This is also true of patients with hyperthyroidism, unless they are very ill and emaciated.

Paraldehyde is soluble one part in ten of water and the dose by rectum is reckoned as one drachm per stone of body weight dissolved in saline. The solution is given one hour before operation; a suppository of chloretone gr. x ten minutes beforehand aids retention.

It is excreted mainly by the lung but to some extent in the urine. Elimination is slow and patients may sleep for several hours.

Avertin. Avertin (syn. Bromethol)[6], a white crystalline substance, is tribromethyl alcohol, $CBr_3.CH_2OH$. It is supplied as avertin fluid which is a solution in amylene hydrate; 1 gm. in 1 c.c. Administration is per rectum by a 2·5 per cent. solution in distilled water. This is warmed to body temperature (if allowed to cool below 90° F. much of the avertin will come out of solution). The solution is best kept in a vacuum flask until actually administered and it should be shaken vigorously before each portion is poured from the flask. At least ten minutes should be taken to run in the whole dose and administration should be started about forty minutes before the patient is due in the theatre.

The usual dose is 0·075–0·12 gm. per kilogram body weight and tables are supplied by the makers setting out the amounts of avertin fluid and distilled water needed for patients of different weights. In thyrotoxic cases it may be sometimes necessary to give as much as 0·15 gm. per kilogram to ensure complete unconsciousness. It is usual to give a small dose of omnopon at least one hour before the avertin, so that its depressant effect on the patient's respiratory centre will have passed off to a large extent before the avertin has its full effect.

Chloral[7]. A method of premedication for thyroid patients which we have used for some years is a combination of chloral hydrate by mouth and

omnopon-scopolamine hypodermically. It appears to be more satisfactory for thyroid cases than any other drug or combination of drugs in use. The patients do not come to the theatre unconscious; they are sleepy and can be roused; the most striking fact about them is that they lose practically all the nervous symptoms associated with their hyperthyroid condition. They are wholly placid and usually allow the local infiltration to be done without a murmur.

The method and dosage are as follows:

1. On the night before operation, in some cases for two or more nights, the patient receives:

Chloral hydrate: gr. xxx by mouth.

This is an average dose and may be modified to suit the case. Chloral is a reliable sedative and its use at this stage also provides a valuable test of the patient's reaction to the drug.

2. Four hours before operation, a dose of chloral hydrate is given by mouth and is calculated as follows:

With a normal basal metabolic rate:	4 grains for every stone of body weight.
For every increase of 10 per cent. in the B.M.R.:	An increase of 0·2 grains for every stone of body weight.
For every decrease of 10 per cent. in the B.M.R.:	A decrease of 0·2 grains for every stone of body weight.

3. One hour before the local infiltration is carried out or approximately one and one-half hours before operation, a hypodermic injection of:

Omnopon gr. 1/30
Hyoscine hydrobromide gr. 1/1000 } for every stone of body weight.

After receiving this injection patients are blindfolded or the room is darkened.

Local anaesthesia. Two methods of local anaesthesia are applicable to thyroid surgery; cervical plexus block and infiltration. We prefer the latter for the following reasons:

1. Anaesthesia is more complete than with cervical block.
2. The vaso-constriction obtained by adrenaline in the anaesthetic solution serves to reduce the number of bleeding points to be tied and thus shortens the operation.
3. Its performance is slightly less distressing to the patient.

Infiltration. The infiltration is done in the anaesthetic room, if possible half an hour before operation. An automatic syringe is best used because it appreciably shortens the time required.

The syringe illustrated (Fig. 138) has the advantage of being small (5 c.c.), and therefore easily handled, and also of being self-filling by reason of a spring-loaded piston.

Technique of infiltration (Fig. 139). Intradermal wheals are made:

1. In the episternal notch.
2. Immediately above the clavicle, at its mid-point or further out according to the size of the gland.
3. On the neck just lateral to the greater cornua of the hyoid bone.

From each wheal a subcutaneous and a deep infiltration are carried out.

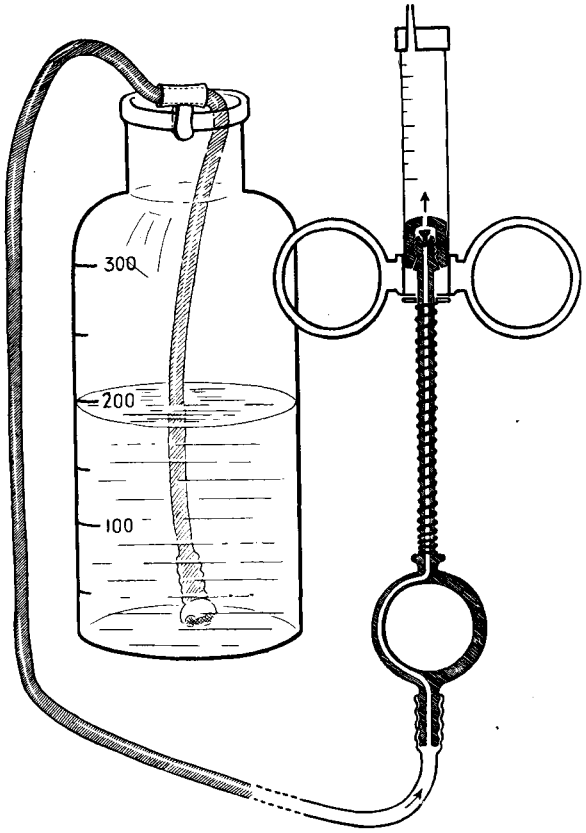

FIG. 138.—Diagram showing details of author's automatic syringe.

For making intradermal wheals a fine needle (Fig. 140) such as is used for the Schick test adds much to the comfort of the patient; by placing it on the skin bevel down, it is possible to produce wheals almost painlessly; the needle is afterwards pushed through the wheal and the subcutaneous tissue infiltrated.

Subcutaneous infiltration. The subcutaneous injections take the form of fans which meet so that the whole area is raised by a layer of anaesthetic solution. The needle is passed through each wheal into the loose subcutaneous tissue and the solution injected as the needle is advanced, so that

the needle point is actually preceded by the solution, which, as it were, opens up a way for it. Performed in this manner the injection is practically painless. The injection is continued as the needle is withdrawn.

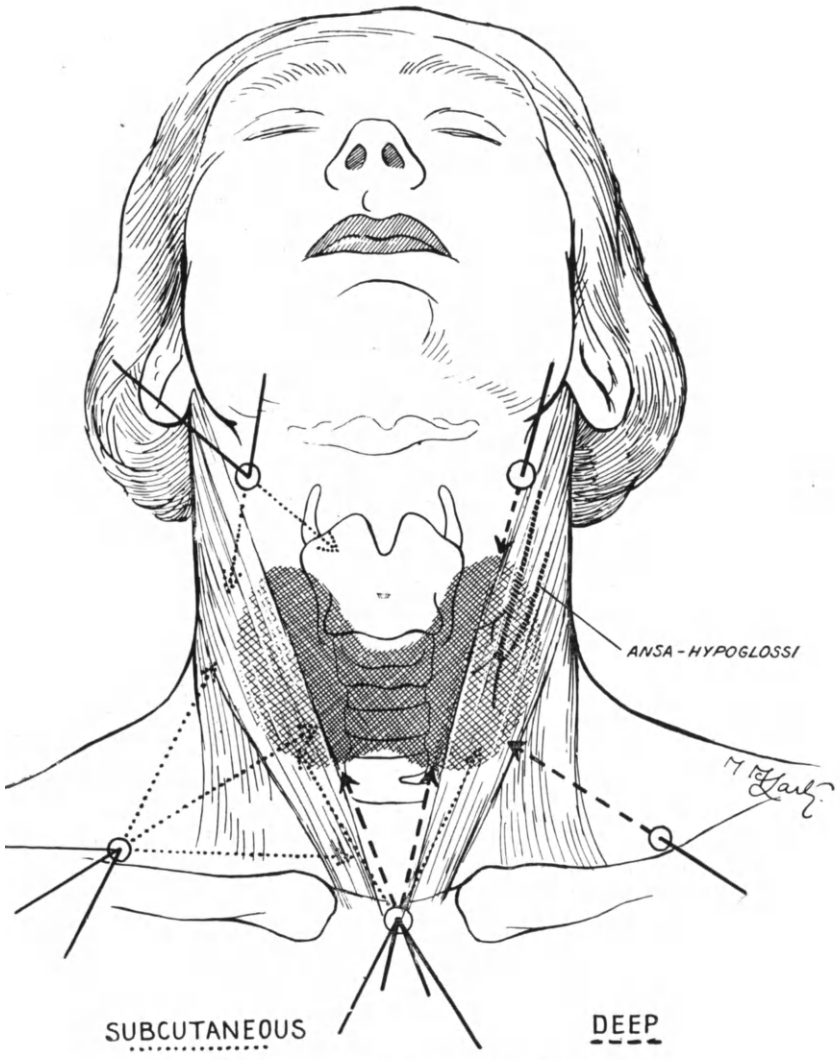

FIG. 139.—Scheme of infiltration for thyroidectomy.

It often happens that difficulty is experienced in keeping the needle within the subcutaneous layer because of the contour of the goitre. It tends to run into the deeper tissues; but this can be largely avoided by the use of a bent needle (Fig. 141).

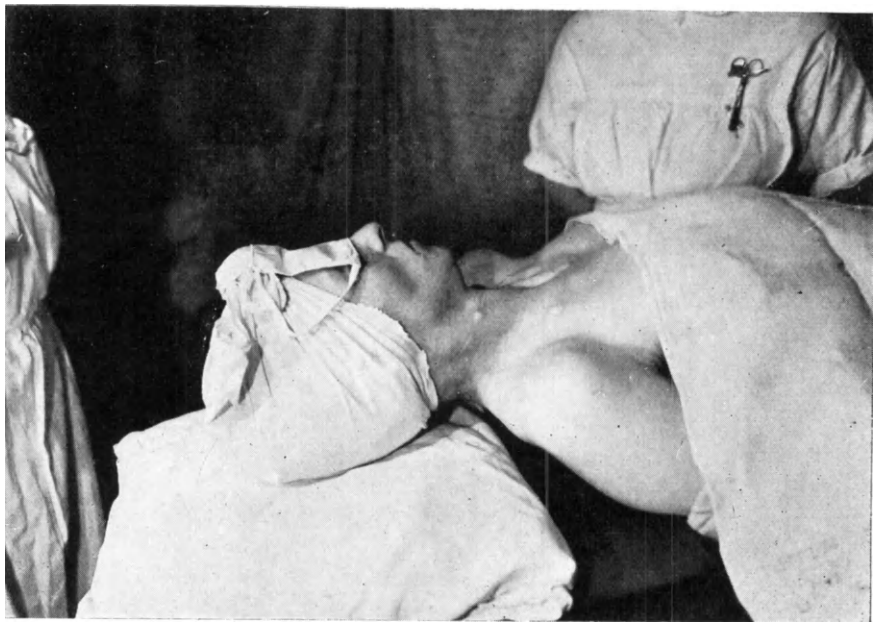

FIG. 140.—Intradermal wheals.

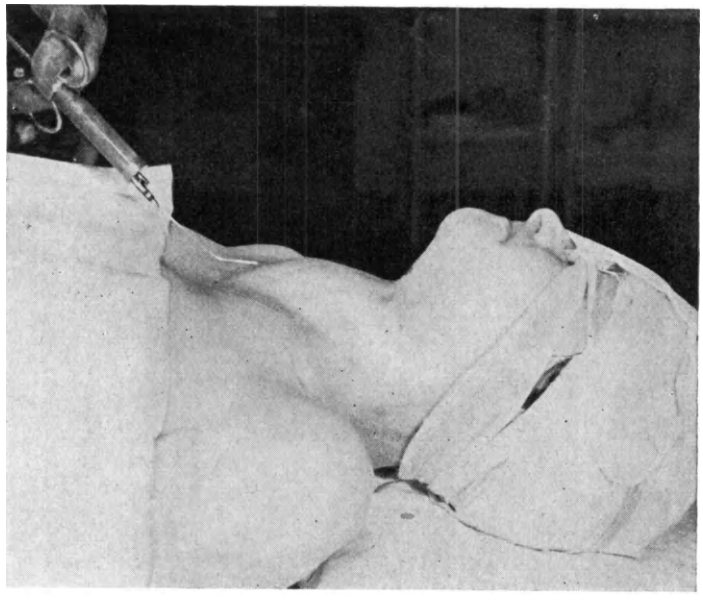

FIG. 141.—Needle angled near its point for subcutaneous infiltration over large goitres.

Deep infiltration. The deep injections follow the subcutaneous infiltrations and are made through the same wheals without withdrawing the needle completely. During the injection the needle is held still; it is preceded by aspiration in every case.

The following deep injections are made:

1. On each side of the trachea (Fig. 142). The object of these injections is to bathe the inner and posterior surfaces of the lower pole and the isthmus of the gland with anaesthetic solution. The needle, pointing up the neck at an angle of about 45°, is advanced to make contact with the trachea. Its direction is then changed and it is pushed on a distance of about 1 cm. so as to

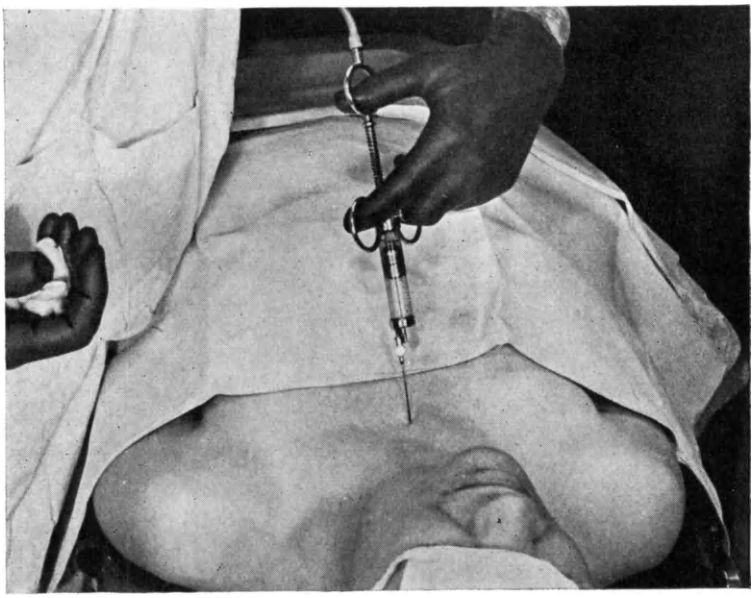

FIG. 142.—Deep, paratracheal infiltration.

bring its point to the side of the trachea where 5 c.c. of the anaesthetic solution are injected. A similar injection is then made on the other side.

In substernal goitre about 20 c.c. of the solution are also injected in a downward direction so as to surround the lobe which has extended into the chest. The needle may be entered for a distance of 2–3 cm. from the episternal notch; but no attempt should be made to advance it into the thorax blindly.

2. Laterally at the sides of the gland (Fig. 143): The needle is advanced through the head of the sternomastoid muscle down to the surgical capsule of the gland which is tough and can be felt easily with the needle. After aspiration, 10 c.c. of anaesthetic solution are injected to surround the side of the gland and its lower pole.

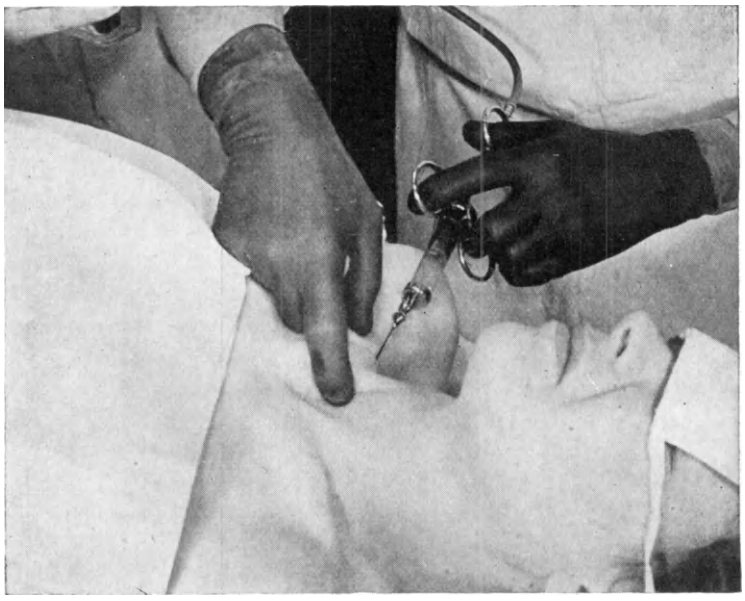

FIG. 143.—Needle passing through sternomastoid muscle to lateral aspect of gland.

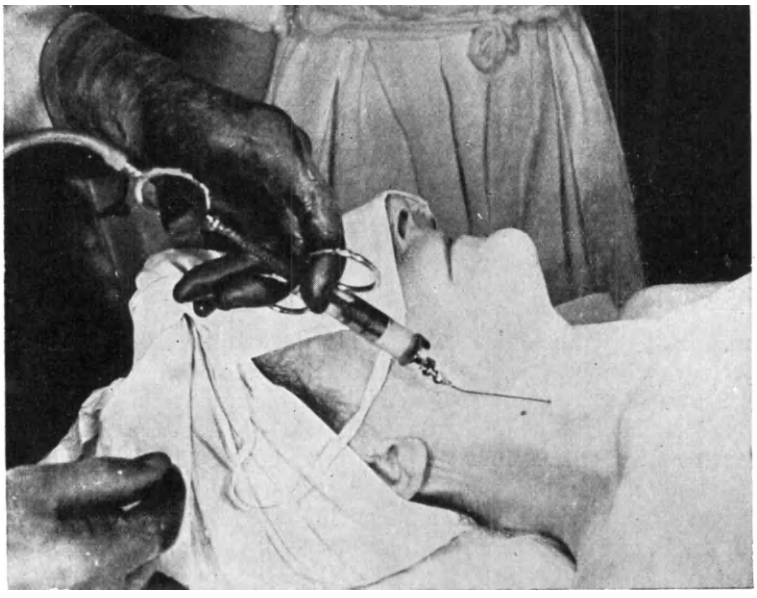

FIG. 144.—Infiltration around upper pole of gland.

3. Around the upper pole (Fig. 144): The needle is advanced through the upper wheal to make contact with the upper pole of the gland. This can be appreciated by sense of touch transmitted through the needle, in the same way as the side of the gland was felt in 2. After aspiration, 5 c.c. of anaesthetic solution are injected.

4. The ansa hypoglossi (Fig. 145): Using the same wheal as when infiltrating the upper pole, the needle is advanced for a distance of about two inches parallel to but beneath the anterior border of the sternomastoid. This muscle covers the carotid vessels, and the loop of the ansa lies in front of

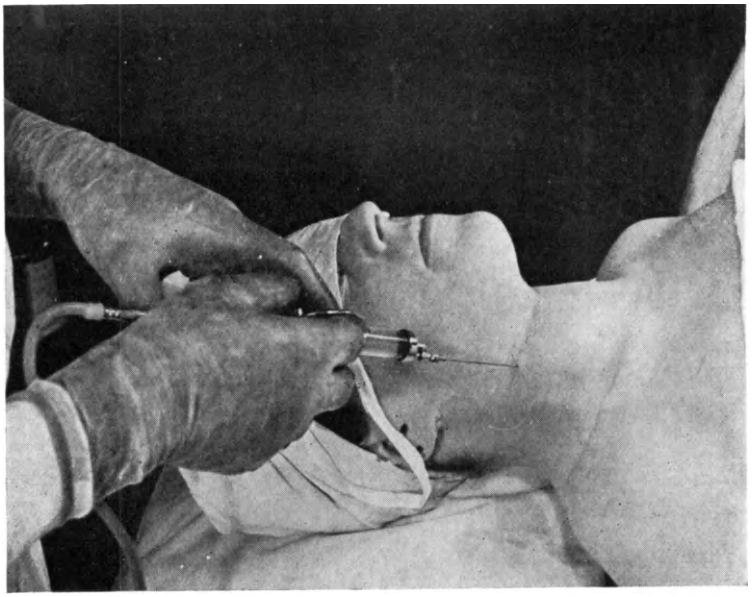

FIG. 145.—Infiltrating deep to anterior border of sternomastoid muscle to block ansa hypoglossi.

them. Whilst advancing the needle aspiration is performed; 5 c.cm. of the solution are injected as the needle is withdrawn.

The point at which the actual loop of the ansa occurs is variable. The method of approach described above is carried out easily through wheal 3, and it saves making another wheal. Relaxation of the infrahyoid muscles obtained by blocking the ansa is well worth the extra trouble involved.

Local anaesthetic solution. The solution used for local infiltration is:

Amethocaine hydrochloride 1 in 4,000
Adrenaline hydrochloride 1 in 400,000 } in normal saline.

A dose of 150 c.c. is never exceeded for thyroidectomy. Amethocaine gives excellent results in a concentration of 1 in 4,000, and the anaesthesia lasts

longer than with procain, nor does it in this strength cause vasodilatation. Used with a concentration of 1 in 400,000 of adrenaline (0·25 c.c. to 100 c.c.) vaso-constriction is excellent.

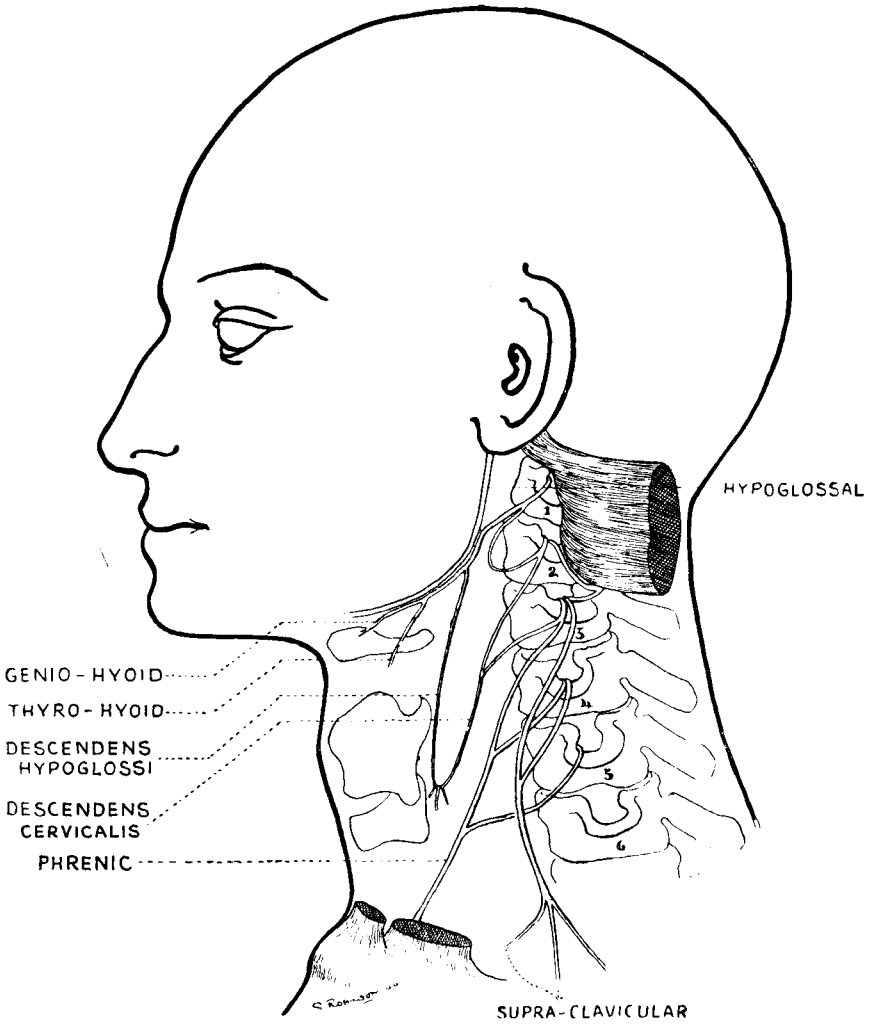

FIG. 146.—The cervical plexus.

Cervical plexus block. To perform this block (Heidenhain),[9] the patient should lie on her back with her head on a low pillow, turned away from the side which is being injected.

On emerging from the intervertebral foramina the anterior primary rami (Fig. 146) of the upper four cervical nerves join to form the loops of the

plexus in close proximity to the transverse processes and it is sufficient to deposit the anaesthetic solution around the ends of the processes to anaesthetize the whole cervical plexus.

The cervical transverse processes lie on a line running from the mastoid process to the prominent anterior tubercle of the sixth cervical transverse process, sometimes called the carotid or Chassaignac's tubercle, which is situated at about the level of the cricoid cartilage. Palpation and the use of the injection needle, unconnected with the syringe, as a seeker are the most satisfactory methods of finding the transverse processes. The anaesthetist has to make contact with the end of each process with his needle, and the

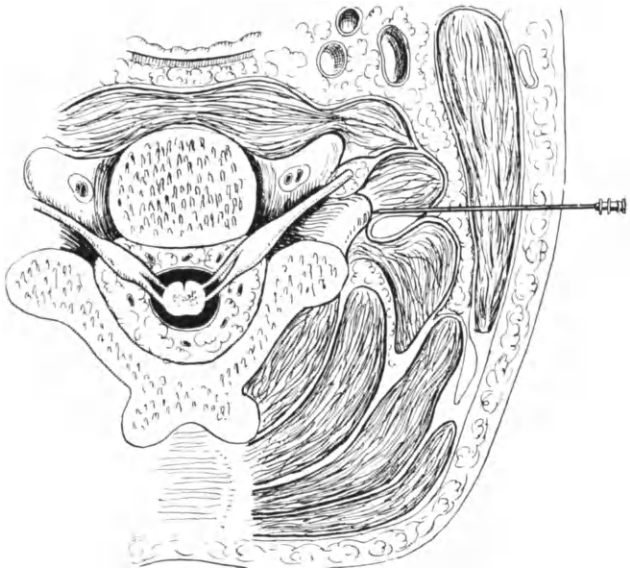

FIG. 147.—Cross-section of neck showing direction of needle and its relations both to the vertebral vessels and to the carotids and internal jugular vein.

needle is the best means of finding it; it should strike the transverse process (Fig. 147) superficially, and will by a small change of direction be found to slip off and sink into the deeper tissues around.

The transverse processes, then, should be envisaged as lying on a line from the mastoid process to Chassaignac's tubercle; the second is about one finger's breadth below the tip of the mastoid process. The third and fourth, which are more superficial, can almost always be palpated at similar intervals below.

Generally three skin wheals are made over the processes, but on occasion it may be possible to perform the block through two, or even only one wheal. Labat[10] recommends that in short necks a wheal should be made on the posterior border of the sterno-mastoid muscle 1·5 cm. behind the external jugular vein and all three transverse processes approached through it.

It is sometimes advantageous to leave the needle in contact with a transverse process, whilst seeking the next with another needle; the processes are only about 1·5 cm. apart and when approached through the same wheal it is easy to contact the same process twice, mistaking it for that below.

A needle of from 6 to 8 cm. in length is advanced through each wheal and contact is made with the transverse process directly beneath. Labat states[11] that the direction of the needle should be backwards rather than forwards, for not only may the vertebral vessels be punctured and a haematoma result, but the fluid may be injected into, or cause pressure on, the carotid sheath. The circulation of the brain may thus be impaired.

Having made contact with a process the needle is held against it and the syringe connected. Aspiration is now performed for blood or cerebro-spinal fluid, and 1–2 c.c. of anaesthetic solution is then injected very slowly. Aspiration is repeated and a total of 6 c.c. is injected around each process.

The anaesthetic solution used may be 1 in 2,000 amethocain hydrochloride with 1 in 400,000 adrenaline hydrochloride, or a 1 per cent. solution of procain with 1 in 100,000 adrenaline hydrochloride. Anaesthesia after cervical plexus block is not fully complete for about fifteen minutes; the operation should not therefore commence before such a period of time has elapsed.

The phrenic nerve is blocked partially in every case. Bilateral cervical plexus block, however, seems to have little effect on the respiration.

When cervical plexus block is performed it occasionally happens that the solution reaches the sympathetic chain, thus paralysing the cervical sympathetic. This produces Horner's syndrome: myosis, ptosis, anhidrosis of the forehead and cheek and swelling of the nasal mucosa on the affected side. No subjective symptoms are produced and the paralysis passes off with the anaesthesia.

Alternative approaches to the cervical plexus have been described; Macintosh[12] recommends the anterior and Kappis[13] the posterior, but we find the lateral approach which we have described the easiest to perform and most satisfactory.

General Anaesthesia

Intubation. We prefer to intubate in every case; but we are well aware that all authorities do not acknowledge this to be the best procedure. One argument against it has been that deeper anaesthesia is needed for intubation; but this is not the case. There is no need for deep anaesthesia with the technique to be described.

As an alternative to intubation, special masks, such as those designed by Magill (Fig. 148) and by Hewer, enable towels to be arranged so that the anaesthetic need not in any way hamper the surgeon; but the complete freedom of airway under every condition afforded by intubation is a boon which it is impossible to exaggerate.

Cocainization of the larynx. Anaesthetization of the throat and larynx enables the patient to tolerate a tube under first-plane anaesthesia; it also makes easier the actual intubation. Spraying the nose also prevents bleeding

caused by passage of the tube: cocaine is an intense vaso-constrictor; when other anaesthetic agents are used a vaso-constrictor is added to the solution.

A 10 per cent. solution of cocaine hydrochloride, used in a fine spray, has for many years been found very satisfactory. The cocaine must reach the glottis. There are two methods of ensuring this:

1. The author's curved spray[14] (Fig. 149) which is passed either along the floor of the nose or through a Phillips airway (Fig. 150) to direct the anaesthetic solution directly on to the glottis. The patient is asked to take deep breaths whilst the bulb is squeezed. The spray is designed to be used with the patient lying flat. Malleable sprays have also been produced by Macintosh[15] and Kenton[16] which direct the solution on to the glottis.

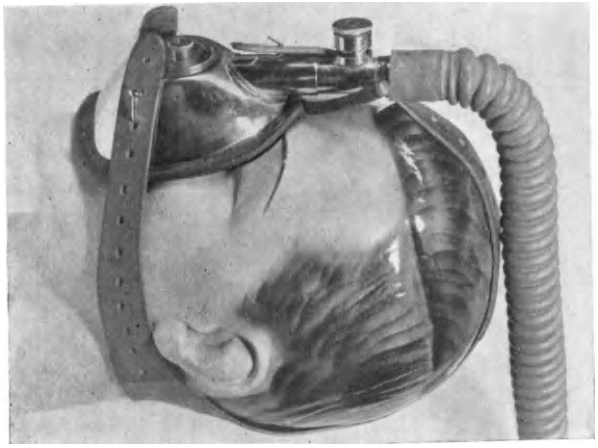

FIG. 148.—Magill's thyroid mask.

2. Spraying the solution down a Magill's tube which has been passed into the pharynx but lies just short of the glottis. This method is used after the patient is asleep and the spray is operated during inspiration only.

Special Groups

The following require consideration:

A. Simple goitre (non-toxic).
B. Toxic goitre.
C. Patients with respiratory obstruction.

A. **Simple goitre.** No one type of anaesthetic is specially indicated. Chloral with omnopon-scopolamine premedication, local infiltration and gas-oxygen by endotracheal tube is as satisfactory a combination as it is for toxic cases.

B. Toxic goitre. Toxic cases, primary or secondary, the latter often complicated by myocardial lesions, may present some of the most difficult problems with which an anaesthetist is called upon to deal. Nevertheless, since the introduction of thiouracil the hazards have been greatly reduced.

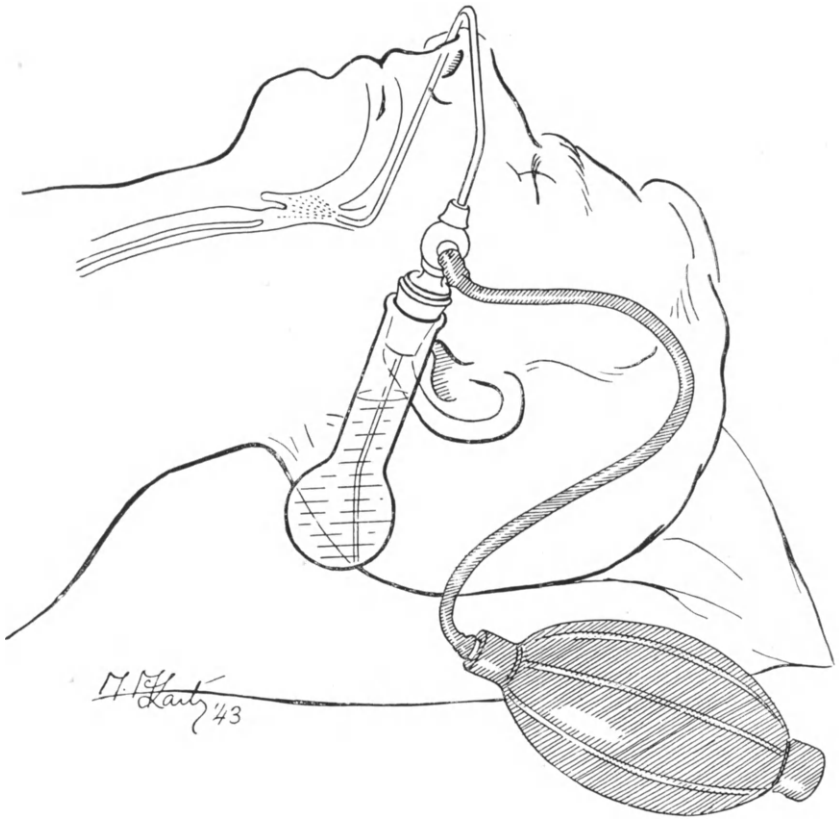

FIG. 149.—Diagram showing author's special spray in position for cocainizing the larynx.

There are three essential rules the observance of which is vital for the safety of these cases:

1. Anoxaemia, even in the slightest degree, must be avoided.
2. A perfect airway must be maintained throughout the operation. Even short periods of respiratory obstruction place a great strain on the heart.
3. An even plane of light anaesthesia (first or very early second plane) must be maintained.

The following procedure is recommended for toxic cases.[17] Premedication is carried out as already described. The patient is brought to the anaesthetic

room, with her eyes covered, fully half an hour before the operation. Local infiltration of the neck is then performed.

The throat and larynx are now cocainized, although this may be done equally well after induction. Anaesthesia is induced with a small intravenous dose of pentothal sodium (average 0·25 gm.). This is given slowly, the injection being stopped as soon as the patient is asleep. Depression of the respiration must be avoided.

An endotracheal tube, lubricated with 10 per cent. nupercaine ointment, is now inserted through the nose and into the pharynx. No attempt is made

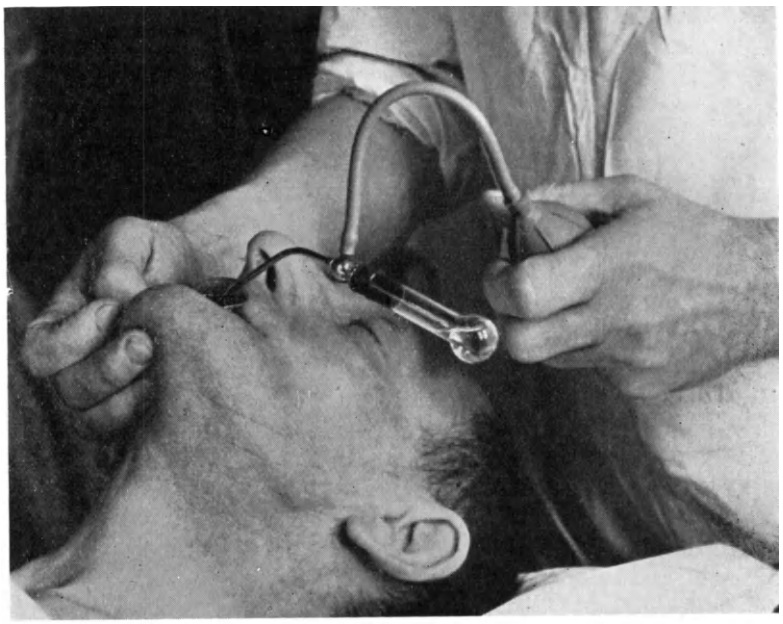

FIG. 150.—The larynx may be cocainized by passing the spray through an oral airway.

to intubate at this stage; but the anaesthetic is carried on with nitrous oxide-oxygen so that smooth, uninterrupted anaesthesia is maintained.

When the patient is breathing regularly and moderately deeply, blind intubation is carried out. If not successful at the first attempt the mask is re-applied. Sometimes a little carbon dioxide is added to the mixture. Only one or two attempts are made at a time and the mask is re-applied before the anaesthesia becomes light. Great care is taken to maintain smoothness of anaesthesia, and cyanosis is always carefully avoided.

Blind intubation is sometimes difficult when the trachea has been displaced from the midline, pulling, as it often does, the larynx with it. A study of the radiogram is helpful in showing the position of larynx and trachea. We have sometimes found it useful to push over the thyroid cartilage from the outside

whilst advancing the tube, so that the glottis is brought to the midline at the moment of intubation.

Occasionally it may be necessary to use a laryngoscope: as often as not this may be accomplished under gas and oxygen, but if the jaw is not sufficiently relaxed, ether should be added to the mixture rather than attempting to deepen anaesthesia by cutting down oxygen.

C. **Respiratory obstruction.** Patients may suffer from respiratory obstruction due to pressure on the trachea either in the neck or thorax. Whatever arguments may be raised against intubation in other varieties of goitre, there can be none here; intubation is a necessity. Without it, operation is fraught with the greatest danger from respiratory obstruction. Often the patient suffers from extreme dyspnoea and comes to the theatre cyanosed and unable to lie flat. There are two problems in such cases: induction and intubation.

Heavy premedication is contra-indicated. The more advanced cases are given a hypodermic injection of one-hundredth of a grain of atropine only; those cases not so severely obstructed receive in addition one-thirtieth of a grain of omnopon per stone of body weight. Before induction, it is beneficial for the patient to breathe oxygen for half an hour.

The larynx and throat are well sprayed with 10 per cent. solution of cocaine hydrochloride. Induction should be rapid; struggling must be avoided if possible. The patient is placed in the position she finds most comfortable, generally propped well up. A small dose of pentothal sodium intravenously, sufficient only to produce unconsciousness, is followed by cyclopropane-oxygen. The extra pillows are now removed and intubation is performed. The tube should be of good size, new and thick-walled; it must be long enough to extend beyond the obstructing goitre and be sufficiently rigid to maintain a clear airway.

Intubation may be carried out "blind", via the nose, or by direct vision. In obstructed cases we prefer the latter. It is positive and certain, whereas an attempt at blind intubation may result in delay, especially in those cases when the larynx has been pushed to one side by the goitre. Spasm of the glottis may also result and it is a serious matter in this type of patient. Occasionally it is so difficult to push the tube through the narrowed trachea, that it has to be advanced inch by inch, gripping it with Magill's forceps.

An X-ray of the neck (Fig. 151*a* & *b*) will have been studied beforehand, the site of obstruction determined, and an estimate made of the distance necessary to pass the tube. This must be well beyond the obstruction. Such obstructions do not involve the bronchi, but the trachea may be bowed in its whole length and it may be necessary to pass the tube almost to its bifurcation. Care must also be taken not to push it too far, i.e. into one of the bronchi. To be certain this has not occurred one should listen with a stethoscope and make sure there is full air entry to both lungs. When the tube has been correctly placed the excess length is cut off and it is connected up with the anaesthetic apparatus.

After operation a suction catheter may be passed down the tube to clear the trachea and bronchi of secretions or blood. The tube should be removed

slowly, inch by inch, the anaesthetist meanwhile listening to the breathing, to verify that the airway has remained patent. In some cases following compression by a goitre, the trachea collapses when the support afforded by the endotracheal tube is removed: when this happens it should be replaced immediately and the patient sent back to bed with the tube *in situ*. Attempts at withdrawal may be made later—when in most cases the trachea will remain patent; but the withdrawal should be cautious and the anaesthetist should be at hand to replace it if necessary.

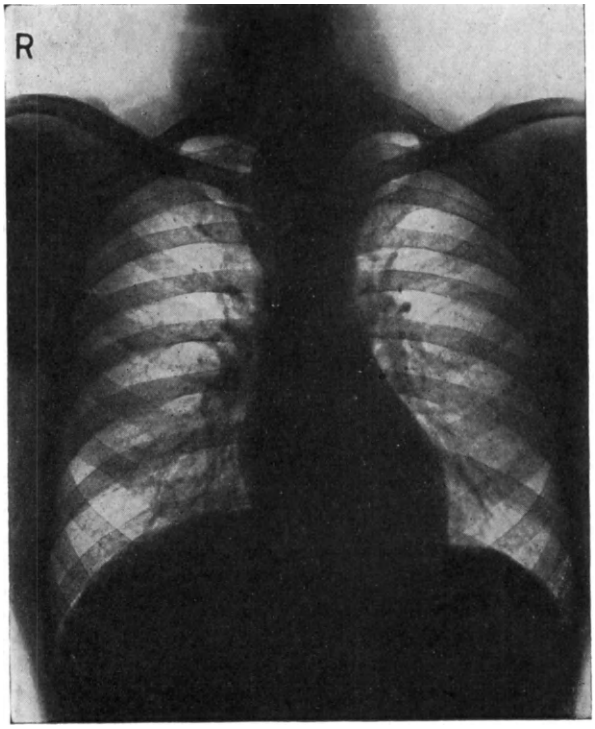

FIG. 151a.—X-ray showing trachea pushed to right by a large substernal goitre.

Cases have been reported in which partial collapse of the trachea has occurred some hours after operation, the airway having remained patent when the tube was removed in the operating theatre. Re-insertion of an endotracheal tube or tracheotomy is necessary if the obstruction is severe.

Emergency operations. Emergency operations do not occur often in goitre. They are always for the relief of urgent respiratory obstruction. There are two occasions when they may be necessary:

1. In colloid goitre. Rapid increase of colloid in a young person with a soft trachea.

2. Haemorrhage into a cyst of the thyroid.

The patient may be *in extremis*; unconscious and very cyanosed. Obviously in such a case no anaesthetic is needed; but the anaesthetist may, by intubating, save the patient's life. Emergencies occur which have not reached such a desperate state. They should be intubated always and regarded as serious anaesthetic risks.

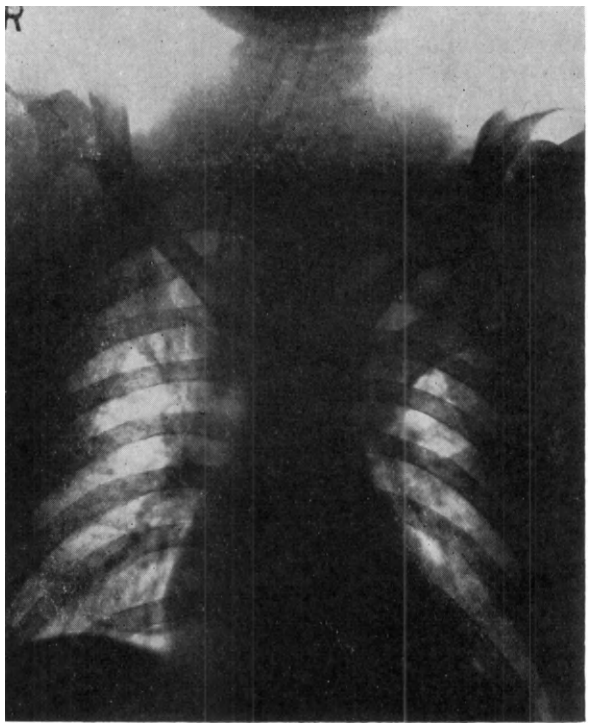

FIG. 151b.—The same with endotracheal tube in position.

Recurrent laryngeal nerve paralysis Certain cases of goitre develop pressure paralysis of a recurrent laryngeal nerve. This produces abductor paralysis of the corresponding vocal cord. It is usually symptomless and is only discovered during routine examination of the larynx. Paralysis of a cord may cause difficulty in two ways during induction of anaesthesia:

1. **By spasm.** Such cases appear to be specially liable to develop spasm of the glottis during induction. It is a wise precaution to spray the cords particularly well, beforehand. Pentothal should be given in minimal dose: and when intubating the patient, the anaesthetic should be carried well into the second plane before attempting to pass the tube.

2. **During " blind " intubation.** The paralysed cord is unable to move out during inspiration (at a later stage of paralysis it may be drawn across the midline by overaction of the adductors) and it often obstructs the passage of the tube through the glottis. This, of course, is only the case when intubating by the blind method. In these cases it is better to intubate under direct vision.

Patients with a tracheotomy. In certain cases of malignant disease of the thyroid when the growth has severely compressed the trachea or ulcerated

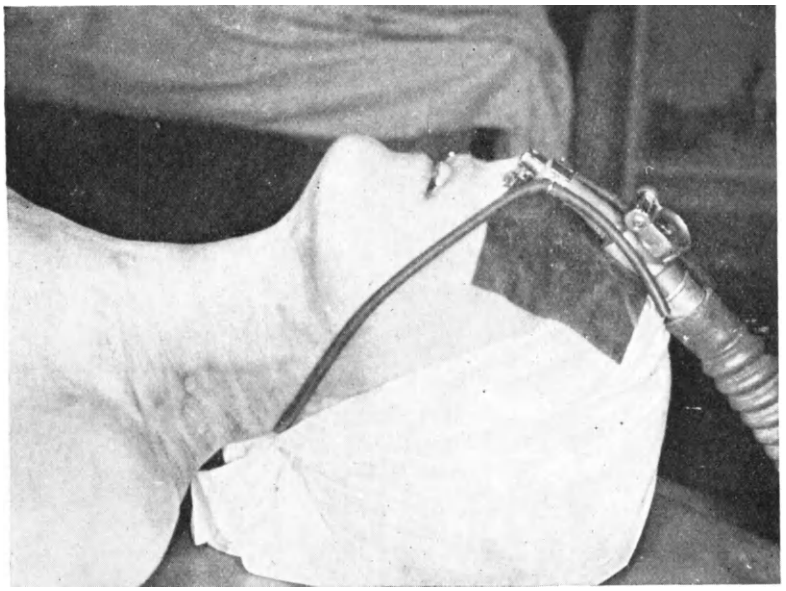

FIG. 152.—Oiled silk is placed over the eyes.

into its lumen, low tracheotomy is necessary. In such circumstances special arrangements must be made for administering the anaesthetic.

A short length of rubber tube which will just pass through the outer tracheotomy tube is fitted with a curved angle piece. After induction this tube replaces the inner tracheotomy tube and is connected with the gas-oxygen apparatus.

When the patient has been anaesthetized and intubated, the endotracheal tube is connected with an anaesthetic apparatus. In goitre operations there is no need for a special type; any modern gas-oxygen machine will serve the purpose. The tube may be held in position by strapping or by a special harness. The most satisfactory method appears to be a length of round elastic placed below the occiput and fastened to hooks on a ring round the rubber connecting tube.

The eyes (Fig. 152) of the exophthalmic patient must be protected from injury during operation. Sterile paraffin is instilled and they are covered with

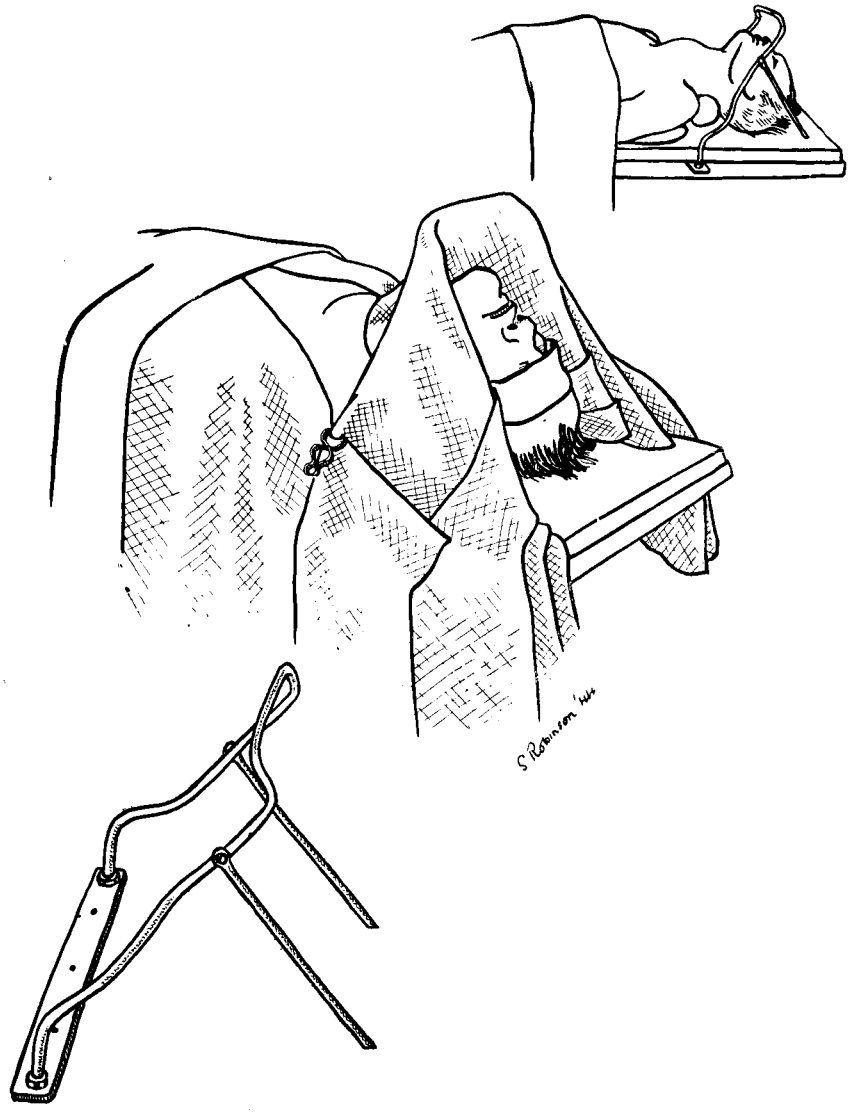

FIG. 153.—Author's screen for use with local anaesthesia.

a piece of oiled silk. In extreme exophthalmos or if the cornea be ulcerated, the eyes are closed with elastoplast or by a fine stitch through the edges of the lids.

When the operation is performed under local anaesthesia alone, the patient is blindfolded, the ears are plugged with vaseline wool, and the towels arranged over a low frame. The screen illustrated (Fig 153) is rigid and will not collapse even if leaned upon.

Blood pressure and pulse readings should be recorded by the anaesthetist at five-minute intervals. The systolic blood pressure and the pulse rate are the best guides to the patient's condition. A falling systolic pressure and a rising pulse rate should be regarded with alarm. Whilst controlled auricular fibrillation does not greatly increase the risk of operation, if it becomes associated with tachycardia, acute myocardial failure may supervene.

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CHAPTER XXVI

THE OPERATION OF THYROIDECTOMY FOR THYROTOXICOSIS

Principles and Practice of Thyroidectomy — Revisor's Preliminary Note — Certain Points in the Technique of Resection for Recurrent Thyrotoxicosis — Position of Surgeon and Assistants — Instruments — Incision — Division of Infrahyoid Muscles — Separation of Muscles from Gland — Ligation of Middle Thyroid Veins — Dislocation of Lateral Lobe — Ligation of Inferior Thyroid Artery — Of Inferior Veins — Continuation on Right Side — Resection of Gland Tissue — Completion of Haemostasis. Thermo-electric Methods. Wedge-resection. Testing Haemostasis — Closure of Wound — Drainage — Dressings.

Principles and practice of thyroidectomy. 1. The aim of the operation is to resect a sufficient portion of the hyperactive gland to reduce the production of thyroid hormone to within normal limits. This must be done with a minimum risk to life and of complications leading to chronic disability. The three principal complications are tetany, recurrent nerve injury, and cachexia strumipriva.

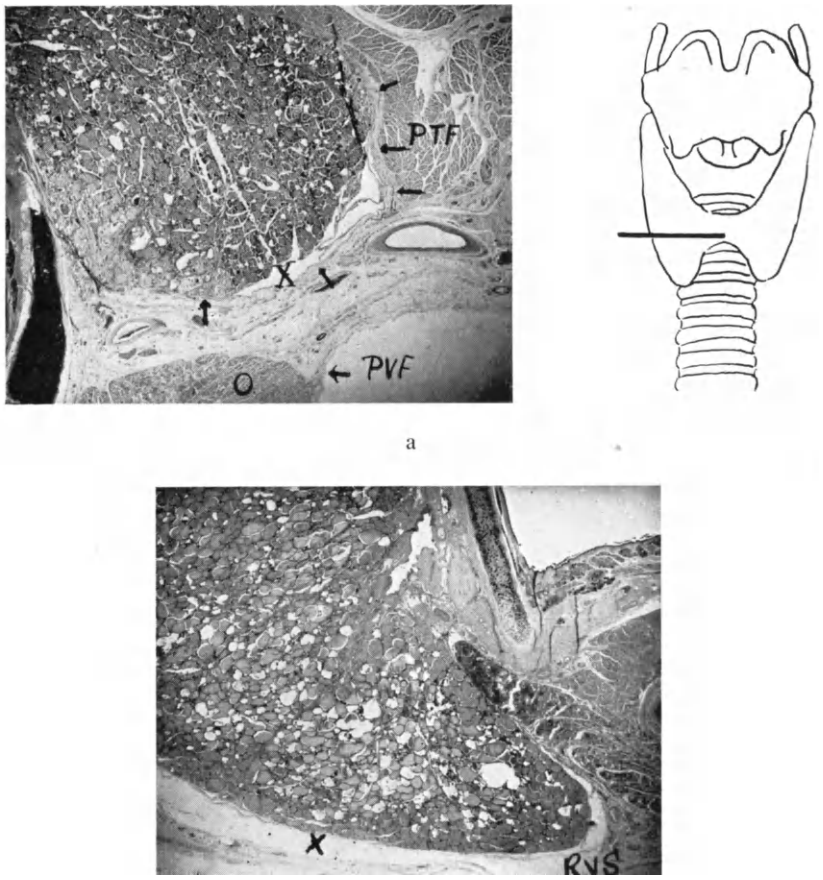
2. All the preliminary steps, adjusting the patient's position, incising the skin and reflecting the flaps, dividing and widely retracting the prethyroid muscles and fascia, are aimed at achieving complete exposure of the gland and its vessels of supply. Free and easy exposure makes for effective haemostasis and gentle manipulation, and hence minimizes the risk of injury to important structures nearby in the neck; it also allows an accurate and deliberate assessment of where the gland should be sectioned.

3. The accent throughout is on the prevention of complications; the antero-lateral false capsule of the gland (pretracheal fascia) is reflected and preserved to prevent injury to or removal of the parathyroid glandules. The upper pole is carefully delivered from its capsule and the superior vessels cleaned and doubly ligated by techniques that avoid injury to the superior laryngeal nerve and its external laryngeal branch. Gentle handling and early and accurate control of the vessels of supply prevent primary haemorrhage and shock. Early identification of the trachea, exposure of the recurrent laryngeal nerves, and identification of the parathyroid glandules minimize risk of damage to these important structures. Similarly, ligation of the inferior artery at a distance from the gland lessens the risk to branches of the recurrent nerve. Its ligation also reduces the incidence of recurrent thyrotoxicosis.

The plane in which the surgeon's forceps must dissect is indicated by crosses in Figs. 154 *a* & *b*. Intracapsular mobilization and delivery of each lateral lobe is essential to a safe technique.

Revisor's preliminary note. The text of this chapter is virtually unchanged from that in the first edition. Up to his untimely death, the original author

used the technique here described in over 9,000 thyroidectomies. The only modifications noticeable in later years were that he did not divide the infra-hyoid muscles, unless the goitre was especially large, adherent, or infiltrating, and that he dispensed with routine draining of the wound.



a

b

FIG. 154a and b.—Showing the pre-tracheal fascia (P.T.F.) in relation to the posterior surface of the lobe at the level of the isthmus. The ' X ' marks the potential space in which the surgeon's finger-tips work in the process of dislocation of the lobe. The prevertebral fascia (P.V.F.) is shown passing posterior to the margin of the oesophagus (O). (× 7.)

It will be noted by the reader that Joll's technique largely commits the surgeon to completing the removal of both lobes at the first operation, and this was of course his almost invariable practice. Moreover, in many respects the method is only well-suited to the surgeon who is a master of general technique and of thyroidectomy in particular.

For those who prefer to be able readily to limit the scope of the operation, it is generally better to section the first lobe as soon as its vessels of supply have been cleared and ligated. If this is done the gland may be resected as far as the isthmus only, and the second lobe left till another occasion. Other modifications favoured by the revisor are: (i) Division of the deep cervical fascia along the anterior borders of the sternomastoid muscles in the infrahyoid region, which immediately allows the goitre to come forwards, and facilitates complete section of the infrahyoid muscles. This technique is also employed by Lahey (1944b) and Heyd (1947).

(ii) Complete division of the infrahyoid group of muscles in all except single nodule operations. The incision through the muscles should be inclined upwards towards the superior pole on each side, thus facilitating access to the latter (Fig. 155). Such high division of the infrahyoids must improve access, is a trivial addition to the operation, and results in no disability. Lahey (1944b, 1947) divides these muscles routinely.

(iii) Gentle intracapsular dissection of the upper pole. The superior vessels are carefully cleared and doubly ligated, the ligatures being passed from the inner side to avoid injury to the external laryngeal nerve. A haemostat is left on the glandular ends. Roeder (1932) and Eades (1936) emphasize the importance of intracapsular dislocation of the upper pole. Only if the upper skin flap is reflected very high and the muscles divided can this be clearly done under vision. Coller and Boyden (1937) and Dixon (1937) deliberately divide the superior ligament of the gland in order to enter the crico-thyroid space. If the pole is now drawn laterally the external laryngeal nerve may be seen and dissected medially (Vandenberg, 1944). The usual mistake is to aim at the vessels too low down. Rogers (1929) has pointed out that the superior artery may divide high up and the posterior branch pursue a relatively independent course to the posterior aspect of the gland. If dislocation of the upper pole causes restlessness the tissues may be infiltrated with local anaesthetic solution (Dinsmore, 1937).

(iv) Resection of the superior pole and deliberate division of the superior thyroid ligament between ligatures.

(v) Resection of the whole of the pyramidal lobe as a routine. This is also advocated by Lahey (1944b), Kent and Sawyer, (1945) and Sandlin (1946), *inter al.*

(vi) Routine dissection and identification of the recurrent laryngeal nerves and inferior parathyroids, and ligation in continuity of the inferior thyroid artery just after it emerges from behind the carotid sheath. The inclusion of nerve fibres in the ligature must be scrupulously avoided. Damage to vagal and sympathetic branches at this point has been reported (Fischer, 1947).

Haemorrhage must also be avoided at this stage. Should it occur, it must be controlled by pressure or accurate seizure of the bleeding vessel. On no account should a mass of tissue be blindly grasped with the haemostats and ligated. Joll for many years advocated ligation of the inferior artery, a

step which does much to minimize recurrent nerve injuries and the recurrence of thyrotoxicosis. To Lahey (1939 and 1944a) belongs the credit for advising routine exposure of the nerves. The nerve can often be felt before it is seen and the same is true of course for the artery.

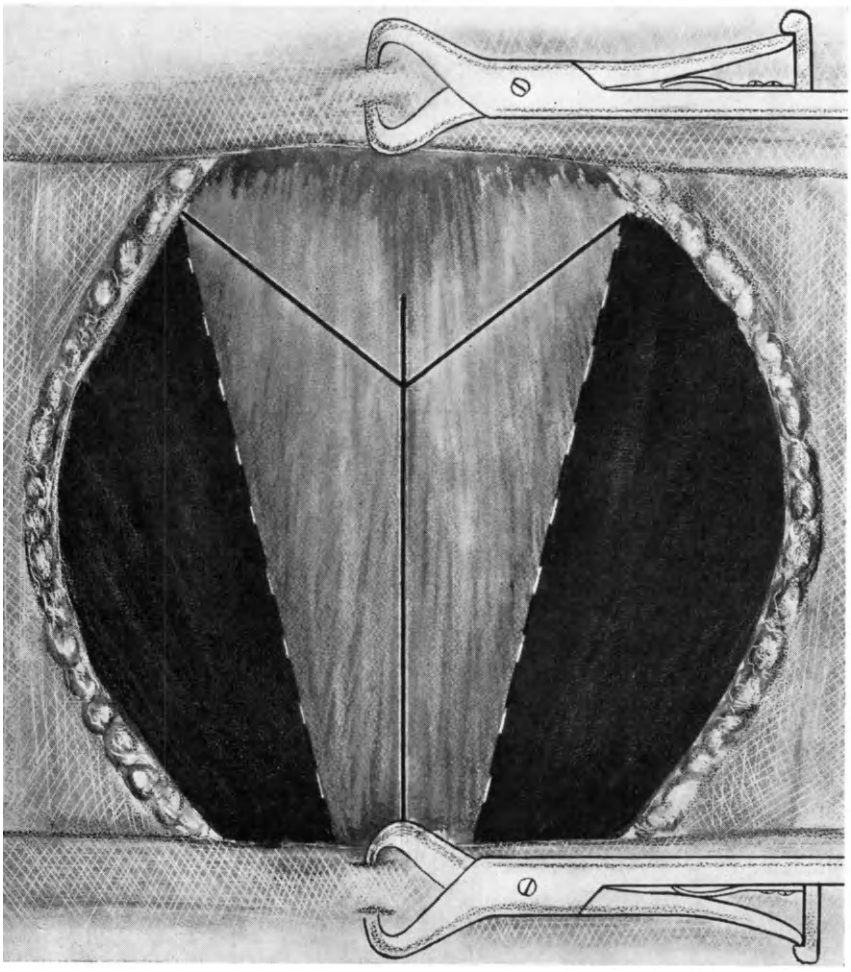


FIG. 155.—The deep fascia is incised along the anterior border of the sternomastoid muscles. A Y-shaped incision is then made through the infrahyoid muscles.

(vii) Section of the lateral lobe between small haemostats. Even though the superior and inferior arteries have already been tied, this will further reduce primary haemorrhage from anastomotic tracheal vessels. When approaching the trachea, the haemostats should be applied from within

outwards. To facilitate this the isthmus should first be lifted up from the front of the trachea and divided. This is readily done in the mid-line where the two are connected by only loose and delicate connective tissue (Fig. 156).

(viii) Constant reference to such important landmarks as the prominence of the inferior crico-thyroid articulation, and the trachea itself. The recurrent nerve enters the larynx below and behind the crico-thyroid articulation and in removing the upper pole it is essential to keep any haemostats anterior to this cartilaginous prominence. If the trachea is cleared early it will serve to keep the surgeon orientated throughout the operation.

(ix) Avoidance of deep stitches in the thyroid stump, for these involve great hazard to the recurrent nerve. Capillary haemorrhage can be controlled with oxycel, while larger vessels can be picked up and ligatured. A

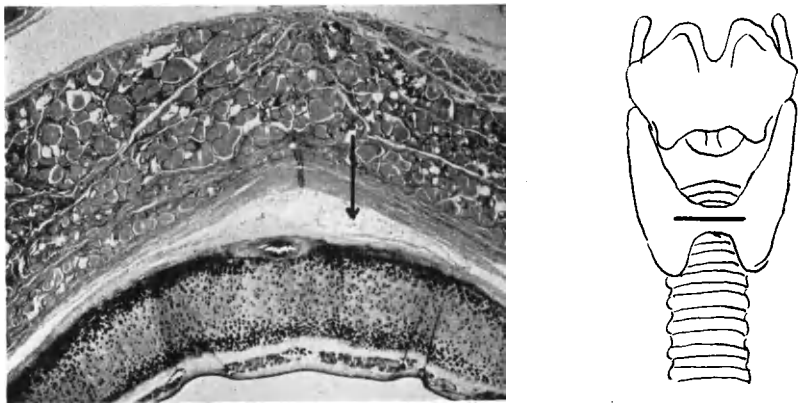


FIG. 156.—Isthmus and anterior aspect of the trachea. Note the loose fibro-fatty tissue intervening between them which enables the isthmus to be mobilized and transected if necessary. (× 7.)

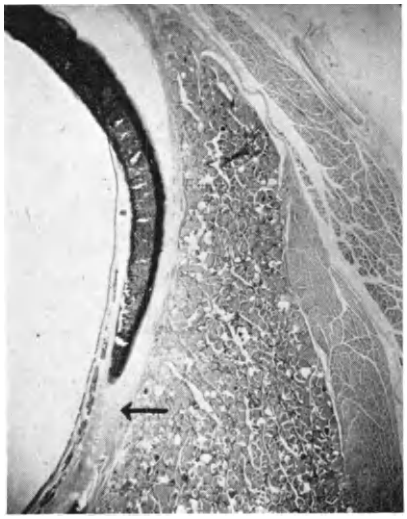
series of fine atraumatic sutures is then passed through the *outer* edge of the cut surface of the stump and sewn to the tracheal fascia. Thus the raw surface of the stump is turned in and applied to the lateral surface of the trachea.

(x) Fine cotton ligatures and sutures are used throughout, since these excite a minimum of reaction and exudate in the tissues and thus promote quicker and sounder healing (Meade and Ochsner, 1940).

(xi) Drainage through the lateral ends of the wound by tubes piercing the sterno-mastoid muscles after all operations for recurrent goitre and others in which much post-operative oozing is thought possible.

Whatever technique is used for thyroidectomy, careful planning of the operation in steps is essential if skill and precision are to be attained. It should be emphasized too that with modern methods of preparation there is no longer any need for a speedy technique. The revisor's standard technique for subtotal thyroidectomy is summarized in the following steps:

1. A low curved transverse incision with very high elevation of the upper skin flap.
2. Incision of the deep fascia along the anterior borders of the sternomastoids and high, complete Y-shaped division of the prethyroid muscles.
3. Ligation and division of the superior thyroid vessels above the upper poles.
4. Complete mobilization of the lateral lobes.
5. Visualization of the recurrent nerve, the inferior parathyroid glandule and the inferior thyroid artery, the last of which is ligated at a distance.



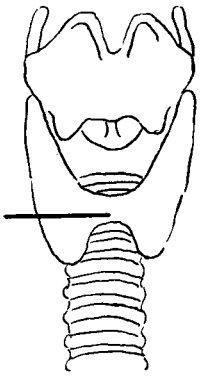


FIG. 157.—Note the strong fascial connexions between the lateral surface of the trachea and lateral lobe of the thyroid (the " lateral thyroid ligament"). During thyroidectomy, the lobe is swung about this point as a fulcrum. (× 7.)

6. Section of the lateral lobe between haemostats.
7. Mobilization of the isthmus.
8. Control of haemostasis.
9. Closure of prethyroid muscles, platysma and skin.

Certain points in the technique of resection for recurrent thyrotoxicosis. To the genuine cases of recurrence must be added those with *persistent* thyrotoxicosis in which an inadequate amount of gland has been removed at the previous operation. Whenever a second intervention is decided upon, it is important to determine in advance the exact status of vocal cord function. The existence of an immobile cord may sway the decision against further surgery. In any case it will emphasize the need for exposing and conserving the nerve on the functioning side. Even with this precaution temporary tracheotomy may be a wise step (Cattell, 1948).

Both sides of the neck should be explored even if a regrowth of tissue is palpable on one side only. This ensures that any deeply placed gland fragment will be found and dealt with.

The previous skin incision and subjacent scar tissue should be excised down to the deep fascia. Even in making this incision, care should be exercised since a minimum of tissue may overlie the carotid sheath including the internal jugular vein. The latter may be displaced and even adherent to the side of the trachea.

The anterior borders of the sternomastoids should be defined and retracted laterally. This is best done by commencing at some distance from the adherent scar tissue and working through it until complete separation is achieved.

The infrahyoid muscles are carefully freed from the trachea medially, the internal jugular vein laterally, and finally the gland remnants. It is a wise precaution to identify and, in some measure, clear the trachea at an early stage and it is essential that the sternothyroid, as well as the sternohyoid, should be completely freed from the gland remnant. Indeed, as in primary operations, the surgeon should aim at working *within* the false capsule of the gland throughout.

Next the gland remnant is delivered. Middle thyroid veins may be encountered and will need to be ligated and divided. This will enable the carotid sheath and its contents to be retracted laterally. The main difficulties of the operation are now over.

The inferior thyroid artery is found and ligated where it emerges from behind the carotid sheath. The recurrent nerve is clearly identified throughout the relevant part of its course. The parathyroids are preserved by keeping intact as much as possible of the fascia posterior and inferior to the remnant.

Finally before proceeding to section the remnant the trachea should be further cleared and its precise location determined. Neglect of this precaution may result in its injury during secondary operations.

Resection must be drastic, no more than a " button " of gland tissue being preserved. Particular care should be taken to excise the pyramidal lobe, if it be present, and to explore for possible retrovisceral or retrosternal extensions of glandular tissue. Careful suture of the muscles is necessary to prevent an adherent scar, and the wound should always be drained.

Thyroidectomy for Toxic Goitre

By the late C. A. JOLL, M.S., F.R.C.S.

Position of surgeon and assistant. I prefer to stand on the right of the patient, with one assistant facing me and the other to my right. Only when operating on a very large left-sided goitre do I stand on the left side of the patient. In addition to the two principal assistants, who take a large share in haemostasis as well as in the ligation of vessels, four other assistants

are desirable: one of them is employed in handing artery-forceps to the surgeon and chief assistants, a second presides over the instrument table, another hands swabs to the chief assistant on the left side of the patient, and a fourth is available to hold retractors and to remove fragments of ligature material from the neighbourhood of the wound.

Choice of position of patient during operations on the thyroid. My own custom is to have the patient lying horizontally, with a small, firm sand-pillow placed beneath the shoulders to allow extension of the neck on the thorax, and a smaller cylindrical pillow under the neck to secure adequate extension of the neck itself (Fig. 158). The head is allowed to embed itself slightly in a softer pillow. By a suitable combination of these pillows it is

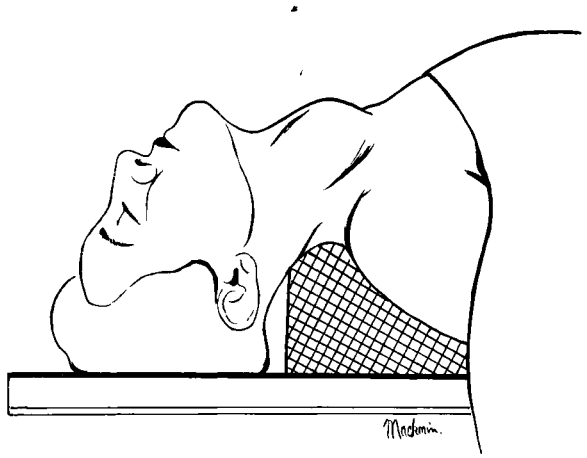


FIG. 158.—Showing the patient's position on the table for thyroidectomy. The neck should be extended and the chin drawn well up.

possible to secure a comfortable position for the patient and also to obtain adequate surgical exposure.

Alternative methods, such as the reversed Trendelenburg position with a special head-rest, are used by de Quervain and other surgeons, and are undoubtedly valuable when grave pressure symptoms exist, but they have certain drawbacks, the chief being that a special table has to be reserved for thyroid operations, which is a disadvantage in a general surgical clinic. The advocates of the reversed Trendelenburg position and of the semi-sitting posture assert that haemorrhage is lessened, owing to the diminished congestion of the head and neck in this posture, but in the majority of cases the difference is small, and I find that access to the deeper parts of the wound low down in the neck is somewhat hampered.

Instruments used in the operation. The choice of instruments must inevitably be a matter for the individual surgeon, but it is perhaps worth while to emphasize the necessity for providing a very large number of

efficient artery-forceps of good design. It is my custom to have six dozen pairs of these artery-forceps available for every goitre operation. The pattern I find most satisfactory is one with rather fine, straight jaws, which are serrated for the terminal $\frac{3}{4}$ in. only, and not throughout their length. Such forceps permit extremely accurate haemostasis, and if provided with box-joints wear for years without developing any tendency to "scissor action" when an extra strain is thrown upon them. They should be not less than $5\frac{1}{2}$ in. in length, and should have specially large finger-loops in order to facilitate rapid handling. One assistant being deputed to hand artery-forceps to the surgeon and to both his chief assistants as may be needed, with the organization which I have described above, it is very rarely necessary for the surgeon or principal assistants to have to ask for an instrument.

Instruments which are highly important:

(1) *A special Self-retaining Goitre Retractor.* My special goitre retractor produces a satisfactory exposure for all classes of goitre and does not exhibit the irritating tendency to slip possessed by many retractors which depend on the action of a ratchet.

(2) *Angled Retractors* of several sizes are necessary for drawing aside the infrahyoid and sternomastoid muscles, particularly during the ligation of the inferior thyroid artery. The special retractor for this purpose should be hollowed out in such a way that the artery can be isolated and, at the same time, the contents of the carotid sheath and the overlying muscles retracted.

(3) A *Gland Enucleator*, or blunt director of Kocher's pattern, is almost indispensable for the ligation of the superior poles, and is helpful in many stages of the operation.

(4) *A set of three Aneurysm Needles* should be included: the smallest is used for ligation of the smaller veins and of the inferior thyroid artery; the intermediate size suffices for the larger thyroid veins; and the largest instrument should be utilized for ligation of the superior pole, in conjunction with Kocher's gland enucleator described above.

In addition to these instruments the ordinary dissecting instruments are necessary, and straight and curved scissors of Mayo's pattern are helpful.

I. **The incision.** The object which the surgeon has in mind in making the incision is to get satisfactory access with the best possible cosmetic result. The two desiderata are to some extent antagonistic, so that in certain cases a compromise between them may have to be adopted. In the case of very large goitres and especially in malignant ones, an incision which aims strictly at cosmetic results will unduly hamper the surgeon in obtaining adequate exposure of the tumour to be removed. In the majority of cases, however, the most satisfactory incision is one which I am in the habit of describing as the "necklace incision," for the reason that it corresponds to the level at which a closely-adjusted necklace lies. This level can be accurately marked out on the individual patient by means of a trial necklace; but for practical purposes the line can be visualized in all but very large or

irregular goitres, and it is in these cases that any preliminary attempt to mark it out usually fails. The line of the incision is slightly convex downwards, reaches to within ¾ in. of the suprasternal notch, follows the general line of the clavicle on each side, and extends outwards as far as the jugular vein (Fig. 159). If this line is adopted it must be visualized, or marked out with sterile carbol-fuchsin and pen nib before the neck is fully extended;

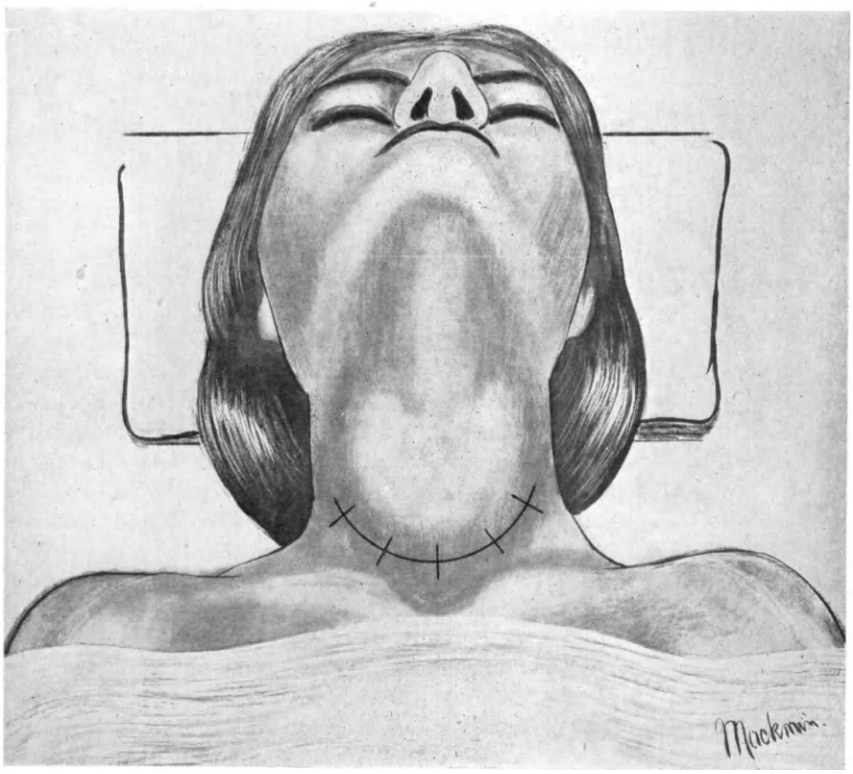


FIG. 159.—The line of the incision is carefully marked out with a solution of carbol-fuchsin. It is placed about ⅞ in. above the sterno-clavicular joint margins so that the neck is no longer hyperextended it drops down to their level.

otherwise, when the normal position of the head and neck is resumed it will be found that the incision has been made at too low a level, and the scar will come to lie over the upper part of the manubrium sterni, where it is undesirably conspicuous. In operations for exophthalmic goitre the incision should be of the full length from one external jugular vein to the other, and may be extended a little beyond these limits in specially difficult cases.

In operations for adenomatous goitre, especially when one of the nodules is exceptionally prominent, the incision should be made at a rather higher

level on the more protuberant side, as only by this means is it possible to obtain a symmetrical scar when the bulky underlying tumour has been removed. If this modification is not made the scar tends to be asymmetrical, lying lower down on the side corresponding to the larger tumour.

In operations for very small adenomata, and especially for thyroglossal cysts and tumours, the length of incision can be considerably reduced, but there is in my opinion little object in attempting to carry out the more extensive operations on exophthalmic and other goitres through a short incision, as it is a continual hindrance to the surgeon throughout the necessary manipulations. It is almost invariably found that the lateral portions of the scar are really less conspicuous than the median, so that it is a matter of trivial importance from the cosmetic point of view whether a short or a long incision is made, though to the surgeon it is, of course, often of prime importance.

As a preliminary, a series of lines with the point of the pen nib at right angles to the line of the projected incision provides a means of accurate suture of the skin flaps (Fig. 159).

In carrying the knife through the tissues it is very important to keep the blade at right angles to the surface throughout the incision. This applies more particularly to the right-hand extremity, which, if the surgeon is right-handed, is, of course, the last portion of the incision to be made. There is a great tendency for the inexperienced to incline the knife-blade upwards and thus to bevel the skin-edge in this region; this may be followed by a hypertrophied or puckered scar. The incision should be carried through skin, superficial fascia, and platysma; a flap is then raised by dividing the areolar tissue between the platysma and the deep fascia. Special care is necessary to maintain the dissection in this plane, for if the deep fascia is incised damage may be done to the anterior jugular vein, lying in close contact with its surface; this may lead to considerable loss of blood and to delay at a stage when it is particularly undesirable. The presence of the local anaesthetic fluid, while it may embarrass the surgeon who is not accustomed to it, is really helpful in following the correct plane of cleavage, as a certain amount of the fluid is usually forced into the several fascial spaces, which are thereby more clearly defined. It is important, as the dissection of the flap proceeds, to control a number of small arteries and veins which are particularly numerous along the line of the anterior border of the sternomastoid muscle. The reflection of the flap is facilitated, once it has been begun, by grasping it forcibly with a piece of gauze and drawing it, upwards and outwards, away from the underlying tissue. The correct fascial interval is thus made obvious and the knife can be used with greater freedom (Fig. 160).

The flap should be raised, in the majority of cases, as far as the upper border of the thyroid cartilage. In operating on small adenomata it may not be necessary to proceed beyond the level of the crico-thyroid membrane, but with malignant goitres and with large thyrotoxic and simple goitres it is often desirable to reflect the flap as far as the hyoid bone.

The lower edge of the incision should also be undercut for a short distance near its middle part. This is done merely to provide a satisfactory hold for the mechanical retractor and to permit the separation of the infrahyoid muscles right down to the upper edge of the manubrium sterni. It is not

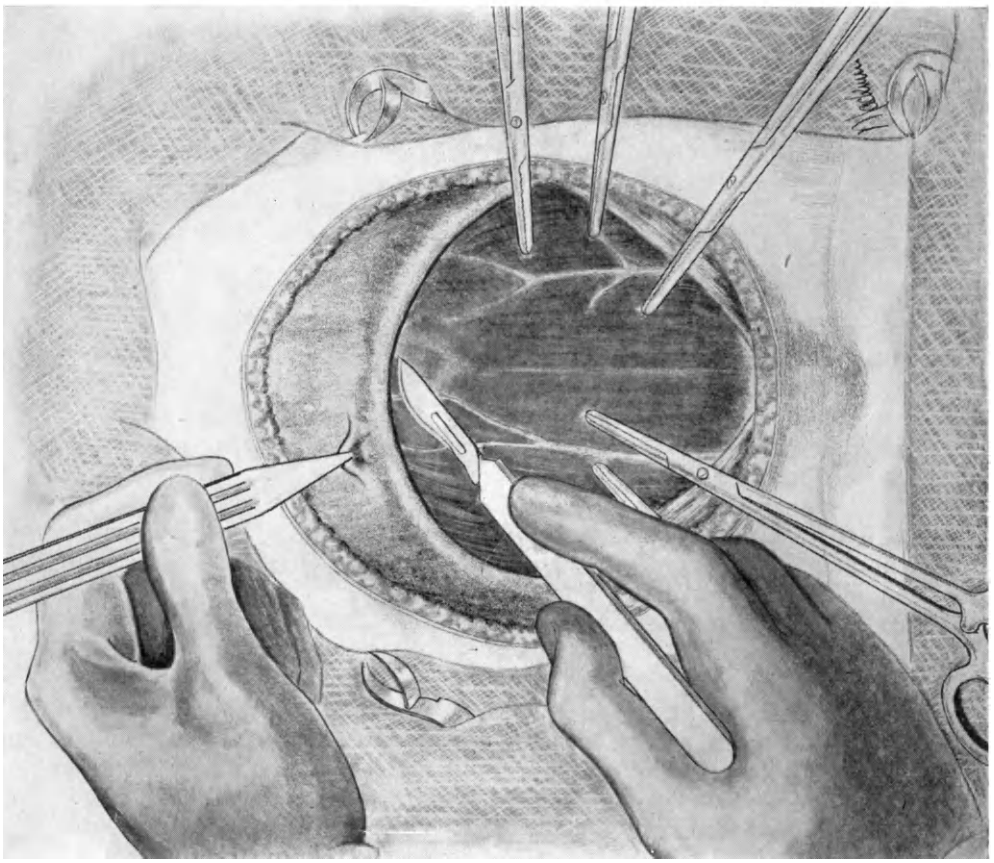


FIG. 160.—Reflection of the upper skin flap, deep to the platysma. It should be raised very widely to guarantee complete freedom of access to the upper poles.

necessary to undermine the tissues downwards towards the lateral extremities of the incision.

II. **Exclusion of operation area from surrounding skin surface.** Small aseptic towels are now clipped to the edges of the wound, and the mechanical retractor is adjusted to the desired position. It is important to see that

the upper claw of the retractor takes a grip of the flap as near as possible to the thyroid cartilage, so that the maximum exposure of the infrahyoid muscles may be obtained before they are divided.

III. **Division of the infrahyoid muscles.** Considerable difference of opinion exists as to the necessity for the transverse division of the infrahyoid muscles. Some surgeons prefer to make it a routine practice, while others employ this step only in cases of special difficulty.

The advantage of the method is that it provides a much freer exposure of the lateral aspect of the lobes and therefore facilitates the ligation of the middle thyroid veins and the dislocation of the thyroid lobes. Any risk of damage to vascular structures, or to the thyroid tissue itself in cases where this is especially firm or friable, is reduced to a minimum. My own practice, for all exophthalmic goitres and for intrathoracic and malignant goitres, is to make a free transverse division of the infrahyoid muscles at the level of the upper border of the cricoid cartilage, carrying the incision outwards as far as the anterior border of the sternomastoid, and to be prepared to divide some of the fibres of the latter in cases of exceptional difficulty. The disadvantages of this incision are few, for, although it is necessary to spend a few moments in suturing the muscles afterwards, any disability which results is, as far as I can determine, negligible: the muscles appear almost invariably to heal satisfactorily and to carry out their normal functions. I have repeatedly examined these muscles in secondary operations on the thyroid gland and found no evidence of serious atrophy, or of cosmetic or other defects.

In most cases of colloid goitre and in many adenomata transverse division of the muscles is unnecessary, because the gland itself is so soft or elastic that it can be coaxed out from between the muscles if these have been freely separated in the middle line. In all cases, however, where inflammation or malignant infiltration of the peri-thyroid tissues exists, free division of the muscles is imperative.

Whether divided transversely or not, the muscles should be separated vertically as far down as the manubrium sterni, starting above from the lower border of the thyroid notch. In making this incision it is often impossible to avoid one or both of the anterior jugular veins, which frequently lie very close together in the middle line, and it is wiser, therefore, to ligate them at this stage. At the lowermost part of the incision a transverse communicating branch between the two anterior jugular veins is commonly encountered. This should be secured by two pairs of artery-forceps before division, and it is usually best to replace these two forceps by ligatures at an early stage of the operation, otherwise the handles of the forceps tend to lie over the field of operation and to incommode the surgeon throughout the later stages. Furthermore, should the pressure forceps be accidentally torn from these veins, air may be sucked into the circulation. In general, it is better not to interrupt the operation for the purpose of ligating the vessels secured by the various artery-forceps, but to delay this until the goitre has been removed. Exceptions to this general rule are made whenever it is

found that artery-forceps have been applied which cannot easily be held aside out of the field of operation by one of the assistants.

In making the transverse incision of the muscles it is better, I think, to pick them up with the dissecting-forceps and divide them with the knife or scissors, securing the various vessels as one proceeds, rather than to adopt the method which is frequently recommended of grasping these muscles with crushing-clamps. In the latter case the handles of the clamps constantly embarrass the surgeon, whereas if artery-forceps are placed on the individual vessels they fall aside comfortably when the muscles themselves have been freely divided. In addition to this, even though the crushing-clamps control the bleeding-points during the operation, when they are released for the suture of the muscles bleeding-points have to be picked up, and no time is saved; on the contrary, the temporary occlusion which such clamps afford may sometimes be followed by recurrent haemorrhage as a result of the rising blood pressure during the first few hours after the operation.

IV. (a) **Separation of the left infrahyoid muscles from the surface of the goitre.**

(b) **Ligation of the left middle thyroid veins.**

This is one of the most important and delicate stages of the operation. The actual separation is made between the true capsule of the gland and the covering layer of deep fascia, which for convenience is called the false or surgical capsule. This space is a potential one in the majority of goitres, and very great care is necessary to maintain the dissection strictly within this plane. In many cases it will be found that the infrahyoid muscles attach themselves firmly to the surface of the gland and, their colour being very similar to that of the underlying goitrous tissue, one is likely to leave muscle fibres behind and to attempt to carry out the dissection in a plane which is too superficial. This renders impossible the satisfactory definitions of the limits of the goitre, and also precludes easy dislocation of the tumour from its bed. On the other hand, if, in the endeavour to avoid the error just mentioned, the true capsule of the gland is penetrated, troublesome haemorrhage will occur from the thyroid tissue, and while this may not necessarily be a serious matter in the case of small or simple goitres it is one of the greatest technical mishaps in cases of exophthalmic goitre, for the damage so done may be impossible to retrieve by the usual haemostatic methods; if artery-forceps are applied to the gland under these circumstances they frequently fail to control the bleeding and, in fact, may often cause still further haemorrhage as a result of the damage inflicted by them on the vascular and friable tissue. For this reason I have made it a rule to avoid placing artery-forceps on the surface of the gland, particularly in exophthalmic goitre, preferring to tie the veins doubly by means of an aneurysm needle and to apply a finger to, or, better still, to press gauze over, any oozing surface.

As the infrahyoid muscles are separated from the lateral aspect of the gland, the assistant not only pulls them aside, but also lifts them slightly

from its surface with the retractor, in order to facilitate the division of the fine strands of connective tissue which pass between the true capsule of the gland and the layer of deep fascia which constitutes the false capsule. The surgeon meanwhile retracts the gland towards the opposite side, relying on a piece of gauze pressed against its surface for this purpose. As the dissection proceeds, the middle thyroid vein or veins are exposed, and on the accurate and early control of these vessels depends a great deal of the success and ease of the later steps in the operation. The veins vary much in size and position. It is not uncommon to find them entirely absent, in which case the separation of the corresponding lobe and its dislocation are usually simple matters. When middle thyroid veins are encountered great care should be taken in isolating them, so as to avoid damaging them in any way; if a middle thyroid vein is torn, the cellular tissues quickly become infiltrated with blood, and accurate work may be very much hampered. Having tested the various methods of controlling these veins, I prefer ligation with the aneurysm needle, even though the use of this instrument, as compared with artery-forceps, may involve a very slight extra expenditure of time in the conduct of the operation (Fig. 161). It will be found convenient to arrange that the chief assistant ties the ligatures in connexion with the left lobe and the surgeon those of the right. The aneurysm needle should first be passed near to the gland, and then again as far from the gland as possible, and when the second ligature is firmly tied the vein should be divided so as to allow a considerable length of vessel wall to project beyond the knot. By this means the risk of venous haemorrhage during and after thyroid operations is largely avoided; artery-forceps are far less satisfactory for this particular purpose, for under the best possible circumstances they may occasionally be torn off or otherwise displaced during an operation. When this happens grave haemorrhage may occur before the bleeding vessel can be secured.

V. **The dislocation of the lateral lobe of the gland.** It is usually easier to begin with the dislocation of the superior pole of the left lobe. This is done, after the ligation and division of all middle thyroid veins, by introducing the right forefinger behind the upper pole and levering it downwards and forwards with a sweeping movement. Some difficulty may be experienced in this manoeuvre in cases of exophthalmic goitre owing to the rigidity of the gland, and also in colloid and nodular goitres because of the extent to which the upper pole may pass behind the larynx and pharynx. All traces of muscle and fascial tissue must be separated from the anterior and lateral aspects of the superior pole before an attempt is made to carry out this dislocation, but if the separation has been effected carefully it will be found that, however large the gland, it can be completely drawn forward into the wound and fully displayed. Once the pole has been dislocated, Kocher's blunt director should be insinuated between the larynx and the gland and made to emerge on its outer side. In this way the upper pole of the gland, with its vessels, comes to lie superficial to the instrument, and the largest aneurysm needle, carrying a strand of No. 3 chromicized catgut,

or of No. 2 China twist silk, should be passed along the groove in the director either by the assistant or by the surgeon. The assistant now gently draws the gland downwards with one hand and retracts the muscular tissue upwards. The ligature is tightened, and, owing to the conical shape of the superior pole, it automatically slips upwards and secures the vessels exactly at the point where they enter the thyroid tissue. At the moment when the first knot is tied, the assistant should relax the tension on the gland so as to enable the knot to be made absolutely fast. It is desirable to use three hitches for this very important ligature. Its ends should be left long and secured with a pair of artery-forceps, as this allows rapid access to the upper pole should difficulties arise later with haemostasis in this region.

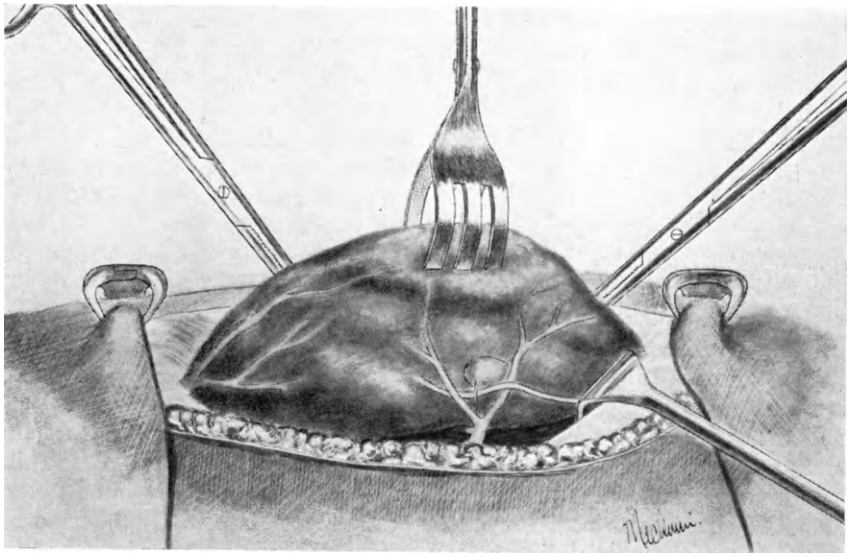


FIG. 161.—With the lateral lobe turned medially the inferior thyroid artery, recurrent nerve and inferior parathyroid glandule are identified, the artery being ligatured in continuity at its exit from behind the carotid sheath.

The lower pole of the gland is now dislocated from its bed. On the left side this is done by using the index finger of the left hand while the assistant retracts the muscles laterally. A little blunt dissection may be necessary in order to strip the fascial and muscular envelopes away from the extreme postero-inferior border of the gland, and, occasionally, accessory inferior thyroid veins may have to be dealt with before the pole can be satisfactorily displaced. It has been objected that the complete exposure of the gland postero-laterally is associated with risk of damage to the recurrent laryngeal nerve, but my own view is that the nerve is more likely to be injured if this

step is omitted. Further, unless the gland is exposed fully an inexact estimate may be made of the amount of it which should be removed.

VI. **Ligation of the inferior thyroid artery in continuity.** This step is, I consider, almost essential in operating for exophthalmic goitre and for some large colloid and adenomatous or nodular goitres. It has frequently been stated that the ligation of one or both inferior thyroid arteries is fraught with danger to the blood supply, and therefore to the function, of the parathyroid bodies, but the evidence for this is very trivial. It is, of course, well established that the parathyroid glandules receive their main blood supply from the inferior thyroid artery, but it has been shown by Curtis (1930) that these arteries do not constitute their sole blood supply; furthermore, practical experience has established the fact that evidence of interference with the function of these bodies rarely, if ever, follows the ligation of both arteries. It is virtually certain that, like other vessels ligated in continuity, the inferior thyroid artery recanalizes in a high proportion of cases. I am so convinced of the safety of this step that I have made it a routine procedure in every case of primary thyrotoxicosis on which I have operated during the last ten years, and have yet to see an instance of post-operative tetany.

It has also been contended that the recurrent laryngeal nerve is in danger of inclusion by ligatures applied to the inferior thyroid artery. This contention certainly has weight if the ligature is applied to the artery in a haphazard way, for the intimate relationship between the artery and the nerve makes it inevitable that unless the ligature is applied as far away from the gland as possible the nerve must occasionally be included. It is, however, possible in all cases to secure the artery at such a distance from the posterior border of the gland that the ligature lies from $\frac{1}{2}$ in. to $\frac{3}{4}$ in. or more from the danger zone.

In order to secure the artery it should be sought as it approaches the gland, and then traced outwards and upwards, the assistant meanwhile retracting the carotid sheath. The small aneurysm needle, carrying a strand of No. 000 silk or of No. 1 chromicized catgut, is passed under the exposed artery approximately $\frac{1}{4}$ in. from the inner border of the carotid. This safeguards the recurrent laryngeal nerve, and also the sympathetic nerve, which might be endangered if the ligature were passed too close to the carotid sheath itself. There is no necessity to tie the artery doubly and divide it, for not only does this take longer, but the division of the artery must involve the possibility of a slipped ligature and consequent haemorrhage. The inferior thyroid artery gives off no branches to the gland near its origin, and therefore nothing is gained by double ligation and division. It is often by no means easy to locate the artery itself, because a certain amount of fascial and fatty tissue, and sometimes a lymphatic gland, covers it near the point where it reaches the thyroid, and some little dissection may be necessary to identify it. It should always be borne in mind that the inferior artery is a lateral artery in respect to the thyroid gland and seldom enters the latter below the junction of the upper two-thirds with the lower third. Frequently, especially in large goitres, the artery enters at a much higher level, occasionally

even as high as the junction of the lower two-thirds and upper third. The artery almost always passes from behind the carotid sheath downwards to the gland, though there are exceptions to this statement if the artery has an

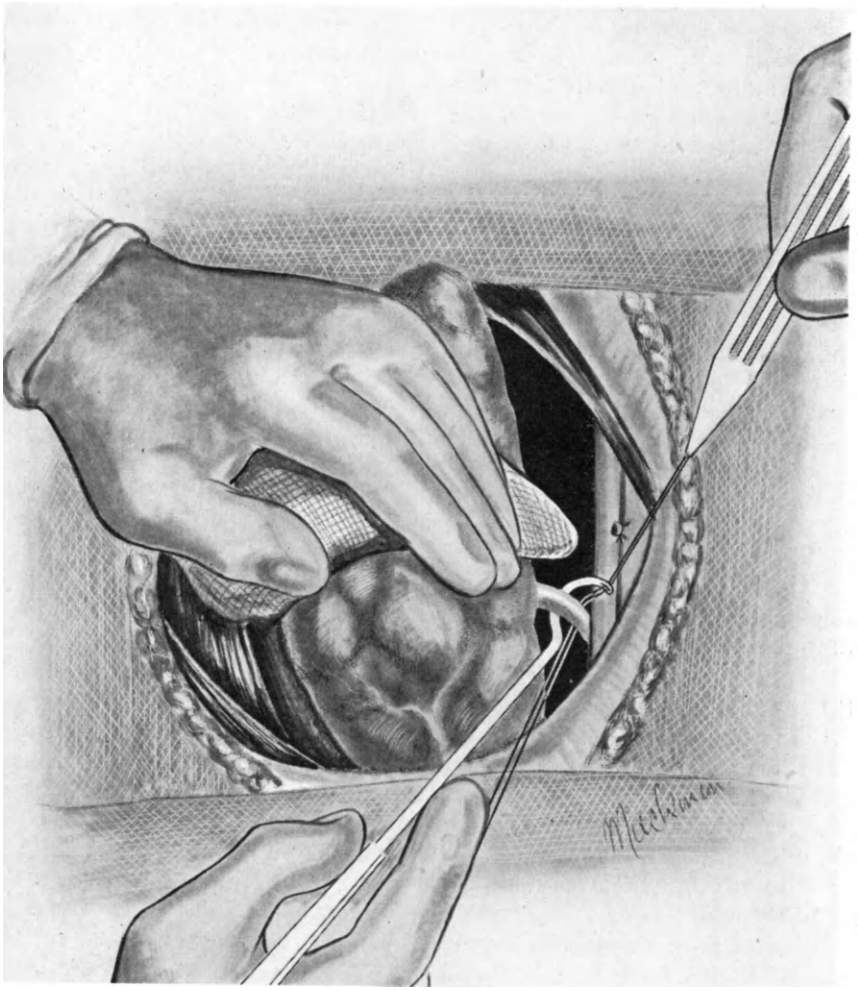


FIG. 162.—Ligature of the left inferior artery in continuity at its point of exit from beneath the carotid sheath.

abnormal origin. In very rare instances the artery reaches the gland at or near the region of the inferior pole, but in this event it is usually small and also probably abnormal in its origin. It must also be remembered that the inferior artery, though generally large and conspicuous, may be small

or even entirely absent, not only on one side but on both. If this be so, its absence can generally be detected from the undue mobility of the lower and posterior part of the gland, which, under ordinary circumstances, is to a considerable extent tethered by the artery and the periarterial fascia. When this condition is found it is not necessary to delay further in endeavouring to locate and tie the artery. It is well to remember that if both inferior arteries are absent the thyroidea ima may replace them; in such cases it is often an artery of considerable size.

VII. **The ligation of the inferior thyroid veins.** This step should ordinarily be carred out after the ligation of the inferior thyroid artery, for then the lower part of the corresponding lateral lobe can be pulled forward and the plexus of veins which is found associated with the lower pole and lower margin of the isthmus secured. The step is an extremely important one, but may be difficult owing to the number and distension of the veins and the amount of dense fascial tissue which is often found in their neighbourhood. Very gentle dissection with a blunt instrument is necessary. Each vein should be isolated separately as far as possible, and then doubly ligated as described for the middle thyroid veins, viz. the first ligature should be tied near the gland, and the second as far away from the first as possible, in order to leave the maximum space between the two for safer division of the vessel. When the veins on the left side have been dealt with it is wise to complete this stage of the operation by tying those on the right, at the same time securing the thyroidea ima artery, should it exist : it can usually be identified by its thicker wall and its comparatively superficial position.

This stage of the operation having been completed, it will generally be found that the trachea is exposed for some distance between the lower margin of the thyroid isthmus and the manubrium sterni.

VIII. (a) **Separation of right infrahyoid muscles from the gland.** (b) **Control and division of middle thyroid veins passing from the right lobe.** (c) **Ligation of right inferior thyroid artery.** These steps are carried out in exactly the same way as on the left side, except that the assistant makes traction on the gland itself while the surgeon retracts the muscles and, with the blunt dissector, dissects in the fascial space between the true and the false capsules. The middle thyroid vein is doubly ligated and divided, as are also any accessory veins. It is now possible to dislocate the right lower pole, its main veins having already been controlled, and to follow this by ligation of the right inferior thyroid artery in continuity exactly as for the left lobe.

IX. **Dislocation of the right superior pole.** The last step in the operation before attempting resection of the gland is the dislocation of the right superior pole, which is best done with the index finger of the left hand. The superior vessels are controlled as described above for the left lobe. When this is completed the gland is fully isolated from its bed. All the main veins and arteries have been controlled, while the posterior border of the gland has not been interfered with in any way, so that the parathyroid bodies and the recurrent laryngeal nerve have been left intact.

X. **Resection of the gland.** An assistant retracts the muscles thoroughly on the right side, and Kocher's blunt director is reintroduced behind the right upper pole and held by another assistant in such a way as to lever the gland well forward. The lateral aspect of the gland is now clearly exposed, and the line of resection can be mapped out with precision, leaving exactly the amount of gland tissue which is regarded as desirable. Ordinarily in exophthalmic goitres one should aim at conserving not more than one-eighth of each lobe, and in cases of exceptional toxicity one-tenth is quite sufficient, while, on the other hand, in cases of lesser severity it may be preferable to conserve as much as one-sixth to one-quarter of each lobe.

Artery-forceps are so placed as to grasp the main vessels visible on the surface of the gland, just behind the plane chosen for resection. One blade of the artery-forceps should be thrust into the gland for a short distance and the forceps closed in order to secure not only the vessel, but a small portion of the capsule and gland tissue. In this way a firmer hold is obtained and the artery-forceps are not so easily displaced, nor are they so likely to tear the friable tissue of the gland. When the row of artery-forceps has been placed, the gland is divided in the coronal plane of the body so as to leave behind a slice of the thyroid tissue occupying the groove on the lateral aspect of the trachea. The incision is carried down to the trachea, thus baring its anterior surface. Objection has been made to this step on the ground that it increases the liability to post-operative tracheitis, but it is a mistake to believe that the preservation of a small amount of thyroid tissue on the anterior surface of the trachea really protects it from the risk of catarrhal changes in its mucous lining: practical experience has shown that tracheitis is no more likely to occur when the trachea is exposed than when this step is deliberately avoided. In very bulky glands the plane of section should be sloped, so that, while a sufficient amount of the gland tissue is removed, protection is afforded to the lateral wall of the trachea. This is an extra safeguard to the recurrent nerve.

At this stage the bulk of the right lobe and the isthmus have been lifted forward and are free from their connexions. Haemorrhage is not at all common from the mass of tissue which is being detached, but if it occurs it can be controlled either by artery-forceps or, more conveniently, by grasping the whole firmly in the hand with a piece of dry gauze. This compression is quite sufficient to prevent any important degree of oozing from the gland, which is, of course, now almost entirely deprived of arterial blood supply. It is quite otherwise, however, with the small portion of gland which is conserved, as in a considerable number of cases the arteries supplying the posterior part of the gland, which come from the oesophageal and tracheal arteries, are so much enlarged that haemorrhage may be brisk, especially towards the tracheal aspect of the remaining fragment. It is generally possible to control these with the special sharp-pointed artery-forceps, or, if the gland is particularly friable, by exerting digital pressure from the outer aspect of the fragment against the trachea itself until one or more haemostatic mattress sutures can be introduced through the gland tissue.

The completion of the resection is carried out by working from below, the gland being drawn forward with the left hand while the assistant retracts the muscles on the left side and lifts forward the superior pole with the blunt director. Artery-forceps are put on the gland in exactly the same way as on the right side, but beginning from below and working upwards.

Finally, haemostasis is completed by controlling the vessels which run in the pyramidal lobe. A strand of No. 2 chromicized catgut is passed underneath it by means of a curved needle and the gland tissue divided after tying the suture.

XI. **Completion of haemostasis.** The resection being now complete, the next stage is the replacement of the numerous artery-forceps by ligatures. This very important step is often the most tedious part of the operation, for, in difficult cases, several dozen artery-forceps may have been used. It is usually easier to tie off the artery-forceps at the periphery of the wound before proceeding to those attached to the deeper parts. In exceptional cases, if trouble is being experienced with oozing from the cut surface of the gland, it is better to tie off first those artery-forceps which are attached to the deeper structures. It is generally sufficient to use plain or lightly chromicized catgut of sizes 0 to 1. I prefer to employ the catgut made up in loose cocoons, each sufficing for many scores of ligatures. For the deeper parts of the wound No. 000 silk is admirable, but I hesitate to use it near the surface for fear lest the ligature should be extruded later. It is a good rule to tie three hitches on all ligatures placed on important vessels, even though this takes a little longer. When all vessels have been secured the long sutures which were left on the superior poles can be cut short, and the remaining portions of the gland will then be found to retract behind the muscle into the sulci which they formerly occupied. Additional mattress sutures of catgut, passed in such a way as to avoid any risk of including the recurrent nerve, should in all cases be applied to the resulting cut surface of the gland.

Thermo-electric methods as applied to the surgery of the thyroid gland. I have had only a small experience with haemostatic methods based on the use of electro-coagulation. With the Bovie-Cushing apparatus it is possible to do the complete operation without recourse to the ordinary surgical knife. Haemorrhage from the smaller vessels is very readily controlled, but the more vascular thyroid tissue does not appear to me to be suitable for this particular method. The healing of the wound seems to be at least as satisfactory as after ordinary surgical methods, and there is a striking freedom from post-operative pain in the neck.

Wedge-resection. Some surgeons have advocated the resection of the thyroid in a wedge-shaped fashion, with the object of suturing the resulting cut surface in such a way that it is reduced to a mere line, thus avoiding those adhesions between the muscles and the gland which so generally follow the more usual methods. It is easy to plan such a wedge operation for small, diffuse colloid goitres in which sutures hold firmly, but fibrous and friable goitres, both of which are common in thyrotoxicosis, cannot be

sutured so satisfactorily. In the former type the rigidity of the tissue prevents the edges of the wedge from being brought into apposition, and in the latter the sutures cut through the friable mass. Wedge-resection is also adopted by some surgeons who avoid the free exposure and dislocation of the whole gland which I have advocated and described above, and who prefer to cut out a wedge from each of the lateral lobes and to secure haemostasis with ligatures and mattress sutures applied to the cut surfaces. Such operations often fail because the arterial supply of the gland is not sufficiently controlled, and therefore recurrent hyperplasia of the thyroid tissue is to be anticipated in a high percentage of the cases. The proportion of the whole gland which can be removed by means of a wedge-resection will be found to be less than might be anticipated, and operations done by this method are seldom, if ever, adequate in thyrotoxic cases. It is therefore a type of operation to be condemned.

XII. **Testing haemostasis.** If the patient is sufficiently conscious he should be directed to strain in order to induce congestion of the vessels of the head and neck, and thus put extra tension on the ligatures. With very light general anaesthesia this step can be accomplished by gagging the mouth open and stimulating the pharynx by means of a swab held on a pair of forceps, or, alternatively, by suddenly increasing the concentration of the anaesthetic for a few seconds. In one or other of these ways this important step should invariably be carried out, for it will be found that in an appreciable number of cases one or more vessels, usually veins, will bleed under the extra strain. These bleeding points are then secured before proceeding to the next step, namely, the closure of the wound. Omission of the haemostatic test is the most common cause of post-operative reactionary haemorrhage.

XIII. **Closure of the wound.** (a) *Suture of the infrahyoid muscles.* The position of the head and neck is altered by rearrangement of the pillows in order to relax the tissues which up to this point have been on the stretch, otherwise it is impossible to suture the various muscles efficiently. A continuous suture of No. 2 or No. 3 chromicized catgut is then introduced, starting at the left extremity, so as to bring the divided infrahyoid muscles together accurately. The only difficulty which may arise at this stage is due to the accidental pricking by the needle of one or more of the veins lying on the front of the muscles. This mishap should therefore be carefully guarded against, but if haemorrhage occurs great circumspection should be exercised to secure the punctured vein above and below the puncture, otherwise a post-operative haematoma may form underneath the flap. The muscles are then sutured by a similar continuous catgut suture in the middle line; it is sufficient here to secure the deep fascia which covers the muscles and to ignore the muscle fibres themselves. The suture line should be carried downwards to a point approximately half an inch above the suprasternal notch, so as to leave a gap for the insertion of the drainage tube.

(b) *Insertion of the tube for drainage.* Many authorities have raised

doubts as to the necessity for drainage after thyroid operations. The disadvantages of drainage are that there is a small gap in the median portion of the wound, and the possibility of infection through the open sinus. These disadvantages are, in my estimation, negligible: the small gap which remains in the centre of the wound after the removal of the tube rapidly becomes sealed, and the cosmetic result is not in any way modified. Infection of such wounds is extremely rare, and cannot, I think, ever be ascribed to drainage. The sinus may remain open for a few days, or, occasionally, it may, after closing, re-open at the end of from five to ten days, but the amount and degree of infection in such cases is never serious. On the other hand, if drainage is omitted, haematomata occasionally form in the depths of the wound. Such haematomata may give rise to few symptoms and be absorbed in the course of time without evidence of infection or of external discharge; in the majority of cases, however, they are attended by troublesome sequelae. Thus, when large they lead to pressure on the trachea and oesophagus, associated with dyspnoea and sometimes with dysphagia; or they become infected, and tedious suppuration ensues. When drainage is deemed necessary, I use Kocher's drainage tubes, made of glass, because they are not likely to be obstructed as a result of the movements of the patient's neck, and also because they can be coated with paraffin, thus minimizing the risk of clotting within the lumen. Such tubes should be short, extending down only to the neighbourhood of the trachea. Longer tubes are useful in draining wounds after unilateral operations, but are not satisfactory for bilateral cases.

If the mass of tissue removed is small, and especially when the excision has involved the upper rather than the lower part of the affected lobe, it is possible to obliterate much of the resultant space by sutures passed through the remaining portions of the gland and the infrahyoid muscles. Great care is needed to ensure that no fresh bleeding occurs from small veins in the muscles. There is no objection to using this method for small toxic goitres, as drainage is to be regarded not as a means of facilitating the escape of toxic secretion, but merely to prevent blood and serum from collecting in the wound. Large goitres are not suitable for this method, as the cavity resulting is too great to allow of adequate obliteration. " When in doubt, always drain," is a good rule in thyroid operations.

(c) *Suture of the platysma* (Fig. 163). This important step should be carried out with great care, using fine, curved needles and No. 00 or No. 000 plain catgut. The suture should be commenced at the left extremity of the wound and continued until the drainage tube is encountered, when it can be interrupted and restarted on the other side of the tube or, what is preferable, the suture is passed round the tube so as to lie deep to the small studs which project from its surface.

Exception has been taken to the suture of the platysma on the ground that it is unnecessary, and it has been asserted that the cosmetic result is in no way influenced by this step. The objection is perhaps cogent when the sutures for the skin are passed sufficiently deeply to include the underlying platysma muscle, but where metal clips of the Michel type are employed the

platysma stitch not only acts as an extra support, but permits of the removal of the metal clips at a much earlier date than would otherwise be desirable, and in this way helps to improve the cosmetic result.

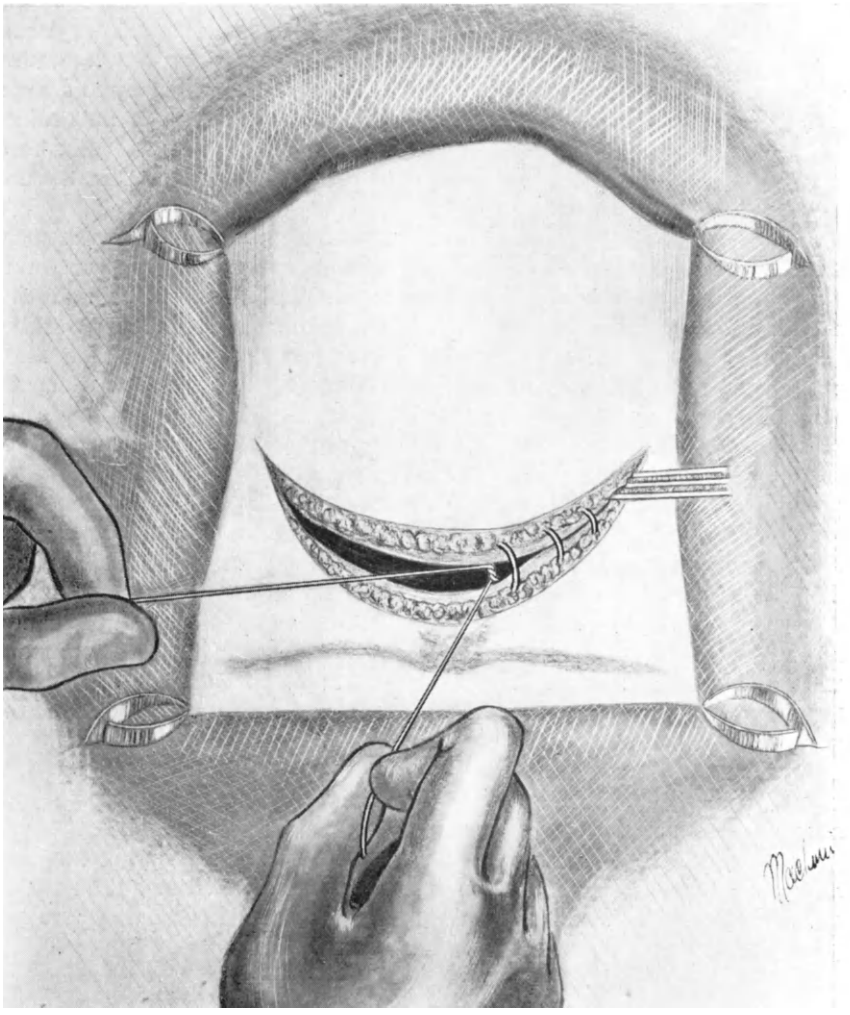


FIG. 163.—Approximation of the platysma and subcutaneous fat with interrupted sutures of fine thread, the knots being tied on the deep aspect.

The final skin coaptation is carried out by means of Michel clips. This provides an extremely accurate suture line and brings into contact not only the extreme cutaneous edge, but also a little of the underlying fibrous

elements, so that haemorrhage or serous exudate is prevented and healing thereby facilitated.

Subcuticular sutures of catgut, fishing gut, silk, and other materials have been used in preference to Michel clips by some surgeons, but I have found in the case of the unabsorbable materials, that, owing to the somewhat curved line of the incision, the withdrawal of the stitch is not always easy; it may break, leaving a portion in the wound. With absorbable material there is a tendency to superficial inflammation and subsequently to a hypertrophic or keloid scar. Very good scars can be secured by an ordinary continuous suture or by the buttonhole method, using very fine silk, horsehair, or catgut, but such stitches should be removed not later than the third to the fifth day after operation.

XIV. **Dressings.** It will be found wise to apply the dressings in such a way that they overlap in front of the neck, cover the upper part of the chest, and extend considerably backwards on each side so as to include practically the whole of the neck in their embrace. The dressings should be ample, as oozing from the wound is usually copious, and it is highly desirable to avoid contamination of the surface of the dressings by exuded blood immediately after the operation. The bandages should support the dressings well underneath the chin, otherwise there is always a tendency for them to slip downwards and expose the wound. Crêpe bandages, though perhaps a luxury, are the most satisfactory for this purpose.

In order to apply the bandages without distress to the patient three assistants are necessary—one to support the head, and one for each arm. Traction is made on the upper limbs and if this is properly carried out it is easy both to apply the bandage without disturbing the patient unduly and to secure the dressings firmly. In patients who are specially restless or excitable, the bandage should be carried over the head and secured round the forehead; this dressing, though somewhat irksome, controls the head and avoids the risk of undue traction on the wound during the recovery of the patient from the anaesthetic; it should not, however, he kept on more than twenty-four hours. If the patient is inclined to vomit, it is wise to cover the dressing with a layer of jaconet, fitted to the neck and stitched in position.

Special dressings, depending on the use of adhesive strapping, have been advocated, which eliminate the necessity for bandages, but although these are satisfactory for small, simple goitres I do not find that they give such good results as the method which I have described.

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CHAPTER XXVII

TECHNIQUE OF OPERATIONS FOR NON-TOXIC GOITRE

Operations for Single Adenomata and Cysts — Steps of the Operation of Resection-Enucleation. Operations for Colloid Goitre. Operations for Intrathoracic Goitre. Operations for Malignant Goitre. Operations for Chronic Thyroiditis : Tuberculous — Syphilitic — Riedel's Disease — Struma Lymphomatosa. Operation for Acute Thyroiditis.

I. Single Adenomata and Cysts

These, when of very small size, i.e. not exceeding that of a walnut, may be removed by enucleation, and with this, Lahey (1944) agrees. The incision necessary for the exposure of such goitres can be considerably curtailed, but should be symmetrical; attempts to carry out the operation through a unilateral incision have the disadvantage that the subsequent scar is more, rather than less, conspicuous as a direct consequence of the asymmetry, while the orientation of the several stages of the operation is made more difficult; finally, it is not uncommon to discover that, in addition to the obvious adenoma or cyst, unexpected lesions exist in the contralateral lobe, necessitating proper exposure of that part of the gland. There are, however, important objections to the simple enucleation of thyroid nodules. The one is that bleeding may be copious. It is, of course, possible to arrest haemorrhage under these conditions by packing the resulting cavity firmly with gauze, but almost invariably more blood is lost before satisfactory haemostasis can be secured than would occur with the more formal operation of resection of the nodule. But a more serious objection is that enucleation gives no adequate protection against recurrence, if the nodule should prove to be malignant. On this account, our current practice is to resect the nodule together with a layer of the surrounding thyroid tissue (formal resection). Sometimes, however, only a very thin layer of stretched-out gland substance separates the nodule from the recurrent nerve, and other structures, posteriorly. The operation of resection-enucleation may then be useful to protect these structures; surrounding gland tissue is resected in front, but the deepest part of the nodule is shelled out. The steps in the operation of resection-enucleation are:

(1) **The incision.** This should be made at a slightly higher level on the side corresponding to the tumour, in order to allow for the tendency of the skin, overstretched by the underlying tumour, to be redundant; unless this is allowed for, the resulting scar lies on one side over the lower part of the neck and on the other over the sternum and clavicle. It may also be noted here, that, as the neck is hyper-extended in all goitre operations, the incision as a whole must be placed a little higher than one wants the scar to be, because

when the neck is straightened, the incision will descend towards the sternal notch for from a quarter to half an inch (Lahey, 1943).

(2) **Raising the flap.** The flap is raised in a manner almost exactly similar to that described for exophthalmic goitre, except that in the case of large tumours it is often desirable to reflect the flap to a higher level on the side affected.

(3) **Division of muscles.** It is seldom necessary to divide the infrahyoid muscles transversely as a deliberate preliminary step in the operation, though on the other hand, it is unwise to preserve these muscles on the side affected if any special difficulty is experienced in dislocating the tumour. The infrahyoid muscles must, however, be separated freely along the median line to the fullest extent, and the incision carried downwards as far as the upper border of the manubrium sterni.

(4) **Dislocation of the tumour.** This can be done only after the middle thyroid vein or veins have been controlled. It is often a matter of extreme difficulty to detect the presence of these veins when exposing a large, tense adenoma or cyst, and it is in such cases that transverse division of the muscles is preferable to the risk of wounding the veins, which are often of large size and, in cases of long standing, very friable. When the middle thyroid veins have been doubly ligated with catgut, used on an aneurysm needle, according to the technique already described under thyroidectomy for thyrotoxicosis, a finger can be insinuated behind the tumour and the whole mass dislocated from its bed. Care must be exercised to insert the finger in the proper fascial plane, namely, between the true capsule of the gland and the surgical or false capsule derived from the deep cervical fascia. The tumour is often firmly wedged between the powerful overlying sternomastoid muscle and the trachea, especially when, as so often happens, a portion of the goitre lies below the level of the sternum. Judicious force, combined with manipulation between the fingers of both hands, may be necessary to attain the desired end. It is less dangerous to employ mechanical tractors in this type of operation than in dealing with exophthalmic goitre, so that the objections to this course, which have been fully explained, in connexion with the operative treatment of exophthalmic goitre, are invalidated. It is sometimes helpful to affix a series of broad-jawed artery-forceps of the Lawson Tait or similar pattern, grasping the tissues which lie superficial to the adenoma but avoiding the tumour itself. Thus there should be no risk of lacerating the surface of the latter, which would permit the exit of softened adenomatous tissue, or, in the case of a cyst, its fluid contents. If an adenoma has already undergone malignant degeneration, damage to the tumour in this way may be responsible for subsequent recurrences.

(5) **Ligation of the inferior thyroid artery in continuity.** This step is desirable in the case of nearly all large single adenomata and cysts, because the great majority of such tumours lie in intimate association with the artery; they are much less often found in the neighbourhood of the superior pole though, when this does occur, it is the superior artery which should be tied in preference to the inferior. The method of ligation of the inferior artery is

exactly the same as that described in connexion with thyroidectomy for exophthalmic goitre, but the artery is much more easily seen, owing to the fact that it is stretched and sometimes elongated by the growth of the tumour. The recurrent laryngeal nerve must be exposed and preserved with even greater care than in the case of the bilateral operations for thyrotoxicosis already described, because the deformation and displacement of the tissues by the tumour tend to bring the nerve into more intimate contact with the postero-internal surface of the thyroid gland.

(6) **Control of the blood vessels around the base of the tumour.** This is best managed by thrusting one jaw of the artery-forceps into the superficial layer of attenuated thyroid tissue which overlies the tumour or cyst, and taking a grasp of the larger and more obvious vessels, together with a small portion of the thyroid tissue envelope covering the tumour. If sufficient forceps are placed, in this way so as completely to encircle the base of the mass, it is possible by cutting through the enveloping thyroid tissue in front of the line of haemostatic forceps, to attain direct access to the posterior surface of the tumour itself and to enucleate it from its bed. It is advisable not to carry the knife around the whole circumference at first, but to begin by making an incision an inch or so in length. A blunt instrument or the finger can then be passed behind the adenoma in order to make a small artificial space between what remains of the thyroid lobe and the capsule of the tumour. When this is done, further artery-forceps can be placed so as to control the vessels one by one. This obviates the risk, which is a very real one with a large tumour, of cutting into the interior of the latter with the scalpel, for the layer of thyroid tissue which covers it is often extremely thin. Once the tumour can be pulled forward and a small space made between it and the thyroid tissue, the remainder of the operation can be rapidly proceeded with. Most of the bleeding is controlled by the forceps placed as described above, but some of the larger vessels which pass from the posterior surface of the gland directly into the tumour itself will have to be controlled, preferably before they are divided. They can, if present, be seen as vascular strands when the tumour is pulled forward with the finger.

(7) **Replacement of artery-forceps by ligatures. Control of bleeding points.** This step involves the ligation of several of the branches of the superior thyroid artery, the main trunk of which has not been interfered with. Great care is necessary to make sure that none of these escape control: there is always a tendency for the upper pole to slip back under the infrahyoid muscles, and in so doing artery-forceps may become detached from the vessels secured.

(8) **Suture of the gap in the gland.** This is comparatively easy, because a thin flap of thyroid tissue is preserved around the periphery of the area from which the tumour was removed. A continuous suture of No. 1 or No. 2 catgut, reinforced if necessary by one or two mattress sutures, completes the haemostasis and leaves a clean suture-line, the parenchyma of the gland being thus covered in.

The further stages of the operation are similar to those described under thyroidectomy for Graves' disease.

Cysts of the thyroid are treated on exactly the same principles as are solid adenomata. If small they may be enucleated, but there is always a risk of rupture in the process, and consequently in cysts with thin walls fragments of the latter may inadvertently be left *in situ*. It is a better plan to treat all thyroid cysts by the operation of resection-enucleation, or, in the rare cases where the whole of the lobe is expanded by the cyst, to carry out resection-extirpation of that lobe. The recurrent laryngeal nerve is particularly vulnerable during operations on large thyroid cysts and should always be identified and preserved throughout the relevant part of its course.

II. Colloid Goitre

In this condition the indications are, as a rule, (1) to remove a sufficient amount of the gland to eliminate pressure symptoms; (2) to leave enough thyroid tissue to obviate the risk of cachexia strumipriva; and (3) to take steps to guard as far as possible against recurrence of the pressure symptoms. These three objects are by no means easy to achieve. It is a comparatively simple matter to relieve all pressure symptoms by the removal of the greater part of the goitre; but the necessity for avoiding post-operative hypothyroid phenomena, the result of resecting too much of the gland, demands a higher degree of discrimination than in dealing with thyrotoxic glands. Foss (1925) calls attention to the all too prevalent tendency to operate on every goitre of adolescence, some of which hardly deserve the term. Even if iodine or dried thyroid substance fails to cure, operative treatment in the great majority is unnecessary, as the thyroid enlargement very frequently disappears spontaneously in the course of a few years.

The *steps of the operation* are as follows:

(1) **The incision and raising of the skin flap.** The *incision* should be similar to that described in the case of thyroidectomy for Graves' disease (see p. 442), but where the goitre is large it should be made at a slightly higher level than for smaller goitres; otherwise there is a very distinct tendency subsequently for the scar to lie over the upper part of the manubrium sterni, where it is unduly conspicuous. The transverse extent of the incision should be graduated in accordance with the size of the goitre, but should rarely be less than the distance between the two external jugular veins.

The *skin flap* should be made in exactly the same manner as already described in thyroidectomy for Graves' disease.

(2) **Exposure of the gland.** In this class of case, transverse division of the infrahyoid muscles is often unnecessary. The character and the texture of the goitre are such as to permit of its ready manipulation through comparatively narrow spaces between the muscles and the trachea. Free division of the deep fascia and of the infrahyoid muscles in the middle line as far down as the upper border of the sternum is, however, essential.

The muscles are stripped from the underlying gland, the assistant using suitable retractors while the subfascial space is enlarged and extended posteriorly by means of blunt-pointed scissors, gauze dissection, and the fingers. The middle thyroid veins must be carefully sought for at this stage. Should

they pass, as they often do, from the antero-lateral surface of the tumour into the internal jugular vein, they must be secured and divided before any attempt is made to dislodge the corresponding thyroid lobe, otherwise to do so frequently results in rupture of the veins. Severe primary haemorrhage or, what is perhaps more disconcerting, widespread infiltration of the cellular tissues with blood, owing to the retraction of the vein deeply among the fascial planes of the neck, may supervene on this accident. If the veins originate on a more posterior plane they may be detected only when an effort is made to dislocate the corresponding lobe. Whenever, in the case of a simple goitre, the dislocation proves to be difficult it may be assumed that one of two causes is responsible, (a) undivided middle thyroid veins or (b) imperfect separation of muscular and fascial tissues from the surface of the gland. If the former is the origin of the difficulty further retraction is necessary in order to permit ligation of the tethering vein or veins. With a large goitre, or in short-necked patients, it is essential at this stage to divide the infrahyoid muscles transversely, if this has not already been done, in order to permit more satisfactory access to the vein. The aneurysm needle is for this purpose preferable, both for accuracy and for safety, to pressure-forceps. No. 60 cotton is sufficiently strong and durable for the middle thyroid vein, which should first be secured close to the point at which it emerges from the capsule of the gland, and then a second ligature is passed as far away from the gland as is practicable. At the moment of ligation the tension made upon the vein by the assistant is momentarily relaxed in order that the knot may be drawn as tight as possible, and it is always wise to use a third hitch in tying that end of the vein which lies nearest to the internal jugular. Usually it is possible to place the two ligatures on the vein at least $\frac{1}{2}$ in. apart. The vein is then divided with scissors slightly nearer the first ligature than the second. Finally, both ligatures are cut $\frac{1}{4}$ in. long. By this means the danger of accidental displacement or of the tearing-away of artery-forceps owing to their weight—a very real danger in the case of the more friable veins—is eliminated. Serious recurrent venous haemorrhage during or soon after the operation has become in recent years exceedingly rare in our own practice.

(3) **The dislocation of the gland.** This is carried out in a manner similar to that described for thyroidectomy in thyrotoxicosis. The glands in the two cases are of very different consistencies. The pliability of the gland makes dislocation far easier to accomplish in the case of a colloid goitre, even though it is by no means uncommon to find that the superior pole extends upwards for a considerable distance behind the pharynx, requiring the dislocating finger to be inserted very deeply.

The inferior pole is, as a rule, more rapidly displaced, but the colloid variety of goitre often extends an inch or two into the thorax, giving rise to the common type of substernal goitre. No real difficulty should be found, however, in effecting this dislocation. There are no vascular or other connexions which hold this pole in place, and what veins there are belong exclusively to the inferior thyroid group. These lie entirely anterior and medial to the burrowing lobe, and therefore do not require division at this stage.

(4) **Ligation of the inferior thyroid artery.** The desirability of this step is a highly controversial matter. My own practice is to ligate both inferior thyroid arteries in continuity in all colloid goitres which have grown rapidly or are of considerable size. The rationale of this step is bound up with the necessity for avoiding recurrence of pressure symptoms: the contention is that if the blood supply to the lower part of the gland is shut off there can be little or no tendency to recurrence of growth at this site, and that any subsequent enlargement of the gland must of necessity affect the superior pole, to which the blood supply is left intact. It has already been demonstrated that the site of maximum bilateral pressure in colloid goitre corresponds approximately with the segment of the trachea which lies below the level of the isthmus —in other words, from 1 in. below the cricoid downwards. Recurrence of pressure on this segment can be avoided by ligation of the inferior thyroid arteries. Any increase in the size of the upper portion of the gland will cause no serious dyspnoea, since the larynx is relatively incompressible as compared with the trachea.

Similar steps are next carried out in connexion with the other lobe; the inferior thyroid group of veins should be secured with the greatest care, using the same method as described above for the middle thyroid group, namely, double ligation by means of ligatures passed with aneurysm needles. The cotton used in this situation is the same as that for the middle thyroid veins. The large amount of fascial tissue which surrounds the inferior veins renders them more difficult to obliterate with fine ligatures than are the lateral veins.

(5) **The resection of gland tissue.** Only when both thyroid lobes have been fully displayed by complete dislocation is it possible to plan accurately the amount of the gland which should be removed and exactly how much may be left. As indicated in the diagram (Fig. 164) we remove both lower poles, the isthmus, and the pyramidal lobe (when this exists), preserving the upper poles almost in their entirety, except when the goitre is exceptionally large; in the latter event the anterior part of each lateral lobe is removed, the gland being divided from below and behind upwards and forwards, the plane of section being concave. This involves the preservation of a comparatively narrow strip of the gland below and behind, sufficient only to protect the parathyroid glandules and recurrent laryngeal nerve, while, above, a larger portion of the thyroid is saved. The point at which normally the superior vessels reach the superior pole is not directly interfered with, but the branches of the artery are controlled to correspond with the plane through which the resection is made. In so doing, artery-forceps are placed in the coronal plane of the body, beginning above and working downwards on the right side, reversing this order on the left. One jaw of the forceps is thrust into the gland, and the more obvious vessels, together with portions of the thyroid tissue and of the true capsule, are firmly compressed. Haemostasis is thus more perfectly secured than can be done by picking up individual vessels without any of the neighbouring thyroid tissue. In this class of goitre, haemorrhage from the cut surface is seldom considerable, though extra pressure-forceps will often be needed near the medial border of each lobe where it lies in contact with the

trachea; here are usually found small accessory vessels which have not been secured at any of the earlier stages in the operation.

(6) **Ligation of vessels secured by artery-forceps.** All artery-forceps are now replaced by ligatures of No. 100 cotton. It is better to start with the forceps attached to the gland tissue itself, unless at this stage there are others incommoding the surgeon, which must first be dealt with. When the artery-forceps attached to one lobe have all been replaced by ligatures it is advisable at once to suture the remnant of the gland with interrupted through-and-through or mattress stitches. It is seldom possible to use a continuous suture satisfactorily in these cases. The object of this stitch is to minimize the amount

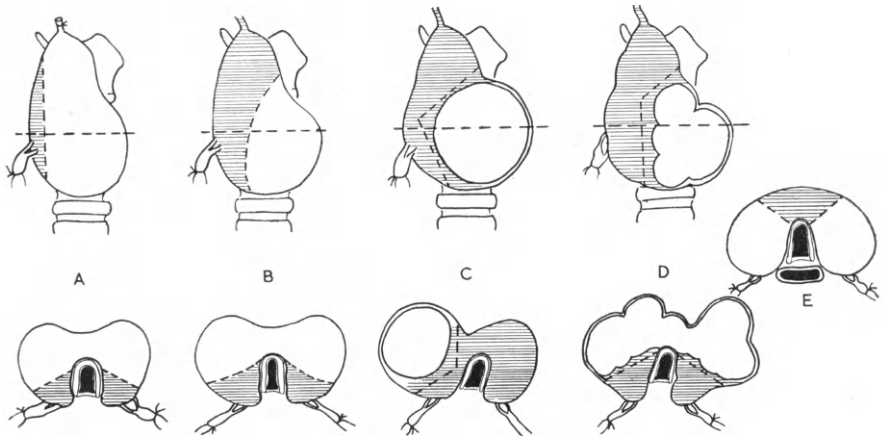

FIG. 164.—Diagrammatic representation of the scope of the operation in: A. Primary thyrotoxicosis. Note that the four main arteries are ligated. B. Colloid goitre. Note that both inferior thyroid arteries are ligated. C. Localized adenoma. Note that one inferior thyroid artery is ligated. D. Nodular goitre. Note that both inferior thyroid arteries are ligated. E. Resection of isthmus in thyroiditis. The infrahyoid muscles are then sutured to the raw gland surfaces.

of the cut surface of the gland exposed and thus prevent the formation of undesirable adhesions. In addition, the sutures complete the haemostasis though here far fewer haemostatic sutures are required than in the more vascular thyrotoxic cases.

Exactly the same steps should then be carried out on the other lateral lobe, the eventual result being that the portions of thyroid tissue which remain are equal in size and placed symmetrically in relation to the other structures in the neck.

The remainder of the artery-forceps are then replaced by ligatures, care being taken not to omit any vessel controlled, however trivial; all short-cuts to haemostasis in goitre operations are to be deprecated, since sooner or later they lead to disaster. Haemostasis should be tested at this stage by the method described in the previous chapter.

(7) **Closure of the wound.** The closure of the wound should be effected in a way similar to that already described for the other types of goitre, and drainage should usually be adopted.

III. Nodular Goitres

The surgical indications in this class of case may be twofold, namely: (1) to remove sufficient of the goitre to eliminate pressure symptoms or serious disfigurement, or (2) as a prophylaxis against these or the development of toxic or malignant changes.

It is specially important in this class of case to obtain complete exposure of both lateral lobes of the gland so that a deliberate choice can be made between the portions which require removal and those which should be conserved. The operation should result in the same symmetrical appearance of the neck the necessity for which has been emphasized above, but while this ideal must be kept in mind it is seldom possible to fulfil it quite so perfectly as with the smoother symmetrical goitres.

The steps of the operation are similar to those already described, up to the stage when the whole goitre lies exposed and dislocated from its bed. In cases where one lobe is very much more extensively involved than the other it is desirable to ligate the corresponding inferior thyroid artery, but to conserve that on the healthier side with a view to preserving an adequate blood supply to the secretory tissue; in deciding on the exact plane of resection consideration must be given to the presence of large adenomatous or cystic tumours, and it is often necessary to modify the operation considerably, as compared with the more formal operation for colloid goitre, in order to avoid cutting into large and often degenerate adenomatous or cystic masses. Fortunately, it frequently happens that the upper and posterior portion of the gland is less affected by the degenerative process, so that a reasonable margin of tissue free from adenomatous and cystic areas may be preserved. These retained portions of the gland should be carefully sutured, so as to reduce the extent of the cut surface exposed and to control haemorrhage.

The other steps in the operation are identical with those described for colloid goitre.

Recurrence after operation for simple goitre. This appears to be much less frequent than after operations for primary thyrotoxicosis, though certain simple goitres show an inveterate tendency to recur. Of the 1,205 patients operated on by the original author for simple goitre in the years 1921–30, thirty-seven had previously undergone surgical treatment at other clinics, and ten others primarily operated on by him had recurrences. One of the former group had had two previous operations, and he performed three subsequently; she developed slight and transient tetany; the goitre was of the nodular type. It must be obvious that when the whole thyroid gland is the seat of diffuse adenomatous degeneration, the portions of tissue preserved are capable of further degenerative changes, so that recurrence of

goitrous enlargement cannot always be avoided. Poate and MacIndoe (1940), in a report on recurrent nodular goitre, mention two patients who were subjected to four and three operations respectively. They emphasize that merely to shell out a nodule is to invite a recurrence. Not only should the whole gland be carefully inspected to detect other areas of degeneration, but possible abnormal extensions should be considered and sought for. It is surprising how easy it is in some cases to overlook a retrosternal or retro-visceral prolongation. Martin (1945) has emphasized that nodules often occur within the substance of the gland which are not detectable on the surface, and, since progressive degenerative changes regularly occur in later life, he advises routine subtotal resection of both lobes in nodular goitre, even if non-toxic. Poate and MacIndoe (1940) do not hesitate to perform total thyroidectomy when the whole gland appears diseased and in this course they had an ardent supporter in Hertzler (1945), who claimed that no ill-effects followed the total operation, and that post-operative myxoedema is more or less of a myth. While not associating ourselves with the routine radical excision practised by Hertzler, we can confirm that surprisingly little hypothyroidism may follow, when it seemed to the surgeon that he left a mere vestige of gland tissue and that of doubtful normality. Piercy (1945) has made the same observation.

IV. Intrathoracic Goitre

The expression " intrathoracic goitre " is used here in the same sense as that insisted on by Lahey (1945), namely one in which the greatest diameter of the goitrous mass is well below the plane of the thoracic inlet.

The operation for intrathoracic goitre may provide one of the most difficult problems in thyroid surgery. Not only is the patient frequently orthopnoeic and intolerant of all forms of inhalation anaesthesia, but the congestion of the tissues and dilatation of veins render even the earlier stages of the operation hazardous.

(1) The first essential is to guarantee an airway throughout the operation by having the trachea intubated, a long semi-flexible tube being used. However, the introduction of such an instrument in a patient—fortunately exceptional—who is under the necessity of using the accessory muscles of respiration, and who will not permit the neck to be extended fully, is a matter of extreme difficulty and sometimes has to be abandoned. In the case reported by Fiessinger *et al.* (1945), the operation had to be done under local anaesthesia with the patient sitting up, because of the urgency of the dyspnoea. But they note that division of the skin, deep fascia, and ribbon muscles may at once relieve the dyspnoea. Gas and oxygen anaesthesia is not always well borne by patients affected with the intense degree of cyanosis so commonly met with in this class of case. We have frequently found it desirable to combine a small amount of ether with the nitrous oxide and oxygen, when local anaesthesia cannot be satisfactorily employed alone. An attempt to use local anaesthesia should always be made in these cases, for even if it is unsatisfactory the amount of ether necessary is minimized.

(2) The *position of the patient* requires special attention, for it is, as a rule, impossible to obtain the degree of extension of the head and neck which is regarded as necessary in most goitre operations. One must frequently be content to compromise between an extension which is satisfactory to the surgeon and the state of flexion which the patient himself finds to be more comfortable. The sitting-up position, similar to that in the dentist's chair, is recommended for this type of case, but with intratracheal anaesthesia the operation can usually be completed in the horizontal position.

(3) The *incision* should be considerably longer than in operations for uncomplicated simple goitres. It must be remembered that the superficial veins are often enormously distended, and those which under normal conditions would be small may reach the size of the internal jugular. All the distended vessels must be accurately controlled as they are encountered. It is safest to secure them, after exposure of an adequate length, by double ligation with an aneurysm needle. Any accidental damage is followed by troublesome or even dangerous haemorrhage, and the risk of air-embolism is not to be ignored. Blood transfusion should be given slowly from the outset, and speeded up as required.

(4) The muscles should be divided freely especially on the side corresponding to the intrathoracic tumour, and in cases of extreme gravity there can be no serious objection to division of part or the whole of the sternomastoid muscle. Where it has been impossible to intubate the trachea, the latter should be identified at once and cleared to facilitate tracheotomy should this become necessary (Dixon and Benson, 1945).

(5) The *thyroid lobe* which corresponds to the intrathoracic tumour should now be separated from its attachment exactly as already described for symmetrical goitres. This involves: (i) the ligation and division of the middle thyroid veins; (ii) the ligation of the superior pole of the gland in continuity; (iii) the ligation of the inferior thyroid artery in continuity; (iv) division of the isthmus of the gland and of the corresponding lobe in such a way as to free completely its anterior and lower portions. When this stage has been reached, the only vascular attachments of the intrathoracic portion are those associated with the inferior thyroid group of veins, apart from the exceptional thyroidea ima artery, which lies close to the inferior veins and can be included with them.

(6) The *recurrent laryngeal nerve* may lie in very close contact with the postero-internal portion of the intrathoracic tumour, and should be specifically sought for and carefully preserved during the subsequent stages of the operation.

(7) Traction on the resected portion of the corresponding lobe of the gland will now make it possible to discover the correct plane in which to attempt the dislocation of the tumour. Into this plane the finger should be inserted to strip the nodular mass from its surrounding false capsule. There is little or no risk in attempting to dislodge it by inserting a finger behind the intrathoracic mass, there being usually no vascular connexions on this aspect. One or two fingers so employed, combined with traction from above with the other hand, will generally, in the case of a tumour of moderate size, enable

one to deliver it whole. With large, relatively fixed, intrathoracic goitres it may be necessary, while holding it up, to incise and thrust a finger into the centre of the mass, so permitting the softened contents to escape or to be removed by curettage and suction, thus reducing the size of the tumour and enabling it to be manipulated through the upper thoracic aperture. With very large intrathoracic goitres, patience may be required in alternately stripping round the mass, and aspirating its contents, as it is steadily drawn upwards by gland-holding forceps applied to the lips of its cavity. We have never yet failed to remove such an intrathoracic mass by means of digital manipulation, with or without breaking it up, but we have witnessed operations where a spoon of special shape or a scoop has been useful in effecting the withdrawal of the tumour. After removal of the main intrathoracic mass, the mediastinal cavity is carefully inspected lest a nodule or nodules remain to undergo necrosis or enlargement, as emphasized by Kent and Sawyer (1945).

In the case of malignant growths other steps may be necessary, but we are convinced that disarticulation of the sterno-clavicular joint (Cogniaux, 1948) or the division of the sternum and osteoplastic operations on the ribs are rarely necessary in the case of non-malignant goitres. However, if the goitre proves to be very deeply placed, adherent, or of malignant type, Dunhill's method (1922) appears to us the most satisfactory. He divides the sternum in the middle line down to or beyond its junction with the gladiolus, and then makes a transverse incision so as to convert the linear incision into a trap-door. Part of the clavicle and of the required number of rib cartilages are reflected, and bleeding from the cut surface of the sternum is controlled with Horsley's wax or with fragments of muscle tissue. By this means the upper aperture of the thorax can be expanded sufficiently to permit of the withdrawal of solid and adherent tumours, and even those very deeply placed in the anterior or posterior mediastinum.

Keynes (1950) used this median sternotomy to gain access to four enormous intrathoracic goitres and concludes that it has a definite place in thyroid surgery.

Hollenberg (1946) has reported an unusual event, a large intrathoracic goitre being removed transpleurally through an incision in the bed of the sixth right rib. This approach was deliberately selected because three previous operations had been done from the neck, including a longitudinal splitting of the sternum. The large size of the mass (6 in. x 4 in. x 4 in.), its low position, the probability of dense adhesions above, and the fact that it was virtually certain that the vascular supply from the neck had been tied off at the previous operations, were thought to indicate a transpleural approach. The operation proved one of great ease and the result was very satisfactory.

The later stages of the operation for intrathoracic goitre are in all essential respects similar to those for simple goitres. If the sternum and ribs have been divided, fishing-gut sutures passed through the skin will bring the osteoplastic flap into position, and healing is usually rapid.

It is desirable to limit the period of drainage; otherwise, troublesome and persistent sinuses may follow. Drainage for four or five hours is sufficient;

the space formerly occupied by the tumour fills with blood clot, which eventually becomes organized. Antibiotics should be given to prevent infection in the cavity.

V. Malignant Goitre

It is clear from a study of the relative incidence of various types of malignant goitre that in most cases the operation will not differ from that described for adenomatous and nodular goitres. This applies to all malignant adenomata which have neither already involved the surrounding structures nor invaded the issuing thyroid veins. In this large group of cases the malignant character of the tumour is, of course, evident only after careful pathological investigation. When, however, it is obvious before the operation is undertaken, a much more thorough and radical method must be employed. The essential steps in the operation are as follows:

(1) An *incision* sufficiently extended laterally to include the whole breadth of both sternomastoid muscles.

(2) The *reflection of a flap* which does not include the platysma and therefore differs from that used in all other goitre operations. The object of this step is to permit the removal of all lymphatic tissues lying in association with the deep fascia of the neck. If the platysma is not preserved in contact with this deep fascia, damage to some of the lymphatic vessels is inevitable during the reflection of the flap, and malignant cells may thus be disseminated.

(3) The *division of both sternomastoid muscles* as close to the clavicle and sternum as possible, followed by the reflection of these muscles upwards.

(4) The *exposure*, and *double ligation*, low down in the neck, of the *internal jugular vein* corresponding to the side of the tumour. The object of this step is twofold, namely: (a) to ensure the removal of that vein which is most likely to have been invaded by the tumour, and (b) to facilitate the removal of lymphatic glands lying along its course. The internal jugular vein on the other side must be preserved, for in cases where it is already involved no radical operation can be expected to succeed, and its preservation is necessary in order to ensure the maintenance of proper circulatory conditions in the brain.

(5) The *platysma* and *sternomastoid* and *infrahyoid muscles*, together with the divided internal jugular vein, are now reflected upwards until the lower edge of the thyroid gland is exposed. The inferior thyroid veins are doubly ligated, and the inferior thyroid artery is tied as far away from the gland as possible, following the usual technique. No attempt is made to conserve any portion of the gland tissue lying posteriorly, so that the corresponding parathyroid glandules, and even the recurrent laryngeal nerve, may have to be sacrificed in order to permit of the removal of every fragment of the gland on the affected side. As the operation progresses, the tumour is dissected cleanly from the sides and front of the trachea, the continuity of both tracheal and oesophageal walls being preserved whenever possible. It is true that successful results have occasionally been obtained by the resection of one or both of these tubes, followed by careful suture of the resulting gap, but in

most cases anything but a localized or trivial involvement of the trachea or oesophagus precludes radical surgical methods. In a case with intratracheal extension, Rob (1949) has reported the successful resection of a length of trachea, and the implantation of a tubular piece of tantalum gauze, followed by primary suture.

The dissection is then carried upwards, and a suitable plane is chosen for the division of the thyroid gland, for it is probably never justifiable to remove the whole gland. If the growth has involved both lobes extensively it is almost invariably beyond the scope of surgical treatment; but the amount of gland which can be preserved will naturally vary materially in different cases. As a rule, the lobe corresponding to the tumour, together with the isthmus and the anterior portion of the contralateral lobe, will need removal. The operation is completed by double ligation of the superior thyroid vessels, after which the internal jugular vein can be stripped upwards for a considerable distance away from the rest of the contents of the carotid sheath, thus permitting the removal of those glands which lie in the neighbourhood of the origin of the superior thyroid artery from the external carotid. When this has been done on the affected side the sternomastoid muscle is divided as high in the neck as possible, the internal jugular vein is again doubly ligated at the upper extremity of the dissection, and the operation is completed by the removal in one mass of the tumour with its surrounding infrahyoid muscles, the sternomastoid muscle, and the internal jugular vein and its glands, while on the opposite side the sternomastoid muscle is removed along with the fascial and lymphatic tissues corresponding to those on the affected side, but with the single exception that the internal jugular vein is preserved.

This operation is a severe one, and whenever possible should be conducted under intratracheal anaesthesia. The manipulations necessary to remove massive and adherent tumours frequently result in occlusion of the trachea, and unless an intratracheal tube is *in situ* severe dyspnoea may supervene, necessitating immediate tracheotomy with its attendant risks. One recurrent laryngeal nerve has frequently to be sacrificed, so that exceptional care must be taken to avoid damage to that on the contralateral side. The same is true for the internal jugular vein and the parathyroid glandules.

The closure of the deeper parts of the wound, after this extensive operation, is difficult, and as a rule nothing can be done to fill the wide gap in the main muscles. The skin flap is closed by one or two silkworm-gut sutures and the exact coaptation completed with Michel clips, the latter being removed after the usual forty-eight hours' interval, the former being allowed to remain for from five to seven days. It is generally wise to introduce more than the usual single small drainage tube, and we are in the habit of employing one on each side of the neck.

In the case of papilliferous adenocarcinoma the operation may have to be extended into the submaxillary or even the submental region, and the posterior triangles frequently need special attention. Secondary deposits are more commonly found in unusual situations in this class of tumour, in which, however, it is reasonable to widen the scope of the operation in view of the

excellent results which follow in what at first appear to be unpromising cases. Nor is a strictly " block " dissection of the glandular territory necessary. Involvement of outlying nodes may be recognized by dark brownish enlargement; cystic and haemorrhagic degeneration are common. Satisfactory results often follow their removal individually, with but a minimum of the surrounding connective tissue.

In carcinoma simplex, in all its varieties, the presence of widespread glandular involvement generally precludes any attempt at radical surgical intervention.

In malignant goitres which originate at a considerable distance from the trachea it is possible to modify the operation and to avoid removing both sternomastoids.

In rare cases it may be justifiable, in dealing with the less malignant tumours, to resect portions of the carotid sheath, including the common carotid artery and the vagus nerve. This has been successfully accomplished on occasion, but the risks involved, especially to the cerebral circulation, are very great, and we have seen a death on the operating-table follow this drastic step.

Metastases. Operations on metastatic thyroid tumours have been carried out by von Eiselsberg, among others, in the belief that the metastasis may be solitary and that others may possibly fail to materialize. This is not, however, in accordance with general experience, and therefore secondary growths are better treated by radio-iodine, X-ray therapy, or by radium. Local recurrences should be dealt with similarly.

Adenocarcinomata sometimes respond strikingly to radio-iodine. This is likely when there is evidence of hyperthyroidism, indicating functional activity in the tumour tissue. Radio-iodine may then be taken up avidly. Given a heavy dosage, there may be much destruction of the tumour tissue. Radical thyroidectomy is a necessary preliminary in order to prevent thyroid tissue in the neck from competing with the metastases for the available radio-iodine.

VI. Operations for Thyroiditis

1. **Tuberculosis** of the thyroid is so seldom recognized either before or during the operation that it is generally dealt with on the lines of a simple goitre, or, in those exceptional cases where toxic features are present, the operation undertaken will partake of the nature of an extensive resection, such as has been recommended for exophthalmic goitre.

In the rare cases correctly diagnosed before or during operation the affected part of the gland should be resected with a reasonable margin of healthy thyroid tissue, as far as this is possible.

2. **Syphilis.** Syphilitic lesions of the thyroid are usually operated on only when the diagnosis is in doubt or the true nature of the condition has been overlooked. In all such cases the mass is generally found to be somewhat adherent to the trachea or the oesophagus, and more than ordinary care is necessary to avoid damage to these structures and to the recurrent nerve.

Healing after the operation is generally less rapid than in cases of simple or thyrotoxic goitre. The recognition, however, of the character of the tumour and the institution of antisyphilitic treatment will generally result in rapid closure of the wound.

3. **Riedel's disease.** This condition is much more likely to be diagnosed correctly before operation than is either of the two forms of chronic inflammation already mentioned. It is true that Riedel's disease is often mistaken for malignant disease, but the comparative smoothness of the tumour sometimes enables a diagnosis to be made with some degree of probability. The thyroid should be exposed exactly as for the simple forms of goitre, but it will be found impossible to trace the normal plane of cleavage between the infrahyoid muscles and the enlarged thyroid lobe. The muscles are so intimately bound to the gland that there is often a temptation to complete the exposure of the affected lobe outside the muscular envelope. If this be done the recurrent nerve on the affected side is extremely likely to be damaged. There are, however, two methods by which this danger may be avoided, namely, either by burrowing by blunt dissection through the muscular tissue along the outer surface of the gland, where the adhesion between these structures is generally less dense than anteriorly, or, as an alternative, by commencing the resection of the affected portion immediately over the trachea instead of laterally. The difficulty of the latter method is that when, as often happens, the inflammatory mass is firmly adherent to the trachea, this structure may be divided or damaged before it is recognized.

We have also found it satisfactory in certain cases to begin the resection a short distance beyond all trace of the dense white tissue of which the pathological mass is composed, and then, after having cut through relatively healthy tissue and found the tracheal wall, to begin the separation at this site, working over towards the affected side bit by bit. The mass can thus be separated from the underlying tissues and resected with a small margin of the healthy thyroid gland, if any can be found. Haemorrhage is not difficult to control, as most of the vessels have already been compressed, or even obliterated, by the constricting fibrous tissue.

Many authorities recommend the removal of only small portions of the inflammatory mass, and rely upon the statement made by Riedel (1910) that the symptoms frequently clear up after such very limited procedures. Our own experience does not permit us to be optimistic about the effect of removal of small portions of the affected tissue, but almost immediate relief follows in cases where a more extended operation has been satisfactorily completed.

4. **Lymphadenoid goitre.** Operative treatment should be avoided if an accurate diagnosis has been arrived at, unless the goitre is pressing on the trachea, when a limited bilateral resection of the gland, without interference with the main arterial trunks, is indicated.

5. **Acute thyroiditis.** Where suppuration has occurred the indication is to provide satisfactory drainage at the earliest possible moment. The anaesthesia should, when possible, be intratracheal, local anaesthesia being extremely

unsatisfactory owing to the widespread infiltration of the tissues with inflammatory material. The incision will be determined by the site of the fluctuating swelling, and more than one opening may be necessary before adequate evacuation and drainage can be obtained. Generally, rapid healing occurs in these wounds, but in the more virulent infections the use of Carrel-Dakin tubes has, in our practice, proved satisfactory. In cases of extreme gravity portions of the thyroid may slough and be thrown off in comparatively large masses. Tracheotomy has occasionally been necessary in this class of case, though it adds materially to the risk of a fatal result.

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CHAPTER XXVIII

DANGERS AND DIFFICULTIES DURING THYROIDECTOMY; USUAL POST-OPERATIVE COURSE AND MANAGEMENT

Errors on the Operation Table. Haemorrhage — Injuries to Trachea and Oesophagus — Tracheal Collapse — Injuries to Pleura — Air Embolism — Wounds of Cervical Sympathetic, Vagus and Hypoglossal Nerves, and Thoracic Duct. Post-Operative Course and Progress — Post-Operative Treatment.

(1) **Errors on the operation table.** Cole (1944) remarks aptly that errors of technique are less important than errors of judgment in the preparation of the patient and the timing of operation. If it has been decided beforehand that only a limited procedure is justified, it is unwise to proceed to the full bilateral operation just because the patient seems to have supported the scheduled procedure well. Similarly if there are undue anaesthetic difficulties and the patient is brought into the operating room with a rapid and rising pulse, it is better to postpone surgery to another occasion. Again, if the heart rate is running at 135–140 after the removal of one lobe, it is generally better to terminate the operation at this point, and likewise if the anaesthetist has persistent difficulty in maintaining proper oxygenation.

(2) **Haemorrhage.** Primary haemorrhage is usually venous in origin. The main arteries are so readily secured and generally so constant in position that they are seldom damaged unwittingly. Indeed, as Crile and Shiveley (1941) remark, haemorrhage during thyroidectomy is usually not so important as the damage done to vital structures in trying to control it. We should avoid haemorrhage and consequent difficulties by operating with ample exposure, good assistance, a good light, and by sharp dissection. Careful double ligation of the superior artery and vein makes primary haemorrhage from these vessels the rarest of all the operative dangers. Even after ligating the inferior thyroid artery as well, haemorrhage from accessory arteries such as the tracheal and oesophageal, may in hard, fibrous goitres or in exceptionally friable ones cause difficulty. For this reason, in vascular goitres it is wise to complete the gland section between forceps, though this method is somewhat tedious. Towards the trachea, the isthmus having been divided, these haemostats can be applied from within outwards, directly across the anterior surface of the trachea, and in an almost transverse direction. Their points are thus directed away from the tracheo-oesophageal groove and the recurrent laryngeal nerve, rather than towards it (Dinsmore, 1941). Should haemorrhage from the stump still be severe it can be controlled by pressing it firmly against the side of the trachea with the fingers or a gauze pad, drying the field, and then accurately picking up the bleeding vessel with a superficial suture.

Venous haemorrhage may occur at any stage. In large intrathoracic goitres causing pressure on the main venous trunks the superficial veins are so engorged and so numerous that the preliminary incision may produce copious haemorrhage. The danger can in some measure be avoided by restricting the depth of the first incision so as to avoid dividing these veins, but, should haemorrhage occur, every bleeding point, however small, must be secured before any further step is taken.

The most common and most dangerous form of primary venous haemorrhage is encountered during the exposure and dislocation of the lateral lobes, and its origin is usually from a middle thyroid vein. Should the latter emerge from the anterior surface of the thyroid it will be seen and easily controlled at an early stage of the exposure. When, however, the vein has a shorter course, and more especially when a large, tense, and impacted or retrosternal goitrous mass is being removed, the taut vein tethering the lateral lobe in position is in danger of rupture if subjected to the slightest extra traction. The haemorrhage is not always evident immediately, but the blood often percolates among the fascial spaces of the carotid sheath, into which the torn vein usually retracts. As soon as the main tumour mass has been dislocated the relief of pressure renders the bleeding both more obvious and more copious. The treatment is (a) *Preventive*, by ensuring the freest exposure of the lateral aspect of the gland in all serious cases. This involves transverse division of the muscles at an early stage of the operation. In addition, the finger which is passed backwards to dislocate the lobe should never be used to break through any tethering strands of tissue, which almost invariably contain veins; under tension these may appear to be trivial in size, but after rupture they retract and bleed copiously, often proving to be of large dimensions. (b) *Immediate*. If damage to a middle thyroid vein of large size occurs, the corresponding thyroid lobe must be dislocated with the minimum delay compatible with avoidance of further damage to veins. (It must be remembered that middle thyroid veins may be multiple.) Adequate retraction and perfect illumination of the wound are essential. Strips of gauze are packed behind the goitrous mass on the side affected until the bleeding stops, and the several gauze strips are then removed cautiously, one by one, until the vessel itself or the hole in the internal jugular can be seen and secured. Too large a retractor may be a handicap in this step by pressing on and obscuring the source of the bleeding.

Capillary oozing is rarely troublesome, except in certain old-standing thyrotoxic cases in which the blood pressure is high and the coagulability of the blood reduced. It may resist the usual mattress sutures, but pressure with gauze pads wrung out of saline at 115° F. will usually control it, as will the new agents, oxycel and fibrin foam.

When the surgeon anticipates that the goitre will be vascular or adherent and in all operations which are likely to be prolonged and difficult, e.g. thyroidectomy for malignant disease or Riedel's thyroiditis, it is a wise precaution to have the patient grouped and a vein cannulated before commencing the operation. As with all other major surgery the aim is to prevent

shock by maintaining the patient's blood volume, not to treat shock by transfusion after it develops.

(3) **Injuries to the trachea and oesophagus.** The trachea is in great danger of injury in all cases of infiltrating malignant disease of the thyroid and in such inflammatory lesions as Riedel's disease. It must not be overlooked that when the trachea is distorted, compressed or displaced, as may happen with almost any goitre, it may be injured before the surgeon is aware of its proximity. This injury is a serious one, because of the risk of infection of the cellular tissues of the neck from the interior of the trachea.

Lahey's (1941) advice is to get the anaesthetist to put on positive pressure at once; this prevents blood being sucked in. And the hole is immediately covered by the surgeon's finger. The wound can then be swabbed dry and the hole in the trachea accurately sutured. At all costs blood must be denied access to the tracheal lumen, because it may lead to uncontrollable coughing and straining which greatly aggravate the difficulty of the repair. If the wound is small in extent and recognized, as it should be, by the bubbling or whistling noise which results it can thus be repaired quickly and usually with success by a few fine cotton sutures, followed by a more prolonged drainage of the wound than would ordinarily be necessary. The chief danger in this class of case is that when the opening made into the trachea is very small, the injury may be overlooked, and thus a route for infection from the interior of the trachea to the tissues of the neck may persist, with the risks of cellulitis and mediastinitis which this involves. Should the trachea be so badly damaged that successful primary suture is out of the question, it is perhaps wisest to insert a tracheotomy tube, either through the accidental wound or through a formal one made at a lower level, according to the special circumstances.

Wounds of the oesophagus during operations on any but malignant and certain inflammatory goitres should never occur. Cases of successful resection of portions of the wall of the oesophagus have been referred to in the chapter on malignant disease, but it must be an exceptional condition which would justify this as a deliberate surgical step. If the oesophagus is injured accidentally it must be repaired with two layers of very fine cotton sutures; after the completion of the operation on the neck a temporary gastrostomy must be undertaken to minimize the risk of leakage and infection—a risk which in this type of accident is particularly serious. De Quervain refers to a case of damage to the oesophagus which resulted from the rupture of a minute unrecognized traction diverticulum of the oesophagus adherent to a goitre.

(4) **Respiratory obstruction and tracheal collapse.** The advisability of using tracheal intubation anaesthesia for all operations on large, nodular, retrosternal or truly intrathoracic goitres cannot be overemphasized. Distortion and kinking of the trachea or laryngeal spasm is often produced during the firm manipulative efforts required for dislocation of the goitre, and even such temporary respiratory obstruction and its consequent anoxia may add seriously to the hazard of the operation.

The term " tracheal collapse " is used to describe certain rare cases of acute respiratory distress occurring during or immediately after thyroidectomy. A theory advanced to explain its production is that the walls of the trachea are softened by the long-continued pressure of the goitre and, the latter being removed, there is not sufficient rigidity remaining in the tracheal wall, which is therefore sucked in at each inspiratory movement and acts as an obstructive valve.

The difficulty which we find in accepting either of these explanations as invariably applicable is that we have met with three cases in which sudden respiratory distress occurred during thyroidectomy, the whole length of the cervical trachea being under direct observation, yet no trace of collapse of its walls or of any serious kink or stenosis was visible. The passage of a large intratracheal tube from above temporarily overcame the respiratory difficulty, but as soon as the tube was removed the dyspnoea recurred. In each case tracheotomy cured the condition. It is difficult to resist the conclusion that some of the cases designated tracheal collapse may be due to laryngeal spasm. It has been suggested that sudden onset of dyspnoea during thyroid operations is due to bilateral injuries to the recurrent nerves; but in the cases to which we have referred, the fact that the tracheotomy tube was removed within a week and that no subsequent trace of laryngeal paralysis could be found make this explanation untenable.

True tracheal collapse is, however, a definite clinical entity and was met with in three cases in our own series of thyroidectomies. It may occur either after the removal of unilateral tumours, or at any stage of the bilateral operation. Usually it follows the removal of the second lobe in the bilateral operation, and the dyspnoea and cyanosis may be very rapid in onset. Sometimes respiratory difficulty, which may have been noticed almost from the start of the operation, becomes intensified after the excision of the goitrous mass. Tracheotomy is necessary in most of the cases though it is justifiable to try to abate the dyspnoea by changing the position of the head, and by relieving the trachea of the weight of any artery-forceps, still attached to the tissues in the immediate proximity. Lahey (1941) has emphasized, and we fully concur, that no patient should be allowed to continue in a state of respiratory obstruction after operation, even overnight. It is better to do a tracheotomy, which need only be temporary, too early than too late. In the case of intrathoracic or retrosternal goitres, should tracheal collapse occur, a special long flexible tracheotomy tube of the König type must be used.

(5) **Injuries of the pleura,** though possible in the course of operations for adherent malignant tumour, are not likely to occur in any properly conducted operation for non-malignant goitre. In the former class of case unilateral pneumothorax follows, but with an intratracheal anaesthetic the interference with respiration is rarely serious.

(6) **Air embolism.** This rare phenomenon is due to the entrance into a large vein, usually at the root of the neck, of a considerable volume of air. Whenever a cervical vein is damaged and is not immediately secured, particularly in patients with severe dyspnoea, air may be drawn into the lumen of

the vein. We have seen it happen scores of times after partial division of superficial veins of the neck, but the actual quantity of air sucked in has been small and no noticeable general effect was produced. Where large quantities of air are concerned, and if the vein belongs to one of the large plexuses at the root of the neck, grave symptoms have been described, and fatal results have been recorded.

Richard (1947) describes one fatal case and two others in which there was transient impairment of cerebral function.

The best way to prevent such accidents is to ensure, by the use of ligatures passed on aneurysm needles, that no large vein is opened to the air at any stage. Should the accident occur, the wound must be flooded with normal saline solution so that the latter instead of air is aspirated into the lumen of the vein, and control of the vein must be regained as quickly as possible by any means at hand. Traction on the goitre in an upward direction will help if the inferior thyroid veins are concerned, and a finger or gauze swab will usually suffice to seal up the gap temporarily until artery-forceps or a ligature on an aneurysm needle can be applied.

(7) **Wounds of the cervical sympathetic nerve,** the vagus, and the hypoglossal nerve have all been recorded, but, except in the extensive resection of tissue necessitated by advanced malignant disease, it is difficult to understand how such mishaps arise. Berry mentions two fatal cases of injury to the vagus.

(8) **Wounds of the thoracic duct** have been recorded, but it is not easy to account for such an accident in an operation for simple or toxic goitre. If recognized at once it is sufficient to ligate the ends of the duct. If the injury is overlooked chyle will accumulate in the wound or escape freely from it. It will then be necessary to open up the wound and locate and tie the leaking duct.

A postoperative reaction always occurs, but with modern methods of preparation, it is usually so mild, even in thyrotoxic patients, as to be almost negligible. With the present-day policy of converting all materially toxic goitres into non-toxic goitres by the use of anti-thyroid drugs, the sharp rises in temperature and pulse rate which were such characteristic features of the patient's chart, are replaced by only the mildest elevations or there are none at all. Similarly the restlessness, excitability, increase in tremor, which regularly followed operations, are now trivial, unless there are respiratory or other special complications.

Auricular fibrillation may appear for the first time or recrudesce after the operation, the post-operative type of paroxysmal fibrillation. This may occur when there has been little or no indication of thyrotoxicity before operation, and when, therefore, no special preparation has been deemed necessary. As a rule the cardiac reaction subsides quickly and uneventfully, but its occurrence indicates the need for constant care in the preoperative management and the selection of cases for surgery.

Post-operative treatment. The patient's airway. From the time when the intra-tracheal tube is first withdrawn until the patient is fully conscious and

breathing easily, her airway must be under constant review. Vocal cord paralysis is usually evident when the intra-tracheal tube is withdrawn, but the severity of the obstruction may not reach its maximum until recovery of consciousness is occurring.

When respiratory difficulty occurs for the first time after twenty-four to forty-eight hours, the possibility of haemorrhage under the sutured pre-tracheal muscles should be considered. As Dixon (1943) remarks it is amazing how small an amount of bleeding can produce stridor and suffocation of the patient within a comparatively short time. So remove the dressing and look at once if stridor and dysphagia develop after operation.

Position. The patient should be kept in the horizontal position until consciousness is regained, and then propped up in a sitting position. The pillows are so arranged that the head is well supported, thus preventing strain on the wound and at the same time facilitating comfortable breathing and free drainage.

Restlessness during the first twelve to twenty-four hours must be combated by sedatives, such as luminal gr. i to iii, or potassium bromide gr. xxx and aspirin gr. x given in the rectal saline, the dose being repeated four-hourly if necessary. Morphine gr. $\frac{1}{4}$ or heroin gr. $\frac{1}{6}$ may be required, but should not be given without clear indication, as these drugs tend to increase cyanosis, which at this stage is one of the most dangerous complications.

Deavor (1924) has advocated the use of ice-bags as a means of reducing restlessness and preventing hyperpyrexia. They are placed over the chest and abdomen, and as many as eight or ten have been employed. Such a method has, in our opinion, only a very limited value and should be used with great discrimination. Acetylsalicylic acid in appropriate doses is probably a better corrective of hyperthermia. But by whatever means, the vicious circle of increasing temperature and increasing metabolism must be broken promptly.

Walton (1923) contends that hyperpyrexia is more likely to occur in patients who are operated on in sultry weather, and advises that thyroidectomy for exophthalmic goitre should not be conducted during the dog-days. Maintenance of control by anti-thyroid drugs until the circumstances are more suitable is now indicated. But it may be noted here that a refrigerated oxygen tent is invaluable for the resuscitation of bad-risk or neglected cases especially during the summer months (Crile, 1941).

Administration of fluid. Restlessness, hyperpyrexia, and aggravation of tachycardia are all best controlled by giving large quantities of fluids by proctoclysis, subcutaneous injections, intravenous infusion, and by the mouth. It is often possible, by a combination of the methods referred to above, to administer to the patient a total of fifteen pints of fluid in twenty-four hours. These methods of administering fluids in abundance to the patient should be continued for forty-eight hours, or longer if necessary. Glucose or laevulose should be added to the rectal saline to make up the equivalent of a 10 per cent. solution and as soon as vomiting has ceased glucose or laevulose may be taken in orange juice, lemonade, and barley water by

mouth. All such fluid administration must as always be controlled by careful records of the electrolyte and water balances, and regular examinations of the relevant blood chemistry.

Iodine medication. In thyrotoxics, during the immediate post-operative period, iodine should be used in quantities similar to those given immediately before the operation. In cases of severe reaction the dosage should be pushed up to from 50 to 100 minims in the first twenty-four hours, but reduced rapidly from this level as soon as an improvement in the general condition follows. At the end of ten days the patient is receiving not more than 10 minims of Lugol's solution daily, and it is entirely withdrawn when she leaves the hospital.

Gade (1946) reports a controlled study in which two large groups of thyrotoxics were carefully observed after operation. One group had no iodine, in the other it was given in decreasing doses but sometimes in quite large amounts. No difference could be detected in the progress of the two groups.

Drainage of wound. If a drainage tube has been used it should be removed within twenty-four hours of the operation in practically all cases. Exceptions to this rule are mentioned in the section relating to intrathoracic and adenomatous goitres.

The Michel clips should be removed, as a rule, forty-eight hours after the operation, but when the patient is of a placid disposition they need not be left in more than twenty-four hours.

Early ambulation. It is our custom after thyroidectomy to get the patient out of bed on the evening of the day following operation, unless cardiac or other complication contra-indicates this. Thereafter progress is rapid and the patient is generally fully ambulatory by the end of seven days after which she is discharged.

Feeding. Food is not needed until the second day and fluid or semi-solid nourishment is ample up to the third or fourth, when a more normal diet may be resumed. From this time on, it is increased, so that towards the end of the first week the patient is taking ordinary meals.

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CHAPTER XXIX

POST-OPERATIVE COMPLICATIONS AND THEIR TREATMENT

Prophylaxis — Acute Crises — Haemorrhage — Cyanosis — Embolism — Respiratory Complications — Wound Infections. Tetany: Treatment — Cachexia Strumipriva — Symptoms — Treatment: Laryngeal Paralyses — Treatment. Injuries to Cervical Sympathetic Trunk. Imperfections of Scar. Swelling of Face.

Hurxthal *et al.* (1945) have reported on 1,016 patients with primary thyrotoxicosis operated on before 1927. Their paper brings home to us the dangers and difficulties of the pioneering days of thyroidectomy. It is a record of patients dying in crisis before and after operation, of persistent and recurrent thyrotoxicosis leading to a fatal issue, of tetany, of recurrent nerve injury and respiratory distress and of post-operative hypothyroidism.

Fortunately that picture has changed completely. Advances in thyroid and general physiology have achieved miracles to make thyroidectomy, to-day, safe, deliberate and efficient. Long accounts of the post-operative complications and their treatment have largely lost their significance. Prevention is better than cure and, with only very occasional exceptions, the old complications can be prevented. Unless the surgical team and equipment are adequate to achieve this goal the patients will be better treated medically: the indications are that there will be no future for anything but the best from thyroid surgery.

Technical advances have contributed to this changed horizon, but more important are the anti-thyroid drugs and iodine, improved methods of anaesthesia and management of post-operative pulmonary complications, the correction of anaemia and hypoproteinaemia by special feeding or intravenous therapy, the prevention of operative shock by blood transfusion during thyroidectomy, and the antibiotics to combat infective complications. There is no need now for speed, the technique should be deliberate, anatomical, bloodless.

(1) **The acute post-operative crisis of thyroidectomy.** This is almost entirely confined to the primary form of thyrotoxicosis and to the most severe grades of the disease, though it may unexpectedly crop up in the milder degrees.

It was formerly feared as the gravest and least controllable of all the difficulties met with after thyroidectomy, but with modern methods of preparation its occurrence should generally be regarded as an equally grave reproach to the surgeon. If sufficient time and care are given to the selection and exhibition of an anti-thyroid drug, the goitre can be converted into a non-toxic one and then the post-operative course will be smooth. Crisis, as

opposed to surgical shock, does not occur after operations for non-toxic goitre.

The exact cause of the condition is not fully known, but formerly it was regarded as being due to the flooding of the wound during and after the operation with thyroid secretion squeezed out from the gland during the manipulations necessary to remove it, and exuded from the cut surface of the remaining thyroid tissue. This conception of the cause of crisis led to the adoption of certain practices during and after the operation, designed to diminish absorption. It was urged that the gland should be handled very gently—advice which has had a most valuable influence in improving the technique of the operation, inasmuch as it has minimized surgical trauma and reduced the dangers incidental to haemorrhage from the surface of the gland. The more gently the gland is handled the less will be the haemorrhage from it. Drainage of the wound has also been insisted on with the object of facilitating the exit of thyroid secretion.

It is almost certain that the post-operative crises have nothing whatever to do with the absorption of thyroid secretion from the wound, for the following reasons:

(i) The same crises may follow any surgical operation on patients suffering from primary thyrotoxicosis, even when it has been conducted under conditions which eliminate the special risks attributable to the anaesthetic or to the operation itself. We have seen the complication after tonsillectomy, after appendicectomy, and after a simple laparotomy, completed within twelve minutes, for torsion of the pedicle of an ovarian cyst.

(ii) Some surgeons dispense with drainage in many operations for thyrotoxicosis without any appreciable increase in the incidence of crisis. If the absorption of thyroid secretion were concerned in the production of the crises, drainage would be essential rather than merely convenient.

Atnan *et al.* (1937) found a marked rise in the blood iodine during the first few hours after thyroidectomy, for example by 21·8 to 39·8 per cent. The level then fell to normal by the end of twenty-four hours. Sturm found experimentally that massage of the gland results in an increase in the iodine content of the thyroid venous blood by 110 per cent. But the rise noted by Atnam and others is non-specific. It occurs after most operations, e.g. herniorrhaphy in an otherwise healthy young subject.

The more probable explanation of the production of post-operative crises is that operations, acute illnesses, accidents and frights, tend to aggravate those thyrotoxic phenomena which are produced by way of the nervous system, and to destroy temporarily or permanently the powers of compensation, so that the temperature may rise as high as 107° F., the heart rate become almost uncountable, and auricular fibrillation may appear for the first time; there is extreme bodily restlessness, usually associated with cyanosis and delirium, the conjunctivae become suffused; and the whole picture of thyrotoxicosis becomes exaggerated.

Treatment is as emphasized prophylactic and depends on the proper preparation of patients and selection of time for operation. The anti-thyroid

drugs are the sheet-anchor of treatment and adjuvants include sedatives, a quiet, darkened room, the antipyretics, the transfusion of blood and other fluids to achieve water and electrolyte balance, and an oxygen tent.

(2) **Haemorrhage.** (a) **Reactionary or recurrent haemorrhage.**

(i) *Occurring deep to the muscles.* This complication is, fortunately, extremely rare with the technique which has been described; but occasionally, even when the greatest care is exercised, serious haemorrhage occurs during the first twenty-four hours. It takes the form of reactionary bleeding in the depths of the wound, either from a small artery which has been overlooked or has escaped from a ligature, or, much more commonly, it is the result of bleeding from a comparatively large vein. The rise of blood pressure which occurs during the few hours immediately after the operation and the strain of coughing or vomiting are the prime factors in its production.

Usually the haemorrhage is detected when the dressings have become soaked so that blood escapes copiously beyond the area covered by the bandages but in some cases the bleeding may be concealed by the clotting of blood in the lumen of the drainage-tube, when a mass of clot will form among the tissues of the neck, extending upwards and downwards alongside the larynx and trachea, and within a comparatively short time producing serious interference with respiration: the patient complains of a choking sensation and a feeling of constriction or tension in the neck; the voice often becomes altered; an irritable, ineffective cough begins; and in some cases definite inspiratory stridor develops. At the same time there is a deterioration in the general condition, indicated by a rapid rise in the pulse rate, pallor, with or without cyanosis, and restlessness which may become almost uncontrollable. It is here that alert nursing can save life.

The only proper treatment for this serious complication, particularly grave in thyrotoxic cases, is to open up the wound fully, preferably in the operating-theatre, and after rapidly clearing out the blood clot, which will be found penetrating freely into all the inter-muscular planes, to seek carefully, especially in the region of the poles of the gland, for the bleeding point or points, and to secure them in the ordinary way. As the patient's condition may give rise to alarm during this operation, intravenous glucose-water and blood should be administered throughout and afterwards until resuscitation is achieved. The wound must then be closed as rapidly as possible, omitting, if necessary, the suture of the muscles, but providing for drainage.

(ii) *Haemorrhage superficial to the infrahyoid muscles.* A less serious form of haemorrhage may occur through damage to one or other of the more superficial veins, either from the raised skin flap or from the surface of the infrahyoid muscles. This accident sometimes follows the puncture of a vein by a needle during the suture of the infrahyoid muscles. It results in the development of a large haematoma between the skin flap and the muscles, and in some cases the blood may find its way through the spaces between the latter into the pretracheal region. Such a haematoma rarely produces serious symptoms, but after from twenty-four to forty-eight hours the neck is found to be swollen to a size often considerably greater than before the operation

was carried out. With the swelling there is a certain amount of irritating cough and some dyspnoea. Discrimination is needed to decide whether to open up the wound and clear out the blood clot which has formed, or to wait a few days until the clot liquefies. If the latter course appears desirable, aspiration with a large needle and syringe will relieve pressure and facilitate the eventual resorption of the remains of the exuded blood.

(b) **Secondary haemorrhage** must be an exceedingly rare complication of thyroid operations. When it occurs it is invariably the result of virulent bacterial infection, and is arterial in origin. We have no personal experience of this complication in thyroid operations, and its treatment must be essentially prophylactic. When met with it can only be treated on general principles, namely, to expose and tie the bleeding vessel and to minimize infection by ensuring free drainage, combined with the use of the antibiotics and irrigants.

(3) **Post-operative cyanosis.** This is a peculiarly common feature in the graver forms of thyrotoxicosis. It may often have been noticed early in the course of the operation, and unless it is found to be due to over-extension of the neck or to temporary difficulties in anaesthesia, we agree with Cole (1944) that it should be regarded as a warning to curtail the scope of the operation. When it becomes obvious only towards the end of the operation, or after the patient has left the theatre, oxygen should be given by means of an intranasal tube, or by means of an oxygen tent or oxygen chamber. If the cyanosis derives from respiratory obstruction which cannot be promptly relieved by simpler methods then a temporary tracheotomy should be done without delay. It should be placed low down, through the third and fourth tracheal rings.

(4) **Post-operative embolism.** Pulmonary embolism occurs after operations on the thyroid both in the thyrotoxic group and in simple goitres, though far less frequently than after pelvic and abdominal operations.

Pemberton (1923) had but one case of pulmonary embolism in 4,970 operations for goitre. Early ambulation as now practised in most good clinics, together with the use of anti-coagulants and vein ligation, when indicated, should reduce its incidence to the vanishing point.

Emboli may occur at other sites. One of our patients, a woman of twenty-five, for seven years had had a severe form of primary thyrotoxicosis. Owing to her unsatisfactory cardiac condition the operation was confined to ligation of the arteries, so that the case cannot be classed strictly among the post-operative complications of thyroidectomy. She had a severe post-operative reaction, but nine days later appeared to be out of danger, when a sudden embolism occurred in the right popliteal artery. Her condition precluded the possibility of embolectomy, and she died three days later, gangrene of the leg being by then evident.

The switch to regular rhythm after thyroidectomy in fibrillators involves a risk of cerebral and peripheral embolism, and this risk is greater when old rheumatic carditis and mitral stenosis have co-existed with thyrotoxic heart disease. Two of our fibrillators have suffered emboli after thyroidectomy, but in neither case was there any evidence of old rheumatic heart disease. In

the one, embolus at the junction of the femoral and profunda arteries on the right side twelve days after operation was followed by exactly the same complication on the left side, forty-eight hours later. Successful embolectomies were done and she made a good recovery, though ischaemic residua were still present in the muscles and nerves of the left leg four years later. In this patient the heart rhythm was noticed to be regular for the first time in the interim between the embolic phenomena. In the other patient, cerebral embolism may be presumed, though no necropsy was done. One month after thyroidectomy for thyrotoxicosis, with fibrillation and severe heart failure, she was found sitting in her chair, unable to speak, and with paresis of the right side of the face and the right arm. The heart was still fibrillating. Six hours after admission, she suddenly became unconscious. There were complete paralysis of the right side of the face, and of the right arm and leg, and an extensor plantar response. She developed Cheyne-Stokes breathing and finally died ten hours later.

5. **Post-operative respiratory complications.** These may be:

I. **Tracheitis and laryngitis.** Formerly, when ether anaesthesia was more commonly used, these sequelae were frequently met with. The patient usually complains of a dry cough and of pain, both in coughing and swallowing. A tenacious, thick mucus forms, which is very difficult for the patient to eject and in the process of expectoration causes cyanosis and distress in breathing. The condition is not unknown with local anaesthesia or with any of the combinations of anaesthetics which we have used, and appears to be more likely to occur in patients with large, hard, primary thyrotoxic goitres of long standing than in those with simple goitres causing pressure. The voice may be altered as a result of the laryngitis which quickly supervenes on the tracheitis, and there is always the risk of spread to the lower respiratory passages and to the lungs. Consequently prompt treatment with penicillin and sulphonamides is indicated. Pulmonary atelectasis must be guarded against by tracheal and bronchial aspiration if exudate is excessive.

Injuries of the laryngeal nerves may result in the secretion of excessive mucus, anaesthesia of the laryngeal mucosa, aspiration of ingested fluids into the trachea, and distressing cough (Roeder, 1932; Johnson, 1935).

II. **Bronchitis, broncho-pneumonia, massive collapse, and abscess of the lungs** are all rare but serious complications.

All these respiratory complications are more common after recurrent nerve injuries and are at least to that degree preventable. The cords being flaccid the cough loses its explosive quality, and the exudates are not brought up. Similarly pneumonia is more common if a tracheotomy has had to be done. Prophylactic chemotherapy is thus strongly indicated in these circumstances.

Bronchitis is to be feared chiefly in those who have already been subject to it, and is more often seen in patients who have had operations for simple goitre causing pressure than in thyrotoxic cases.

Broncho-pneumonia may follow operations on intrathoracic goitres, for in such cases the lung has often been imperfectly expanded for years, and the

patient has generally suffered over long periods from recurrent attacks of bronchitis and possibly asthma. The complication may also follow operations for thyrotoxicosis done in city clinics during wintry conditions.

Mediastinal emphysema and pneumothorax. Mediastinal emphysema and pneumothorax occasionally cause death following thyroidectomy. They usually pass unrecognized, though with prompt treatment the patient's life may be saved.

Keis (1934) reported a case and collected seven others from the literature and since then some ten others have been added including three fatal cases by Barrie (1940). Recent competent reviews include those by Christensen (1948) and Seed (1949).

Usually there have been respiratory obstruction and coughing, with consequent over-inflation of the lungs, during the induction of anaesthesia or during operation. Rupture of intrapulmonary vesicles allows air to track along the pulmonary vessels to the mediastinum whence it passes up into the neck or seeps through into the pleural cavities (Macklin and Macklin, 1944). Dangerous positive pressure may develop in the mediastinum or pleura.

Hence, in the patient with dyspnoea, cyanosis, and short, dry cough after thyroidectomy, it is essential to look for subcutaneous emphysema in the neck, and pneumothorax. Billimoria (1947) stresses the value of radiography; only thus was the bilateral distribution of the pneumothorax detected in his case. Treatment consists in aspiration of the air from the pleural cavities, repeatedly if necessary. Alternatively, under-water drainage is instituted by means of an intercostal catheter. With such treatment recovery is prompt but otherwise this complication is quickly fatal.

Massive pulmonary collapse has been reported after thyroidectomy by Thomas (1938) and Stevenson and Stevenson (1941). In Thomas's case both lower lobes were affected but recovery occurred. Treatment of pulmonary atelectasis demands the prompt aspiration of all excess mucus from the trachea and bronchi. Gravel's method (1948) is simple and adequate, often resulting in dramatic improvement; a bicoude gum-elastic catheter is passed blindly in the ward, with or without local anaesthesia, and gentle intermittent suction applied in the trachea and both bronchi. Fifty or more cubic centimetres of muco-purulent secretions may be aspirated. The procedure s hould be repeated if excess mucus reaccumulates.

Pulmonary abscess has occasionally been met with following thyroidectomy. Chevalier Jackson (1930) attributes such abscesses to obstructive atelectasis followed by multiplication of micro-organisms in the oedematous pulmonary tissue, and advises treatment by aspiration through the bronchoscope. Abscess may also develop after intubation in the presence of severe buccal or faucial sepsis.

Prevention of pulmonary complications is to be sought by avoiding operations on all serious forms of goitre during the winter months, when cold, damp, foggy conditions prevail, and by the most scrupulous preparation of the mouth and teeth in order to minimize the risk of infection of the lungs from the upper respiratory tract. The administration of penicillin, 500,000 U.

daily for three days before and seven days after operation is an excellent prophylaxis against bronchopneumonic and other pulmonary complications. Oxygen administered by means of an intranasal tube or oxygen tent is a valuable addition.

6. Collections of serum in the wound: wound infections. Serious infection of thyroidectomy wounds is almost unknown. It is quite otherwise, however, with localized collections of serum, which tend to become mildly infected and with the localized forms of suppuration which tend to occur at or near the site of the drainage tube. In recent years, great improvement in wound healing has accompanied the more general use of non-absorbable sutures, notably cotton, as compared with former results using catgut sutures and ligatures. Catgut irritates the tissues and excites a serous and leucocytic exudate, with corresponding delay in the appearance of fibroblasts. The correlated clinical phenomena are slight local heat and redness of the wound with the accumulation of serum, and delayed healing.

Fine silk or thread was recommended in the original edition of this book, as being more likely to promote sound healing than catgut, and much subsequent work, ably reviewed and substantiated by Meade and Ochsner (1940), has only confirmed this view. Meade and Ochsner's own work strongly suggests that cotton is in fact definitely superior to silk, and in view of its ready availability, its ease of sterilization and cheapness, we now use it as a routine throughout our thyroidectomies. Number 100 plain cotton is used for small and number 60 for larger vessels. Interrupted sutures are used always and the ligatures are cut on the knot.

Meade and Ochsner (1940), Guthrie and Schimmel (1944) Puestow (1940), have all reported greatly improved healing of their thyroidectomy wounds and greatly decreased need for wound drainage since changing over to non-absorbable sutures.

The wound should, however, always be watched carefully, especially from the fourth to the tenth day after operation, and if any bulging is observed in the centre a probe or an aspirating needle should be inserted and the fluid withdrawn. If this procedure is repeated on one or two occasions usually no further trouble will arise; but should definite suppuration occur, associated with rise of temperature and redness and swelling of the wound, it is better to institute chemotherapy and to provide drainage where indicated. Fortunately the majority of such cases heal rapidly after the evacuation of the pus, and the scar is often very little inferior in appearance to that seen in uncomplicated cases. We have also recently met with an instance of a large localized abscess developing nearly a year after a sub-total thyroidectomy for thyrotoxicosis in a male aged forty-four. The wound healed rapidly after a simple incision.

7. Tetany. Because of the vital role they play in calcium metabolism, excision or destruction of the parathyroids ranks as the most serious of all the long-term complications of thyroidectomy. Prevention of damage to these structures depends on a clear knowledge of their anatomy and relationships and these are only intelligible in the light of their development.

Development of the parathyroid glandules. The more cranial arch tends to be more forward in its development, larger, and to overlap the one below. This is well illustrated in the case of the third and fourth pharyngeal arches. The ventral and dorsal (or lateral) growth pockets of the third pharyngeal pouch are destined to form the thymus and lower parathyroid respectively (Hammar, 1911). These pockets grow down into the subpharyngeal layer of loose mesoderm and carry with them the epithelium of their groove. The whole anlage is only connected with the pharynx by a thin elongated stalk, which passes lateral to the rudimentary carotid trunk and medial to the developing jugular (cf. Fig. 22). The cells at the dorso-lateral angle of the anlage subsequently form the lower parathyroid, those ventrally and medially the thymus. The ventral pocket of the third pouch is from the beginning closely associated with the pericardium. This connexion it retains; as the heart and the pericardium descend into the thorax, the primitive thymus accompanies them. The cephalic end of the third pouch rudiment moves down until it lies definitely caudal to the level of the fourth ventral pouch.

At the 16–20 mm. stage, the third pouch complex has become free from the pharynx and consists of a cranial enlargement, the rudimentary lower parathyroid, and a caudal thymic expansion. An intermediary epithelial cord, the thymic cord of Hammar, connects the two. This elongated structure presents a varying relation to the lateral thyroid lobe, being in relation to its dorsal aspect above, and passing on to its lateral surface below. With the final " descent " of the heart and thymus into the thoracic cavity, the thymic cord ruptures. Parathyroid III is then subject to no special growth shiftings, but because of the expansion of the thyroid it comes to be applied closely to its posterior or lateral surface. It will be apparent, too, that it may occupy a position caudal to the lower pole of the developing gland, or, should it retain its connexion with the thymus, it may come to lie within the thorax.

Because of its later development and growth, complex IV comes to lie medial and dorsal to both the third pouch complex and the developing thyroid lobe. In its downgrowth the fourth pouch complex passes medial to the carotid. It is much less influenced by the " descent " of the heart than the complex III, and having effected partial fusion with the lateral thyroid lobe, remains more or less stationary. Thus, its parathyroid tissue, derived from the dorsal epithelial pocket, lies cranial to that from pouch III. Since complex IV, moreover, effects some degree of fusion with the postero-medial surface of the lateral thyroid lobe, this upper parathyroid comes to lie in very close contact with this aspect of the gland. Not infrequently it is partially or wholly embedded in it.

On embryological grounds, therefore, the inferior parathyroid may be found anywhere on a line joining the side wall of the pharynx, just below the greater cornua of the hyoid bone, and the cranial end of the thymus. The line is a curved one, and extends through the carotid sheath between the carotid artery and internal jugular vein; thence it runs down on the postero-lateral aspect of the lateral lobe of the thyroid.

The superior glandule from the fourth pouch will be found on a line connecting the pyriform fossa of the pharynx and the middle of the postero-medial surface of the lateral thyroid lobe. This line is short and direct, and passes medial to the carotid trunk.

Anatomy of the parathyroid. The following data are largely taken from Gilmour's papers (1937–39) which are models of accuracy and completeness.

Weight of the glandules. In normal adults the average weight of each glandule is about 120 mg., but the parenchyma itself weighs only about 85 mg. The normal range, however, is wide and a glandule cannot be regarded as abnormally heavy even if it weighs 390 mg., and has a parenchymal weight of 190 mg.

Size. In adults the diameters of the glandules average approximately $6{\cdot}5 \times 3{\cdot}5 \times 1{\cdot}5$ mm. Glands beneath the capsule of the thyroid are often smaller than the other glands present.

Form, consistence and specific gravity. The glandules are usually oval or elongated and somewhat flattened, but sometimes they are perfectly spherical or quite flat and leaf-like. Pressure by a goitre frequently produces flattening, occasionally to a paper-like thinness spread out on the capsule of the thyroid. Flattening is most often seen in the position IV 3, where the glandule is compressed between the goitre and the trachea. Parathyroids IV in positions IV 4 and 6, alongside or behind the oesophagus, are often longer than usual, and frequently embedded in rather elongated fatty pads.

The outer surface is characteristically smooth, but a hilum can usually be identified at the point where the vessels enter. Occasionally small glistening or milky cysts can be seen on the surface or within the glandule.

The consistence is characteristically soft and inelastic so that the glands remain in any shape imposed upon them. Lymph glands and thyroid tissue are much more firm and elastic. Congestion, however, tends to make the glandules firmer.

The glandules usually sink in water, but in about 15 per cent. of cases they float, so that this test is only of value in distinguishing parathyroid from adipose tissue when the tissue sinks.

Colour. In adults the glandules are predominantly yellow but most glandules have a brownish or pinkish-brown element in the yellow, congestion increasing this tendency. The yellow colour is due to intra-cellular pigment rather than fat; Gilmour found no fat on microscopic examination of some glands that were pure yellow.

Number. In his 428 dissections, Gilmour (1938) found 1,713 glands, an average of four in each subject, with the following distribution.

2	glands	were	found	in	1 case	(0·2 per cent.)
3	,,	,,	,,	,,	26 cases	(6·1 per cent.)
4	,,	,,	,,	,,	374 ,,	(87 per cent.)
5	,,	,,	,,	,,	25 ,,	(6 per cent.)
6	,,	,,	,,	,,	2 ,,	(0·5 per cent.)

When only two or three glandules were found it was possible that others were overlooked, but according to Gilmour the possibility of a real diminution

in number below four must certainly be recognized. In no case were more than six glandules found.

Position. The topography of the glandules is shown in the figure (Fig. 165) from Gilmour (1938).

(a) Parathyroids III.

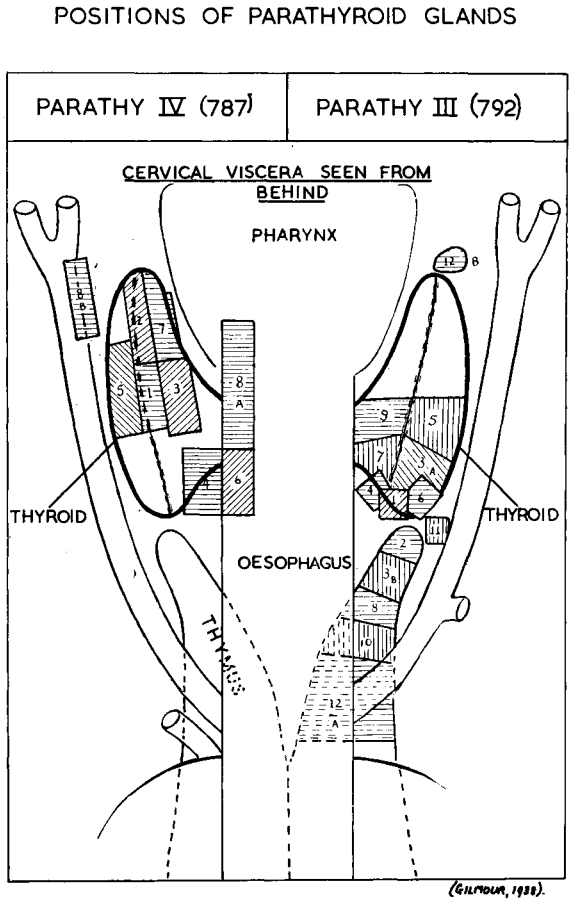

FIG. 165.—The numbers indicate the sites occupied by parathyroids III and IV in order of decreasing frequency, as detailed in the text. The line drawn down each lobe of the thyroid represents the posterior border, which has been retracted laterally. Only 2 out of nearly 1,600 parathyroids dissected, lay on the anterior aspect of the thyroid gland.

Gilmour arranged 792 parathyroids III into fourteen groups which are numbered in the figure in order of diminishing frequency of occurrence.

1. On the thyroid at or just behind its lower pole or not more than 0·5 cm. below the lower pole—53·9 per cent.

2. 1 cm. below the lower pole of the thyroid—12·8 per cent.

3A. On the posterior part of the outer surface of the thyroid 1–1·5 cm. above its lower pole—6·9 per cent.

3B. Two centimetres below the lower pole of the thyroid (6·9 per cent.).

4. On the thyroid just internal to its lower pole and between it and the trachea—6·4 per cent.

5. On the posterior part of the outer surface of the thyroid 1·5–2·5 cm. above its lower pole—5·2 per cent.

6. On the thyroid just external to its lower pole—2·3 per cent.

7. On the medial surface of the thyroid 1–1½ cm. above its lower pole and between the gland and the trachea—1·6 per cent.

8. 3 cm. below the lower pole of the thyroid—1·4 per cent.

9. On the medial surface of the gland and between it and the trachea, 1·5–2·5 cm. above the lower pole—1·1 per cent.

10. 4 cm. below the lower pole of the thyroid—0.9 per cent.

11. Attached to the sterno-thyroid muscle below and in front of the lower pole of the thyroid—0·3 per cent.

12A. 6 cm. below the thyroid—0·1 per cent.

12B. At the upper pole of the thyroid—0·1 per cent.

Only one of the glandules was found on the anterior surface of the thyroid, and this may be contrasted with Millzner's claim (1927 and 1931) that the glandules occur with high frequency on the anterior surface of the thyroid.

(b) Parathyroids IV.

The position of 787 parathyroids IV was in similar manner grouped as follows:

1. On the upper part of the middle third of the posterior border of the thyroid—73·7 per cent. This is the site of election, the glandule often lying in a groove on the thyroid or on a projecting nodule of it. The glandule usually lies above the inferior thyroid artery, but sometimes behind it or between it and the thyroid. It is rarely below the artery.

2. On or close to the upper third of the posterior border of the thyroid—9·4 per cent.

3. On the medial surface of the lateral lobe of the thyroid opposite the middle third of its posterior border, in relation to the entering vessels—7·24 per cent.

4. Between the lower third of the posterior border of the thyroid and the oesophagus and in the same plane as the oesophagus—5.85 per cent.

5. On the thyroid near the middle of the posterior half of the outer surface of the lateral lobe—5·2 per cent.

6. Behind the oesophagus opposite the lower pole of the thyroid or the lower third of its posterior border—1·14 per cent.

7. On the medial surface of the lateral lobe of the thyroid, opposite the upper third of its posterior border—0·63 per cent.

8A. Behind the oesophagus or pharynx opposite the upper two-thirds of the posterior border of the thyroid—0·25 per cent.

8B. Within the carotid sheath lying in a pad of fat on the inner side of the common carotid artery, below its bifurcation—0·25 per cent.

Gilmour gives the methods by which he is able to differentiate parathyroids III and IV in nearly all cases, but they need not be detailed here. It is of interest, however, that parathyroid IV, which develops in close relationship to thymus IV, is often found attached to or within a fatty pad, which is all that remains of thymus IV.

Relationship of parathyroid to other tissues.

Fat. The glandules frequently lie among, or actually within rounded, sausage- or spindle-shaped pads of fat. The glandules can usually be distinguished, however, since they have a delicate capsule, are not sub-divided into smaller lobules and have a small entering blood-vessel. Occasionally, they are greyer than ordinary fat or a gland within such a pad may be visible externally as a brownish area. Most of these fatty pads appear, in fact, to be involuted thymic glands, either thymus III or thymus IV.

Thyroid. The majority of both parathyroids III and IV lie upon the thyroid, though occasionally they may be within its capsule, in a sulcus on its surface, carried partially into it by vessels, actually fused with its substance, no intervening capsule being detectable by microscopy, or, very rarely, enclosed deeply within the thyroid.

Recurrent laryngeal nerve. Parathyroids IV in position 3, and parathyroids III in positions 7 and 9 are occasionally in contact with this nerve.

Sterno-thyroid muscle. Glandules in position III (11) may be attached to this muscle, as may those in III (1 and 2).

Paratracheal lymph glands. In the positions III (2 and 3B) glandules lie in close relation to lymph glands and can easily be confused with them.

Thymus. Close association, sometimes amounting to fusion, between the thymus and parathyroid, was seen naked-eye or microscopically in about 32 per cent. of glandules. In most of these cases, the glandule is in thymus III, or its involuted remains. In about a quarter of all these cases the thymic tissue was in the form of a fatty pad and its true character was only evident on microscopic section.

Walton (1931), emphasizes the changing relationship of the inferior glandule to the pretracheal fascia; more commonly the glandule lies below the level of the main inferior artery and then it is situated in front of the pretracheal fascia. When, however, it lies cranial to the artery, the fascia lies in front of it, and then, unless this layer is deliberately incised, the surgeon may fail to find a tumour of the inferior glandule.

Wellbrock (1929) of the Mayo Clinic, examined a series of 1,056 thyroid glands immediately after removal; in 7·76 per cent., one or more parathyroids were found and verified microscopically, yet only one patient had tetany. It was mild and transient, indicating that the surgeon has a margin of safety within which to work.

The blood supply of the parathyroids. Halsted and Evans (1907) found a special small parathyroid artery to be present in every case. The superior parathyroid receives its twig from the vertical anastomosing ramus between the inferior and superior arteries, or directly from the inferior artery or one of its branches. The inferior parathyroid artery arises from one of the

glandular, muscular or oesophageal branches of the inferior artery. In each case the artery enters a distinct hilus (Halsted and Evans 1907, Millzner 1931) and runs centrally within the glandule, giving off lateral branches to all parts of its substance.

Curtis (1931) has studied the collateral blood supply by injection methods in a series of twenty-five cadavers. He made his injections into the lower thoracic aorta, and, even after ligation of all four thyroid arteries, identified carmine-gelatin, his injection medium, in the parathyroids by means of frozen sections. He states that " the fascial connexions between thyroid and trachea and oesophagus, particularly in the region of the isthmus and the medial borders of both lobes, are important in maintaining this collateral blood supply." Curtis's experiments confirm that ligation of the inferior artery is unlikely to impair the blood supply of the glandules.

Modes of injury and their avoidance. Interference with the function of the glandules may result from manual or haemostat pressure, or from interference with their blood supply. Such direct and indirect traumata are probably commoner causes of post-operative tetany than removal of all four glandules (Harris *et al.* 1947). Palpation is very apt to cause haemorrhage into the substance of the body with at least temporary eclipse of function. In view of Wellbrock's findings given above, it seems that the risk of parathyroid tetany is in general slight.

It cannot be over-emphasized that tetany after thyroidectomy can and should be prevented and the best method of achieving this is to separate and preserve the whole of the antero-lateral layer of false capsules, to clamp and ligate the inferior veins close to the gland and finally to retain a strip of thyroid tissue from the posterior part of each lateral lobe. The last step was first suggested by Mikulicz. Using this technique, Roux, as early as 1894, was able to publish a hundred cases of thyroidectomy without either nerve injury or tetany as complications.

Incidence. The clinical features of post-operative tetany were first described by Weiss of Billroth's clinic in 1880 and though its incidence as estimated from the published statistics is extremely variable, this seems to be clearly diminishing. Thus, von Eiselsberg, in 1914, reported among 1,300 operations for goitre, fourteen mild and three severe cases of tetany, with three deaths.

Broderson and Harbitz (1926) in a series of 132 cases from Lied's clinic noted two cases of tetany.

Grasmann (1927) reported the incidence from three clinics as:

Sauerbruch (Munich)	1·3 per cent.
Schwabing Hospital	2 per cent.
Krecke Clinic	3·4 per cent.

Grace and Weeks (1941), on the other hand, report only one severe case in a consecutive series of 265 thyroidectomies and Vanderlaan and Swenson (1947) only one such in a series of 130 cases. Even better, Lahey (1941) claims that only ten cases of established tetany occurred in a total of 19,700

thyroidectomies at his clinic, and that there was none at all in the last 4,000 operations. There can be no doubt that its incidence falls to vanishing point as the skill and experience of the surgeon increase. Sporadic cases, will however, occur inevitably unless the young surgeon is first trained in an intra-fascial technique.

Clinical features. The clinical features which appear any time between twenty-four hours and some weeks after operation, are very well known from textbook descriptions and may be illustrated here by reference to a case seen at another clinic.

The patient was a tailoress, single and aged twenty-nine. She was admitted with classical Graves' disease and after the usual preparation at that time (1938) was submitted to sub-total thyroidectomy.

The immediate post-operative reaction was slight but five days afterwards she complained of aching in the legs, with tingling and " pins and needles " in the feet, legs, arms, and face. She felt weak (" as if a ton weight were holding me down ").

The symptoms varied in severity. For some hours she would be free of them, at other times they would recur severely, particularly after meals. On the sixth post-operative day, there were very severe spontaneous twitchings all over the body with spasms affecting the hands, feet and face. We observed her in one of these spontaneous attacks and it was exactly similar to the typical localized contractions induced by the application and inflation of a sphygmomanometer arm band; first theh and lay still, then fibrillary twitchings were seen in the forearm muscle groups, followed by spasmodic and irregular extension of one or more fingers, then the wrist became flexed and the hand assumed first the position of gripping and then the characteristic " Main d'accoucheur " posture. The fingers became dusky and cyanotic, and then, anaesthetic. When a cuff was similarly applied to the leg there was again intense discomfort followed by complete numbness, the ankle, tarsal and metatarso-phalangeal joints all becoming strongly flexed. The great toe was adducted, the other toes spread out.

Chvostek's sign was positive.

Apart from tetany, her condition was satisfactory, the temperature and pulse rate were normal, and the wound was healed. Serum calcium determinations, nine in number, between the eighth and sixty-seventh post-operative days, gave values between 5·0 and 6·0 mg. per cent. Throughout this time she was given calcium in large doses, both as the lactate and the gluconate by mouth. Improvement was only slight. When seen three months after operation her pulse and metabolic rates were normal and she had gained a stone in weight, but she still felt " pins and needles " in the fingers and legs and there were occasional twitchings of the face and legs. Her hair had become very thin and there were large areas of almost complete alopecia.

The following is an extract from the letter written by the First Assistant of a second hospital to which she was admitted nine months later.

" With regard to Miss E. N. with attacks of carpo-pedal spasm following thyroidectomy, for three months vision had been deteriorating, the nails had become brittle and there was almost complete loss of hair. Weight had been gained from 8 stone 12 lb. at operation, to 9 stone 11 lb.

Examination showed a well-built, healthy-looking woman with short newly growing scalp hair, defective dental enamel, ridged and brittle nails and early bilateral cataract. Chvostek's sign was positive. Basal metabolic rate was 110 per cent. of normal. Cerebro-spinal fluid was normal. Serum calcium was 4·9–5·7 mgm. per cent., the plasma phosphorus 6·3–9·0 mgm. per cent. Treatment was by a high calcium, low phosphorus diet with dihydrotachysterol (A.T.10) I c.c. of a 5 per cent. oily solution by mouth on alternate days. Discharged home with a view to lens extraction at a later date."

Even if such unfortunate cases are rare, their occurrence emphasizes that thyroidectomy should never be lightly advised and undertaken, especially by the inexperienced surgeon.

Treatment. As Hunter (1930) has emphasized, there are two clinical types of post-operative tetany. The one is mild and transient, the other severe and permanent. Treatment of tetany by calcium alone is unsatisfactory except in the mild post-operative type which, in any case, clears up spontaneously.

In the severe form, calcium must be combined with dihydrotachysterol, or vitamin D, and dietary measures, if the plasma calcium level is to be maintained approximately normal and the severe sequelae of the condition avoided. In an acute emergency, 10 c.c. of calcium gluconate should be administered intravenously. It may be pointed out, however, that though the symptoms of tetany including laryngeal spasm may be terrifying, the condition is seldom fatal. Further, if the blood calcium is kept normal in parathyroprivia, cataracts do not develop but once they have formed they do not regress (Albright, 1941).

Parathormone prepared by acid extraction of fresh glandules contains the active principle. It can be administered subcutaneously (1 c.c. or 100 units of parathormone) and is even active by mouth if given in large doses. One injection quickly corrects hypocalcaemia and the effect persists for up to twenty-four hours. It is unsuitable for prolonged therapy however, as immunity to it gradually develops (MacBryde, 1944).

The goal of treatment in chronic tetany is to raise the level of calcium to normal without overdoing this and obtaining hypercalcaemia. Dihydrotachysterol, like vitamin D, is a photo-chemical derivative of ergosterol and with it the blood calcium can be raised to any desired, or even undesired, level. Hypercalcaemia is indicated by the persistent presence of large amounts of calcium in the urine as shown by the Sulkowitch test. Albright (1941) prescribes about 3 c.c. of a dihydrotachysterol preparation a day until calcium appears in the urine, then the dose is dropped to a maintenance level, *i.e.* about 1 c.c. three to five times a week (1 c.c contains 5 mg. of dihydrotachysterol in oily solution).

Sevringhaus and St. John (1943) report on six women with permanent severe parathyroprivia treated by vitamin D and calcium salts orally, the duration of treatment being two years or more in four of the cases. The diets were unrestricted in respect of meat, egg, and milk intake; even so, symptoms were completely controlled and serum calcium maintained at a normal level. The doses varied from 150,000 to 400,000 U.S.P. units daily.

There were no evidences of toxicity or hypercalcaemia, and such treatment with a vitamin is less expensive than that with dihydrotachysterol.

McChesney and Giacomino (1945) in an experimental study found that though acute tetanic manifestations could be avoided with calcium salts alone, the blood calcium level remained dangerously low. They could find no marked difference between the magnitude and duration of the rise in blood calcium effected by vitamins D_2 and D_3, or dihydrotachysterol.

Anderson and Lyall (1939) did careful calcium and phosphorus balances on three patients with chronic severe parathyroprivia. They found that if the dietary phosphorus was kept at a low level the serum calcium could be raised to, and maintained at, a normal level provided calcium lactate was given in large doses. While the diet used by Anderson and Lyall could not be prescribed for long periods, their observations emphasize the importance of this factor. Thus milk. though high in calcium, is contra-indicated because it is likewise high in phosphorus. According to Albright (1941) the dietary conditions are sufficiently met if milk as a beverage is omitted from the diet, and if a teaspoonful of calcium gluconate or of calcium lactate be taken thrice daily dissolved in water.

To sum up, therefore, parathyroprivia is at all costs to be avoided, but if it does occur, proper treatment will maintain continued good health. Initial or acute manifestations should be overcome by intravenous calcium and intramuscular parathormone. Maintenance treatment includes regular supervision of the blood and urinary calcium, dihydrotachysterol or vitamin D both by mouth, and dietary precautions.

8. Cachexia strumipriva, or post-operative myxoedema. This complication is the result of the removal of the whole of the thyroid gland, or of such a large proportion of it that the remnant is incapable of maintaining normal thyroid balance. In Kocher's early series of operations on the thyroid (1883), in which complete thyroidectomy was aimed at, the incidence of cachexia strumipriva was very high, and the same is true, though in a less degree, of the Reverdins' results (1883). When the association between complete thyroidectomy and myxoedema was recognized by these observers it became necessary to evolve technical methods which would permit of the retention of sufficient thyroid tissue for functional purposes. For some years surgeons attempted to do this by hemithyroidectomy, or by removing the whole of one lobe and the isthmus of the gland, but, as we have described in a previous chapter, it is possible to carry out a symmetrical operation which will fulfil the indications for the relief of pressure and for the removal of sufficient thyroid tissue without jeopardizing the functional value of the remainder. Exceptions to this statement are fortunately rare. When they occur the explanation is: (1) that the portion of thyroid tissue preserved has been the site of extensive pathological change or has undergone further degeneration and fibrosis; or (2) that it is due to prolonged after-treatment with iodine, which is stated to limit or abolish the hyperplastic changes after thyroidectomy; or, finally (3) that it is due to excessive reduction of the arterial blood supply. It is not easy in any given case to decide which of these factors

is responsible for the development of the symptoms of myxoedema, but the fact that all the main arteries can be ligated in many hundreds of successive cases without any subsequent evidence of hypothyroidism makes it unlikely that arterial ligation is the cause. It is remarkable that some patients in whom a negligible fragment of gland tissue has been left, fail to develop overt hypothyroidism, and Hertzler (1945) argues that total thyroidectomy can be done with impunity in this respect. But, while post-operative hypothyroidism does not rank as a serious complication of surgery, it is best and generally to be avoided by preserving a modest portion of the posterior part of each lateral lobe.

Gillespie (1930) followed up 209 cases of thyroidectomy for goitre carried out from one to seven years previously. In approximately 8 per cent., definite hypothyroidism or myxoedema was found, and the B.M.R. ranged from −15 per cent. to −44 per cent. Only the higher degree of deficiency responded well to thyroid medication. Grace and Weeks (1941) found an incidence of only 2·9 per cent. among 360 patients followed up, but Vanderlaan and Swenson found some degree of hypothyroidism in 13·9 per cent. of their series of 130 post-operative cases. It may be noted, however, that all these data relate to the incidence of this complication before the routine adoption of anti-thyroid drugs to prepare patients. They have rendered possible a more deliberate technique and assessment of where the gland section should be made.

The *symptoms* of post-operative myxoedema very closely resemble those exhibited after experimental thyroidectomy. They may not be noticed for several weeks or months after the operation. Mental torpor and drowsiness, associated with a slight increase in the subcutaneous tissues, generally give the clue to the nature of the trouble.

Treatment. In a minority of these cases the condition may gradually improve without special thyroid therapy, but usually regular use of thyroid preparations will be necessary throughout the patient's life. Compressed tablets containing dried thyroid gland are the most generally useful. The dose must be carefully graduated to the necessities of the case. It is desirable to begin with small doses at first, gradually increasing them until the optimum effect is obtained. The clinical results should be controlled by repeated estimations of the basal metabolic rate, in order to obtain the maximum improvement in both the subjective and objective states of the patient. When the optimum effect has been attained, it is usually possible to reduce the dose somewhat and to maintain this smaller dosage permanently.

9. Affections of voice and respiration attributable to injuries of the recurrent and superior laryngeal nerves. (a) Recurrent laryngeal nerve. *Pre-operative states.* The frequency of these complications cannot be estimated unless the condition of the vocal cords before the operation is known. Systematic examination of the vocal cords shows that in addition to unilateral complete and incomplete lesions associated with malignant disease, or more rarely with inflammatory or simple forms of goitre, there is a definite percentage of cases in which patients without obvious change in the voice are found to have

partial or complete vocal cord paralysis. Paralysis may even be bilateral; thus Layton (1921) at a meeting of the Laryngological Section of the Royal Society of Medicine, showed a case of bilateral abductor paralysis of the cords in a patient with exophthalmic goitre who had never had any thyroid operation. Pre-operative laryngeal examinations are therefore essential if exact conclusions as to the incidence of post-operative laryngeal paralyses are to be drawn, but as a practical routine they are too burdensome and we limit them to special cases, namely those in whom laryngeal symptoms are present, the goitre is large, nodular, intrathoracic or malignant, or a previous operation has been done.

Post-operative recurrent laryngeal nerve paralyses. Types and diagnosis. As Heyd (1944) points out, the recurrent nerve may divide into two distinct branches before reaching the larynx. The one contains mainly abductor and the other mainly adductor fibres. One or the other may be damaged slightly, or completely interrupted. The injury may be inflicted at the operation or subsequently by pressure or fibrosis. Clearly there is room for a wide variety of lesions and laryngoscopic effects. The lesions may be classified as functional or organic, immediate or delayed, unilateral or bilateral, incomplete or complete.

It is a life-saving measure to ensure that the breathing be observed carefully when the intratracheal tube is removed and thereafter until the patient is fully conscious. If any respiratory embarrassment is suggested its cause should be at once sought and removed.

In all patients with hoarseness after operation, early laryngoscopy is indicated and will usually make the diagnosis clear. In difficult cases, however, collaboration between the laryngologist, neurologist and psychiatrist may be required.

Should doubt remain, the method advocated by Laszlo and Fiertz (1945) seems worthy of trial. While the cords are under inspection faradic stimulation is applied externally to the motor point of the larynx, on each side of the prominentia laryngea. If a faradic response is obtained the damage is minor and recovery can be expected within about two months; the lesion may be functional. If there is no response to faradism, the anodal closing and cathodal closing galvanic responses are tested, and the results interpreted as in other peripheral nerve lesions. If there is no response whatever to the strongest tolerable galvanism, the nerve is completely interrupted.

(i) Functional.

(ii) Organic.

(i) FUNCTIONAL. *Causation.* The altered physical conditions in the neck in the neighbourhood of the wound, and the onset of laryngitis and tracheitis as post-operative complications, increase the effort necessary for phonation and conduce to functional laryngeal lesions. In many cases an hysterical element is present in addition.

Such post-operative palsies are more likely to occur in neurotic patients, though by no means confined to them. They are not necessarily found immediately after the operation, and the nurse may have noticed the patient

speak with a natural voice while recovering from the anaesthetic. The paralysis may come on within a few hours or be postponed several days, and the voice is of the aphonic, whispering type, free from the hoarseness and diphony of the unilateral forms of organic paralysis, and quite unlike the breathless voice of bilateral partial abductor paralysis. Laryngoscopic examinations of functional paralyses reveal that they are abductor in type, and almost invariably bilateral, though the particular muscle or muscles affected vary, and the laryngoscopic pictures differ accordingly. The functional type of paralysis often clears up suddenly and seldom recurs, but we have known the condition to persist and to require faradic stimulation or similar methods of suggestion for cure. Intractable cases need re-educative measures.

(ii) ORGANIC. These may be unilateral or bilateral, incomplete or complete.

Anatomy. It must be remembered that the laryngeal muscles are supplied by the recurrent laryngeal nerve, but that the crico-thyroid is innervated by the external branch of the superior laryngeal nerve, and the arytenoideus (interarytenoid) supplied by fibres which reach it from the internal branch of the superior laryngeal nerve, as well as from the recurrent nerve. In complete paralysis, therefore, of the recurrent laryngeal nerve there still remains the capacity to keep the vocal cord taut by means of the intact crico-thyroid muscle. In addition, feeble adductor movements, insufficient as a rule to be effective, occur during attempts at phonation in bilateral complete paralysis of the recurrent nerves. These movements are produced by the muscle fibres in the arytenoideus which are innervated by the superior laryngeal nerve.

Physiology. Semon (1881) proved that when damage occurs to the recurrent laryngeal nerve, provided that the nerve is not completely divided or otherwise completely interrupted, the nerve fibres to the abductor muscles are more vulnerable, and therefore abductor paralysis is first to show itself. It has been supposed that the early involvement of the fibres to the abductors is due to their occupying a more superficial position in the nerve, but Negus (1929) has advanced the view that the abductor function, being evolutionally the last acquired, is therefore the first to go in the presence of disease or trauma.

Causation. It is easy to account for the paralyses which follow extensive resections for malignant disease, even when no paralysis existed prior to the operation, since it may have been necessary to extirpate the corresponding thyroid lobe and to ignore the nerve. There is no evidence of any anatomical peculiarity rendering the laryngeal nerves specially susceptible to injury, though the late George Crile described them as being " soft and naked, in contrast with a peripheral nerve." In fact they have the same structure as other peripheral nerves (Judd *et al.*, 1918; Berlin, 1935). The original author was against exposing the recurrent nerve, holding that mere traction on it would be sufficient to produce paralysis, but Berlin dissected out the nerve as a routine in total thyroidectomy for heart disease without causing paralysis, and Lahey (1939) and Cattell (1948) exposed the nerve in a very large series

of thyroidectomies without adverse effect. It seems that far less risk is attached to deliberate exposure of the nerve than to the blind resection of the posterior part of an adherent lateral lobe. The nerve is frequently stretched over the posterior surface of adenomatous or cystic thyroid swellings when these happen to develop in the region where the recurrent nerve lies close to the gland. The nerve is especially vulnerable during the exposure of such tumours, which should not be done with the fingers or by gauze dissection, but cautiously with the scalpel or a pair of scissors of the Mayo type, after locating the nerve. Inflammatory changes of an obscure nature sometimes occur around non-malignant tumours of the thyroid and add to the dangers associated with their removal.

The main source of injury to the nerve is its inclusion in ligatures or in artery-forceps during complete lobectomy, an operation which precludes the preservation of any thyroid tissue posteriorly for the purpose of protecting the vulnerable nerve and the parathyroid glandules. It has been the custom in some clinics to tie the branches of the inferior artery immediately after they pierce the posterior layer of the true capsule of the gland, rather than to secure the main arterial trunk remote from the gland: should any vessel of considerable size bleed during this process, there is imminent danger of damage to the nerve during hurried attempts to check haemorrhage as emphasized by DeCourcy (1950).

When paralysis of the vocal cord occurs at a later stage, it may be due to oedema or to scar tissue spreading into the sheath of the nerve from sutured or ligatured tissues in the neighbourhood. Bérard (1922) concurs in this view as to the origin of late paralyses of the vocal cord.

Laryngeal paralyses may be (1) immediate, (2) delayed. The symptoms may be divided into two main groups, changes in the voice and changes in breathing; there are subsidiary symptoms such as spasmodic cough, difficulty in expectorating mucus or in swallowing.

(1) *Immediate* laryngeal paralyses are due to bruising, stretching, or division of the nerve, or to its inclusion in ligatures. If unilateral and complete, hoarseness is noticeable as soon as the patient recovers from the anaesthetic, though its degree varies considerably in different patients. This variation in the vocal defect apparently depends on the compensating powers of the opposite vocal cord. In certain persons complete paralysis of one cord may be entirely obscured by the overaction of the other, and any slight hoarseness that exists is brought out only by fatigue. In others, the vocal defect is persistent and shows little improvement with time. Dyspnoea is not a feature of unilateral lesions, except in children, unless associated with oedema of the larynx or some degree of laryngitis or tracheitis.

The *prognosis* of these injuries is bad and apart from such amelioration as may be due to compensatory changes in the other vocal cord, we have observed little or no improvement in the majority re-examined at intervals up to three years or more. It happens occasionally, however, that recovery follows in from six weeks to six months, whence it must be assumed that the paralysis was due to bruising or stretching of the nerve.

(2) *Delayed* laryngeal paralyses are due to inflammation, oedema, or haemorrhage in the neighbourhood of the nerve. They may develop within a few hours of the operation or be delayed for many days. The prognosis is on the whole favourable.

i. Unilateral recurrent laryngeal nerve paralysis.

This may be incomplete or complete.

(a) *Incomplete. Abductor paralysis of one vocal cord.* There is little or no interference with phonation, owing to the capacity of the contralateral cord to compensate for the paralysed one. There is, however, some dyspnoea on severe exertion. The laryngoscope reveals the affected cord lying in the midline.

(b) *Complete.* All muscles except the crico-thyroid and part of the arytenoideus are paralysed. The cord occupies the " cadaveric " position, ***i.e.*** midway between the normal resting position and the midline. The opposite cord is still able to meet the paralysed one in most cases, but the difference of tension in the two cords gives rise to a peculiar, hoarse voice, which may have a diphonic quality. In rare cases the paralysis on one side may be of the abductor type, while on the other it is complete. The voice is, under these circumstances, very weak but not quite absent, and dyspnoea is prominent but not grave.

ii. Bilateral recurrent laryngeal nerve paralysis.

(a) Incomplete.

(b) Complete.

(a) *Bilateral incomplete or abductor paralysis.* Both cords lie in the midline close together; no abduction is possible. There is severe dyspnoea of an inspiratory type, associated with stridor. Barwell (1928) points out that spasmodic attacks of dyspnoea may accompany this type of lesion, and that they occur not only after exertion, but also during sleep, and are often fatal. Phonation is good, but is affected by the difficulty in taking a deep breath. If the lesion is progressive, a hoarse aphonia eventually supervenes from paralysis of the thyro-arytenoidei. When this incomplete bilateral lesion occurs during an operation intense dyspnoea and cyanosis follow, and tracheotomy is called for.

(b) *Bilateral complete paralysis.* The two cords occupy the cadaveric position; no effective abduction or adduction is possible; the voice is lost; but dyspnoea is much less pronounced than in the incomplete lesion.

Cinematographic records of the larynx at work (Pressman) reveal many facts of interest to the thyroid surgeon. It appears that when the true cords are functionless the false cords may aid in phonation. In unilateral recurrent paralysis, the ventricular fold is very prominent and tends to overlie the vocal cord which is in the cadaveric position. The contralateral vocal cord develops the most remarkable vigour and mobility in compensation.

The superior laryngeal nerve may be damaged independently of the recurrent nerve, or in exceptional cases both may be damaged. Injury of the

external laryngeal nerve results in paralysis of the crico-thyroid muscle, the tensor of the vocal cord. The latter is therefore lax, baggy or low-lying on laryngoscopic examination (Nordland, 1930). Some hoarseness may be present for a few weeks but no permanent disability results. With injuries of the main superior laryngeal trunk there is superadded weakness of the interarytenoideus causing more marked loss of phonation. There may also be severe pain referred to the jaw and ear. Injury to either superior or recurrent nerves is apt to stimulate the secretion of tracheal mucus (Higgins, 1927; Johnson, 1935). Even when the main superior trunk has been injured, complete recovery is the rule.

Incidence of post-operative paralysis of the vocal cords. Fritzsche (1921) in 332 cases had an incidence of 6 per cent. of laryngeal paralysis. Crotti quotes Billroth's results, viz., twenty-three complete or partial paralyses in seventy-one extirpations of goitre. Jankowski (1885) in a hundred cases of thyroidectomy had fourteen with paralysis of a vocal cord. Wölfler recorded, in 1890, six cases of bilateral paralysis, with four deaths from pneumonia. Leischner (1909), among a series he collected in which this accident had occurred, found four patients with complete bilateral paralysis, two of whom regained normal voice; and six with complete unilateral paralysis, three of whom recovered normal voice. Brodersen and Harbitz (1926) record one case of hoarseness in Lied's series of 132 patients. Elliott (1927) had six in a hundred cases, only two of these being permanent.

With the development of more deliberate techniques of surgery, the incidence of recurrent nerve palsy has fallen. Grace and Weeks (1941) found it in 1·7 per cent. and Vanderlaan and Swenson (1947) found only one permanent paralysis in 130 cases. Good results have been achieved by surgeons of the Lahey Clinic as given in the following table:

RECURRENT NERVE INJURY (CATTELL) 1948

Year	Injury	Number of operations
1942	8	957
1943	4	957
1944	4	937
1945	11	959
1946	6	985
	33	4,795

This gives a total incidence of only 0·7 per cent. though it should be noted that laryngoscopy was omitted in the absence of laryngeal symptoms.

Treatment. *Prophylaxis.* We are chiefly indebted to Lahey and his school for advising the routine exposure and dissection of the relevant part of the extra-laryngeal course of the recurrent nerves during sub-total thyroidectomy. The necessary dissection adds little to the operation and since the anatomy of the nerves is so variable there is no other certain method of avoiding their injury. Such exposure and dissection of the nerve is all the

more important during secondary operations and in operations for malignant or large nodular goitres.

Conservative. In unilateral lesions, compensatory changes fortunately occur and no special treatment is indicated if these changes are adequate. When vocal cord paralysis is persisting and giving rise to disability in breathing and speaking, the conservative treatment described by Weeks and Hinton (1942) should be used. The nerve area is stimulated by an interrupted cathode application and the muscles of the vocal cord by faradic and galvanic stimuli. When such stimulation results in movement of the vocal cords, the latter can be greatly increased by continued treatment.

Operative. This can only be palliative since suture of the divided nerve has given disappointing results. Thus, in three patients reported by Cattell (1948), the nerve was divided during the course of the thyroidectomy, in spite of its previous exposure. Nerve suture was done forthwith, but paralysis persisted in each case. If the opening between the cords is less than 2 mm., tracheotomy is advisable. If it is only a little wider than this the patient should be warned to avoid physical exertion, to guard against respiratory infection, and to return to hospital if dyspnoea worsens. The foregoing applies to patients in whom spontaneous widening of the fissure can be anticipated, but if doubt remains it is generally wiser to resort to tracheotomy without delay. Such tracheotomy need only be temporary.

The plastic operations inaugurated by King (1939) constitute an important advance in this field. They aim at widening the interval between the cords, thus making it possible to avoid permanent tracheotomy. King's operation broadly consists of a sub-mucosal approach to the arytenoid cartilage through an incision in the side of the neck, and suture of it to the lateral lamina of the thyroid cartilage. This results in the homolateral cord being pulled well over to the side of the larynx, thus opening up the glottis, in patients with permanent bilateral abductor paralysis. Morrison (1945) in reviewing and discussing the King method emphasizes the importance of the following three steps: 1. disarticulation of the arytenoid cartilage, 2. freeing the arytenoid from the tension of the inter-arytenoid muscle, and 3. removal of the attached tissue and fixation of the arytenoid in abduction for a period of time to ensure that the scar tissue will maintain it in that position.

Kelly (1941) devised an operation in which he resected a small window in the thyroid cartilage, removed the whole arytenoid cartilage, and with chromic catgut sewed the vocal cord to the fascia externally. Woodman (1946) has described a further modification of the extra-laryngeal approach to arytenoidectomy for bilateral abductor paralysis. Once the glottis is widened sufficiently, the threat to life has been averted and in some cases a surprising degree of recovery of speech may be achieved. The cords are rigid and immobile, but the patient can learn to phonate better with them than when they are lax and paralysed.

Hollinger (1945) has emphasized that in patients with recurrent nerve lesions surgery has often been radical or inept and consequently that medical care for associated tetany or hypothyroidism is necessary.

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10. Injuries to the cervical sympathetic trunk. As mentioned in Chap. XXI, the cervical sympathetic trunk may be involved not only in malignant goitres and in Riedel's disease, but also occasionally in simple goitres, either as a result of inflammatory changes or following a rapid increase in pressure due to sudden haemorrhage into an adenoma or cyst. It is not easy to explain injuries to this nerve during operations, but such are on record. In Fritzsche's series of 332 cases there were no less then four in which injury to the sympathetic trunk ascribable to the operation occurred, and Dubs (1922) had the same number in 840 thyroidectomies.

11. Imperfections of the scar. (a) *Hypertrophic and keloid scars.* A slight thickening of the scar is seen in about 5 per cent. of the cases, and in rare cases it is raised, red, and very conspicuous. In none of our cases has a true keloid scar developed after thyroidectomy, though this sequel may occur. It does not seem possible to predict in which patients hypertrophied scars will develop. We have seen fine, supple scars after thyroidectomy, whereas those of previous abdominal operations in the same patients have been unsatisfactory, and *vice versa*. After the lapse of a few months to a year or two the unsightliness of these scars often diminishes in the absence of any form of treatment, but in the more conspicuous ones X-ray therapy affords the best prospect of improvement.

(b) *Oedema of the flap.* This is seen in a small percentage of cases, particularly in patients who normally have rather a large amount of fat in the subcutaneous tissues of the neck. It is usually obvious before the healing of the incision, and may persist for months, but, though tending to improve, a certain degree of bulging above the level of the incision may remain indefinitely. The cause does not seem to lie, as might be supposed, in any obvious infection of the superficial tissues during healing. Probably it is due to the fact that in flaps containing much subcutaneous fatty tissue lymphatic drainage after replacement is slowly and imperfectly re-established. Some benefit may follow systematic massage of the affected area. It is essential in closing the wound that the skin edges be approximated accurately; on no account should the upper flap edge overlap that of the lower.

(c) *Adherent and puckered scars* appear to be due to excessive scar-tissue formation following a mild local infection near the track of the drainage tube, for we have rarely seen these troubles in a wound which healed rapidly. If the drainage tube has been brought out centrally such scar tissue may extend in to the trachea resulting in an unsightly indrawing of the scar on swallowing. We therefore advise that if a drainage tube be employed, it should be brought out laterally.

But if such indrawing and deformity of the scar does exist and is a cause of distress to the patient, a simple plastic operation, at an interval of from three to twelve months after the original operation, is usually successful in restoring the normal contour of the neck. Great care is necessary during the healing process to prevent the scar from again becoming adherent to the underlying muscles; regular massage of the superficial tissues with a simple

emollient ointment is the method which we have found most valuable in combating this.

12. Swelling of face. This peculiar sequel to thyroidectomy for thyrotoxicosis, first described by Thompson and Thompson (1929) we have seen only once. The case was a severe one in a married woman aged twenty. Within six months of operation the face was much thickened, all the soft parts apparently sharing in the swelling. There was no sign of oedema, the mental condition was normal, and the basal metabolic rate was plus 14 per cent.

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