Goitre : a contribution to the study of the pathology and treatment of the diseases of the thyroid gland / by F. de Quervain.

GOITRE

F. de QUERVAIN.


LIBRARY OF THE
PRESENTED
BY THE EDITOR OF
B. M. J.
BRITISH MEDICAL ASSOCIATION

GOITRE

A CONTRIBUTION TO THE STUDY OF THE PATHOLOGY AND TREATMENT OF THE DISEASES OF THE THYROID GLAND

BY

F. de QUERVAIN

Professor of Clinical Surgery in the University of Berne

TRANSLATED FROM THE FRENCH
BY
J. SNOWMAN, M.D., M.R.C.P.

(With 118 Illustrations and a Bibliographical Appendix)

London:
JOHN BALE, SONS & DANIELSSON, LTD.
83-91, GREAT TITCHFIELD STREET, W. 1.

1924

MADE AND PRINTED IN GREAT BRITAIN

TRANSLATOR'S PREFACE.

THE origin of this book is due to the many requests received by the author, Professor F. DE QUERVAIN, for a summary in French, of his contributions to the pathology and treatment of diseases of the Thyroid gland, which have mainly appeared in German treatises and periodicals.

The book is intended for those who are interested in the problem of Goitre, and no attempt is made to deal with the elementary aspects of the subject. Views which are definitely ascertained and generally accepted are not elaborated except where this is necessary for the proper comprehension of the point at issue. The problem of Goitre is regarded in relation to the anatomy, physiology and pathology of the thyroid gland, and the book reflects the personal experience of the author. The illustrations are taken from his earlier publications and from cases in his own clinic, with the exception of figures 10, 13, 22, 24, 25, for which the author is indebted to Dr. Wegelin, Professor of Pathological Anatomy in Berne University, and figures 1, 5 and 6, the sources of which are indicated. The anatomical specimens were prepared chiefly by Drs. Scabell and Walder, the clinical assistants of Professor de Quervain. The drawings were made by M. Dressler, who is also responsible for the illustrations of operative technique.

J. SNOWMAN.

INTRODUCTION.

An operation for goitre is one which many surgeons undertake with a considerable amount of apprehension. Before the era of aseptic surgery the thyroid was regarded with an amount of respect which discouraged operative intervention, and indeed operations on goitre were prohibited in 1850 by the French Academy of Medicine. This prohibition was apparently justified by the complicated anatomy of the region, by the abundant blood supply of the gland when altered by disease, by its intimate relations to the trachea, and by the fact that the operative mortality was 40 per cent. But owing to the work of Billroth, Kocher, Halsted and Poncet, it is now forty years since operations on goitre have acquired a position among the ordinary procedures of surgery. The actual technique of the operation cannot, however, be said to be definitely established, because a glimpse at the present-day operation theatres and a study of the modern modifications which are suggested, indicate that the last word has not yet been said, nor has perfection been attained. The immediate result of the operation always appears to be the same; the patient is relieved of his goitre and the wound heals by first intention. It seems to matter little whether the actual operation has been difficult and complicated by bleeding, or whether it has been accomplished with great facility. The operative mortality is scarcely 1 per cent., and this can hardly be improved upon by any new operative method, seeing that the main factors in the mortality must be the condition of the heart and kidneys, or any constitutional disorder of the patient. But something beyond operative mortality enters into the question at the present time. Patients are very exacting; they demand a scar which is scarcely visible, running accurately in the fold of the neck; their recurrent nerves and parathyroids must remain unscathed, sufficient thyroid tissue must be left for future requirements, and above all, they must be guaranteed against a recurrence.

Our treatment is therefore not exclusively limited to mere cure by operation, but will also take into consideration all these perfectly legitimate demands. A pre-existing hyperthyroidism or hypothyroidism may be present to render the surgeon's task more difficult, because these complications introduce a problem which is much more indefinite than the surgical anatomy of the thyroid region.

It is not our intention to review here the whole pathology of the thyroid gland; for this purpose the reader is referred to the masterly treatises of Eiselsberg, L. Bérard, McCarrison, Ochsner, Crotti and others. Neither is it our intention to give an account of the numerous methods which have been advocated for the removal of a goitre. Those who are interested in the history of the operation should consult the works of Kocher, Reverdin, Bérard, and especially Halsted. Our purpose is purely practical. It is to describe those few methods which daily experience of the operation has impelled us to adopt, and to emphasize those details which are essential for a beginner to realize. We have no desire to teach surgeons who are satisfied with their own method; our remarks are only intended for those who are searching for a method, or are dissatisfied with procedures they have hitherto adopted.

A few *historical references* must, however, be given, in order to enable the reader to appreciate the present position of the operative treatment of goitre.

The first recorded operation on goitre is said to have been performed by Abul-Kassim in the tenth century, and since that time each century has witnessed a repetition of the attempt. After 1800 these attempts became somewhat more numerous, but the operation was considered to be too hazardous until the period of antisepsis in surgery. Surgeons such as Desault, Walther, Porta, and others of equal eminence, had already adopted the technique of tying the superior and inferior thyroid arteries, and there were many who could neatly enucleate a goitre in its capsule. But it would be a mistake to suggest that there was any well-established technique before the antiseptic period. In order to establish a well-defined method, it was necessary to abolish the fear of septic infection, and post-operative secondary hæmorrhage due to infection. It is for this reason that the modern history of operations for goitre can only be said to date back for the last twenty-five years. When the dread of sepsis was overcome, operative possibilities seemed unbounded, and surgeons sacrificed the entire thyroid gland until the clinical investigations of Reverdin and of Kocher showed the disadvantages of this procedure. Since 1883, therefore, there has been a return to a more conservative attitude towards the thyroid tissue. Billroth and Kocher contented themselves with excising one lobe; Socin and Reverdin enucleated merely those portions of the tumour which were causing most obstruction. The frequency of diffuse colloid goitre in certain countries has led many surgeons to adopt the practice of Mikulicz and his school, and to replace unilateral excision by a bilateral resection—in the shape in which a melon is cut. Fear of injury to the recurrent nerves, and subsequently fear of compromising the parathyroids induced Kocher

to combine resection with enucleation, an operation which aimed at sparing the posterior surface of the gland. This operation was the favourite procedure of this master of thyroid surgery, and in most cases he only performed the unilateral operation—it may be described as a modified unilateral excision. The so-called absorbent ligatures which were sometimes applied on the opposite side were not able to prevent a recurrence, or rather the subsequent development of nodules in the lobe which was not dealt with at the first operation. The modern school has become convinced of the futility of performing an incomplete operation at the outset, owing to the frequency of genuine and false recurrences, and is favouring a bilateral operation, either a resection or an enucleation, or a combination of the two—with due respect, of course, to the recurrent nerves and parathyroid glands. This principle is upheld so emphatically by some keen operators that they leave nothing more of the gland than pedunculated grafts, and the amount of thyroid tissue left after the operation can only be measured in terms of cubic centimetres. But the functional value of the residual thyroid tissue is a matter which should receive consideration, and its importance estimated in different types of goitre. Such an investigation presupposes a standard to serve as a criterion, or, in other words, a biological study of goitrous tissue is required. This is a subject with which current thyroid surgery is now concerning itself, and it forms the leading theme of this book, although complete knowledge has not yet been attained.

In concluding this introduction we cannot do better than quote some remarks made by H. Lebert at the end of his preface to his classical treatise on goitre which appeared in 1862 : "New researches, new discoveries, new points of view appear daily. The purpose of any specific piece of work can only be to contribute something which is calculated to perfect our ideas on some limited field of knowledge." This truth has gained in force with the passage of time.

CONTENTS.

GOITRE.

CHAPTER I.

SURGICAL ANATOMY OF THE THYROID.

THERE is now very little doubt that the *thyroid gland*, in man, is developed entirely from the median pouch, i.e., from the thyroglossal duct, whereas the lateral pouches, products of the third and fourth branchial clefts, form the parathyroids and the thymus.

The weight of the thyroid gland varies from 20 to 30 grm. and is hardly palpable in the normal condition. It fills up the groove situated on either side of the trachea, and it protects the anterior surface of this structure.

In Japan, Horizawa found that the average weight of the thyroid was 17·47 grm. in the male and 15·3 grm. in the female. The weight varies among different races, in the same way as the entire body weight varies.

The thyroid may present certain abnormalities in shape and position which are of surgical importance. Thus the pyramidal lobe of L'Alouette may be absent in some cases, whereas it may be double in others. The isthmus may be missing, and the gland then resembles the thyroid of the dog. In rare instances, scarcely 1 in 1,000, one of the lateral lobes is missing (Stierlin). Sometimes the entire organ is displaced downwards (thyroptosis). In some cases, one of the lateral lobes, or even both of them, slip between the trachea and the œsophagus, or between the latter and the vertebral column (retrovisceral position).

Accessory glands are sometimes met with along the course of the thyroglossal duct, occasionally within the trachea, and very rarely inside the thorax.

In man, the *parathyroid glands* are situated externally to the thyroid,

FIG. 1.—Position of the parathyroid glands, as determined by Halsted and McCallum, based upon 67 autopsies.

on its posterior surface, between it and the thyroid fascia. In the dog, the parathyroids are within the thyroid gland, and this condition is met with occasionally in man. According to Bérard and Alamartine one should differentiate between (1) the *main parathyroids*, of which there are two on each side, (2) the *accessory parathyroids*, which are behind or beneath the thyroid, and (3) the *aberrant parathyroids*, which may exist anywhere within the branchial area. According to these authors, the main parathyroids may occupy one of three positions: high, medium or low. If in the first position, they will be situated at the level of the middle of the thyroid cartilage at the lateral border of the pharynx; if in the second position, they will be at the level of the cricoid cartilage, and if situated low they will be on the posterior surface of the gland beneath the middle branch of the inferior thyroid artery.

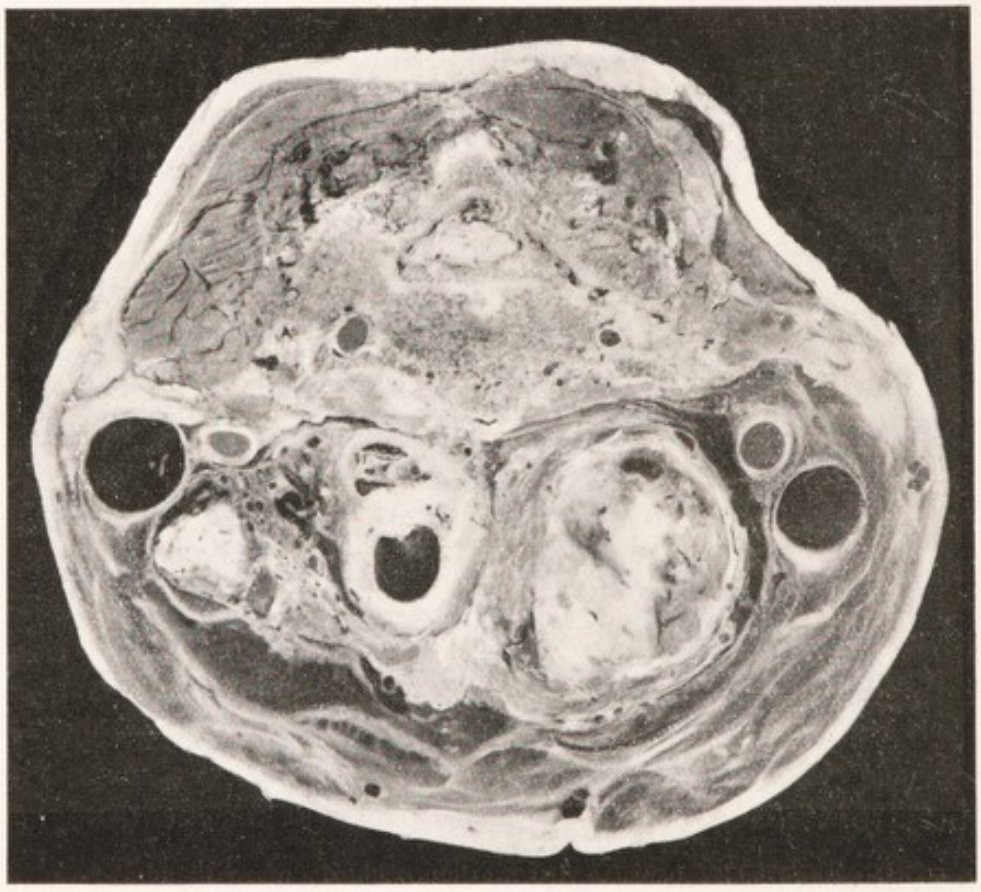


FIG. 2.—Section of neck. Nodular goitre, partly calcified. The interfascial spaces are injected with gelatine.

In fig. 1, which was published by Halsted, McCallum has superimposed the situation of the parathyroids as ascertained in sixty-seven autopsies. This figure illustrates admirably the extent of the limits of the posterior capsule, which we designate, with Crotti, the dangerous area.

The relations of the thyroid gland and adjacent organs to the fibrous sheaths of the cervical region are of the greatest interest, from the surgical aspect. As the descriptions given in most of the anatomical textbooks appear to be imperfect since 1911, we have devoted some detailed study to the topography of this region, partly in the course of operations upon goitres and partly by dissections on the cadaver. These latter investigations were mainly carried out, with the

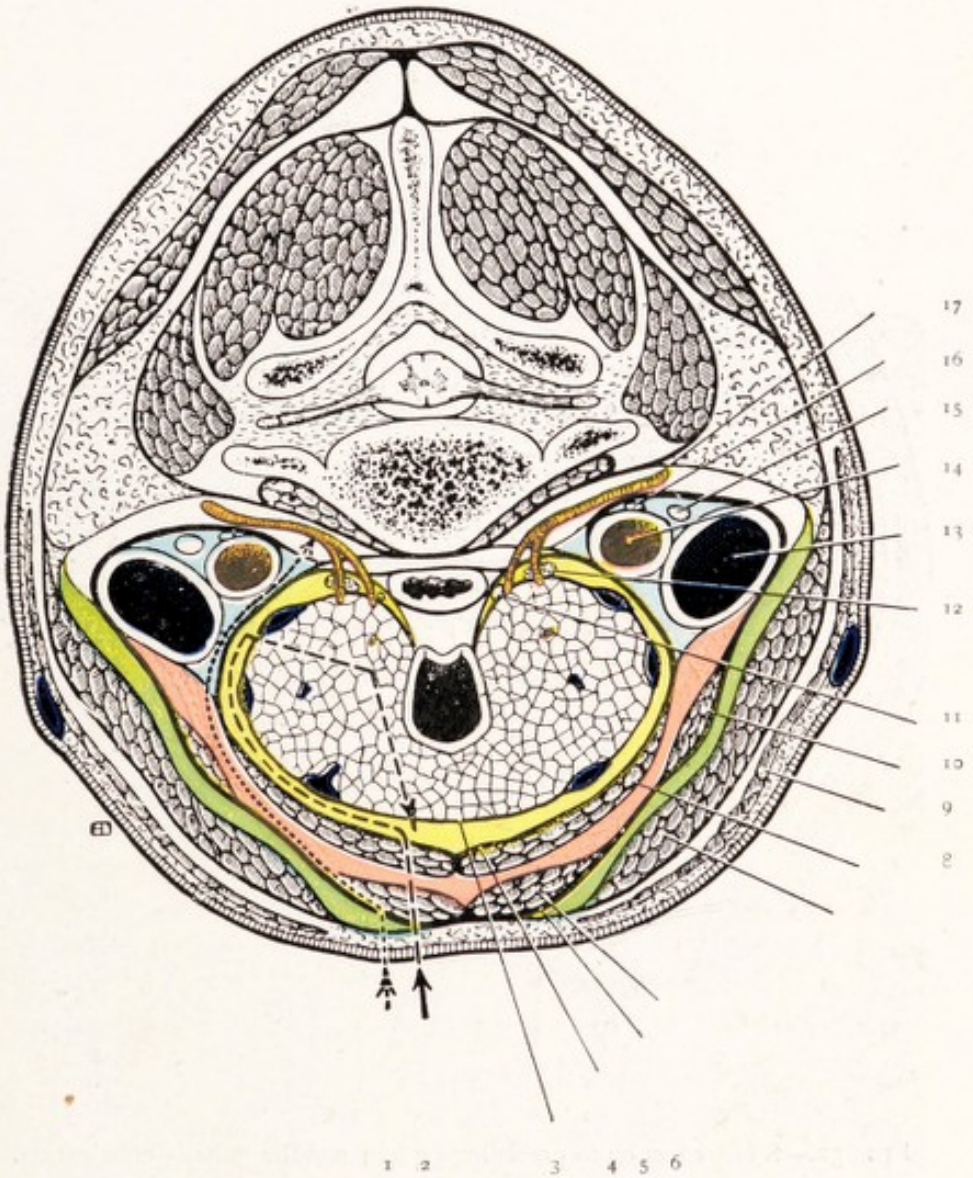


FIG. 3A.—Transverse section of the neck at the level of the isthmus of the thyroid gland. The anatomical arrangement has been obtained by the injection of gelatine into the principal aponeurotic spaces. Diffuse hypertrophy of the gland. Resection.

(1) Extrafascial route of approach (i.e., passing outside the thyroid fascia) towards the inferior thyroid artery.
(2) Intrafascial route of approach (i e., passing within the thyroid fascia), for resection or enucleation of a goitre.
(3) Special capsule of the thyroid.
(4) Thyroid fascia (external capsule).
(5) Exterior sheath of the small perithyroid muscles.
(6) Sterno-hyoid muscle.
(7) Sterno-cleido-mastoid muscle.
(8) Sterno-thyroid muscle.
(9) Platysma.
(10) Omo-hyoid muscle.
(11) Recurrent nerve.
(12) Parathyroid glands.
(13) Internal jugular vein.
(14) Carotid artery.
(15) Vagus nerve.
(16) Cervical sympathetic nerve.
(17) Inferior thyroid artery.

aid of injections of transparent gelatine. The first experiments, made with differently-coloured gelatines, were directed to the study of the various inter-aponeurotic spaces. The results were published in 1912, and it was shown that four compartments existed in the anterior region of the neck.

(1) *The sterno-cleido-mastoid compartment.*—This compartment contains the muscle of that name. Its extent, on transverse section, is

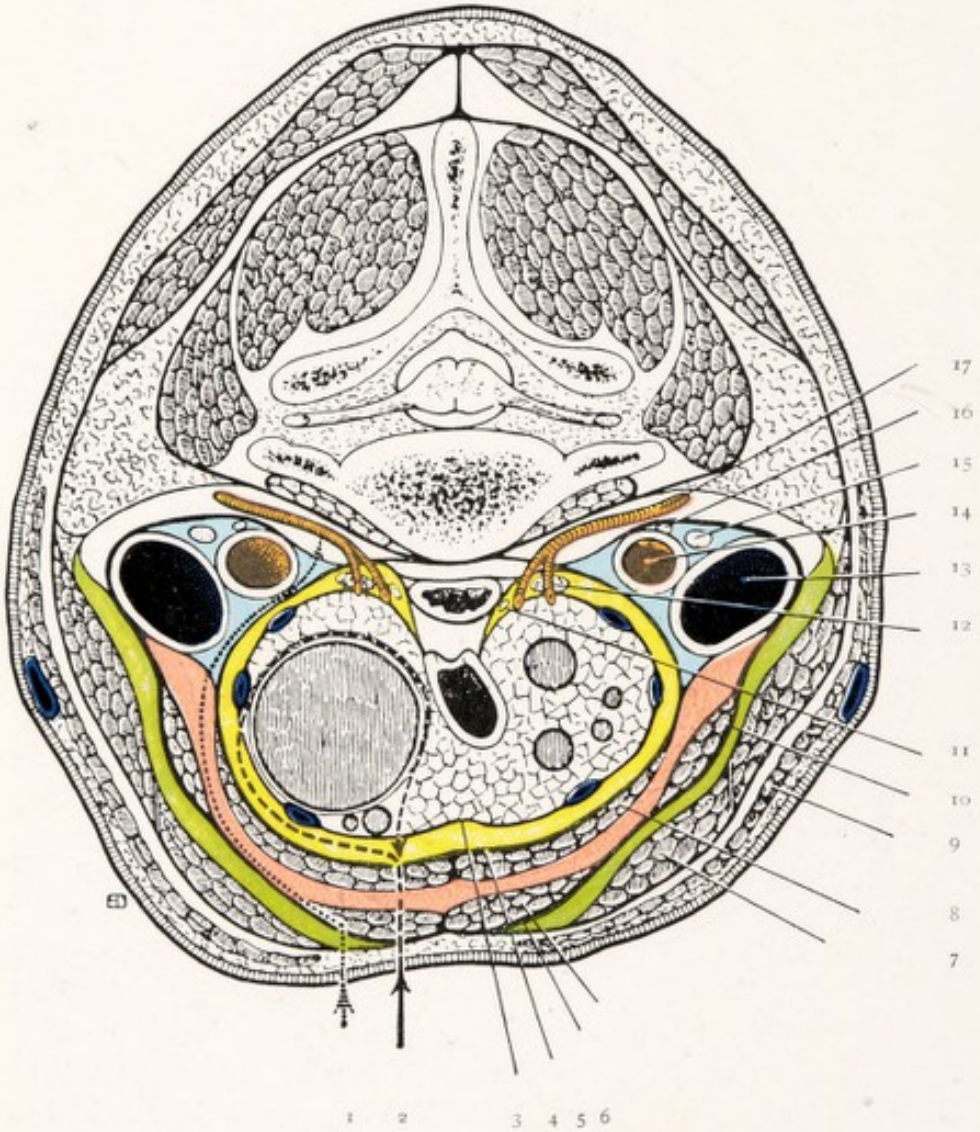


FIG. 38.—Similar section to preceding figure; nodular goitre—enucleation.

from the platysma to the aponeurotic sheath of the small thyroid muscles, and posteriorly it reaches the compartment of the large cervical vessels. It includes in the lower part of the neck the inferior portion of the omo-hyoid muscle, the upper portion of this muscle being in the compartment of the small thyroid muscles.

(2) *The small thyroid muscles compartment.*—This contains the sterno-hyoid, sterno-thyroid and the upper portion of the omo-hyoid. Externally, it is limited by the aponeurotic sheath of the small

muscles, and internally by the perithyroid fascia, which constitutes the deep layer of the sheath of the small muscles. Posteriorly it extends, like the preceding compartment, to the blood-vessel compartment, without however merging with it.

(3) *Thyroid (or visceral) compartment*, which contains the thyroid gland, the trachea and parathyroids. It is bounded externally by the perithyroid sheath (thyroid fascia) and on the visceral side by the true capsule of the thyroid.

(4) *The blood-vessel compartment* contains in two well-defined subdivisions the internal jugular vein and the carotid artery accompanied by the vagus nerve.

These four spaces extend posteriorly as far as the deep cervical aponeurosis, which is itself divisible into at least two distinct layers. The two former spaces merge with each other towards the narrow superior aperture of the thorax; but at the level of the isthmus of the thyroid—which is the important position from the operative aspect—the two spaces are quite separate. Unless one employs a considerable amount of force, it is impossible to make the gelatine pass from one space into another, and this fact renders it quite easy to fill each compartment with a differently-coloured gelatine. As already stated, the parathyroids are within the thyroid compartment, and the same applies to the recurrent laryngeal nerve at this level. The blood-vessel compartment contains the vagus, and also the trunk of the sympathetic nerve, surrounded by a fine lamina of connective tissue. The anterior layer of the deep fascia of the neck separates the inferior thyroid artery from the blood-vessel compartment. The artery passes through this layer behind the thyroid gland, very often at the level of its bifurcation. It is also at this level that it crosses the recurrent nerve.

The following method of investigation was carried out in a second series of experiments. After a preliminary injection of the arteries of the body with red gelatine, and of the veins with blue gelatine, all the spaces of the neck were infiltrated with a transparent colourless gelatine. The neck was then frozen, and a section $2\frac{1}{2}$ cm. in thickness was cut at the level of the seventh cervical vertebra. This section, prepared according to Kaiserling's method, was immersed and preserved in transparent gelatine. The tissues were thus subjected to a kind of artificial œdema, which made the various aponeurotic layers stand out very clearly. This œdema is shown in fig. 2.

The following are the main conclusions which may be derived from a study of these preparations (see our publication of 1915).

(1) The sterno-cleido-mastoid compartment is bounded internally by an aponeurotic layer which is usually thick enough to represent, at the same time, the external layer of the small muscles compartment and the common external sheath of the sterno-hyoid and sterno-

thyroid; posteriorly, this layer merges with the sheath of the large cervical vessels.

(2) The compartment of the small thyroid muscles is bounded internally by an equally well-marked aponeurotic layer, which takes part, posteriorly, in the formation of the vascular sheath. Kocher called this layer the perithyroid sheath; some anatomists call it the thyroid fascia, and most surgeons term it the external capsule. This sheath divides into several layers behind the thyroid, and forms part of the sheath of the large vessels and surrounds the œsophagus. It is lost in the deep cervical aponeurosis.

(3) The thyroid gland has its true capsule which bounds the thyroid (or visceral) space internally, and which meets, behind the trachea, one of the layers of the perithyroid sheath.

(4) The vascular sheath is mainly formed by the aponeurotic layers which we have just mentioned, i.e., by the one which separates the sterno-cleido-mastoid compartment from the compartment of the small muscles, and by the one which separates the latter from the thyroid compartment.

The opportunity of checking these anatomical points daily, on the living subject, confirms their accuracy. Of course, variations do occur in the relative thickness of the layers; these may be peculiar to the individual or they may be the result of the particular kind of goitre. Sometimes the two principal aponeurotic layers are the layer which covers over the small muscles and the one which separates the compartment containing these muscles from the thyroid compartment—an observation noted both in the living subject and in the cadaver. Observation on the living subject also confirms the fact that the most direct method of approach to the horizontal portion of the inferior thyroid artery is through the space containing the small muscles. By keeping to this space there is little risk of injuring the internal jugular vein on the one hand, or the recurrent nerve and parathyroids on the other. It was really the investigation of this route which formed the starting point of our anatomical study.

One of the important facts brought to light by our researches between 1912 and 1915 is the interdependence of the fibrous laminæ forming the sheath of the small muscles, the vascular sheath, and the sheath of the visceral compartment. Sebileau and Herbert were the first to realize this interdependence; later on Cunéo and Descomps described it, and more recently it has been confirmed in a detailed study by P. Truffert. The principal difference between our description and that of Truffert is in the circumstance that we begin with the description of the aponeurotic sheaths of the muscular compartments, whereas M. Truffert begins with the vascular sheaths. But as these sheaths all begin to develop simultaneously, this difference is of no practical importance. The end result is identical.

1.—THE BLOOD-VESSELS OF THE THYROID GLAND.

A.—ARTERIES.

The classical work on the blood supply of the thyroid gland has been completed within the last few years by the researches of Halsted and Evans, Bérard, Landstroem, Delore and Alamartine, Enderlen and Hotz. The following are the main conclusions which follow from a study of these works and from our own personal investigations and observations.

(1) The *superior thyroid artery* is at the same time the primitive artery and the principal artery of the *normal* thyroid gland. Its branches encircle the upper pole of each lobe. The arrangement of these branches is very variable. As a rule there is an antero-internal branch which is a direct continuation of the main trunk; there are also an antero-external and a posterior branch which are both smaller than the first. The posterior branch always anastomoses with the superior branch of the inferior thyroid artery.

(2) The *inferior thyroid artery* is not so constant as the preceding. It is missing in a certain number of cases—in about 2 to 3 per cent. according to our observations. This anomaly is sometimes unilateral and sometimes bilateral, and the artery is compensated for by a greater development of the superior thyroid, or by a well-formed lower artery (the artery of Neubauer). On reaching the gland the artery divides into several branches, one of which anastomoses with the posterior branch of the superior thyroid artery. In exceptional cases the artery takes its origin in the primitive carotid. As a rule, it reaches the gland at the junction of the middle and lower third, and on the posterior surface of the lobe. Its branches intertwine, in this situation, with the recurrent nerve. The trunk of the artery is surrounded by fibres of the cervical sympathetic, at the level of the carotid.

(3) The *lowest artery* (l'artère ima, artery of Neubauer) is somewhat rare, and is very variable in its relations with the other arteries of the gland. It is sometimes present only on one side, and sometimes it is bilateral.

(4) The *parathyroid vessels* are derived from one of the branches of the inferior thyroid immediately outside the true capsule of the thyroid, i.e., in the thyroid compartment previously described.

(5) The thyroid arteries have each their special area of distribution, but they are far from being terminal arteries, for they give rise to a very important *anastomotic network*.

This network comprises :—

(*a*) Unilateral anastomoses (longitudinal) between the two arteries of the same side. We have already mentioned the communicating longitudinal posterior artery.

(*b*) Anastomoses between one lobe and another (transverse). The chief anastomosis is on the level of the upper border of the isthmus. It unites the two superior arteries. The anastomosis at the lower border of the isthmus is less constant and less direct than the preceding one.

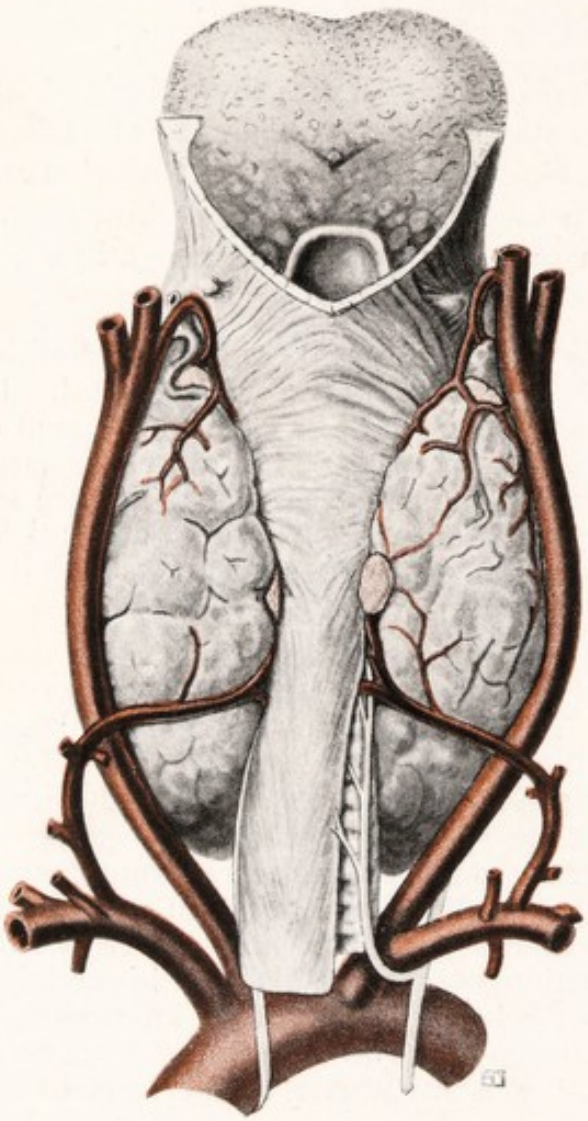


FIG. 4.—Diffuse goitre. Posterior aspect, showing the arrangement of the arteries, the recurrent nerve and the parathyroids (coloured pink). (Original laboratory illustration.)

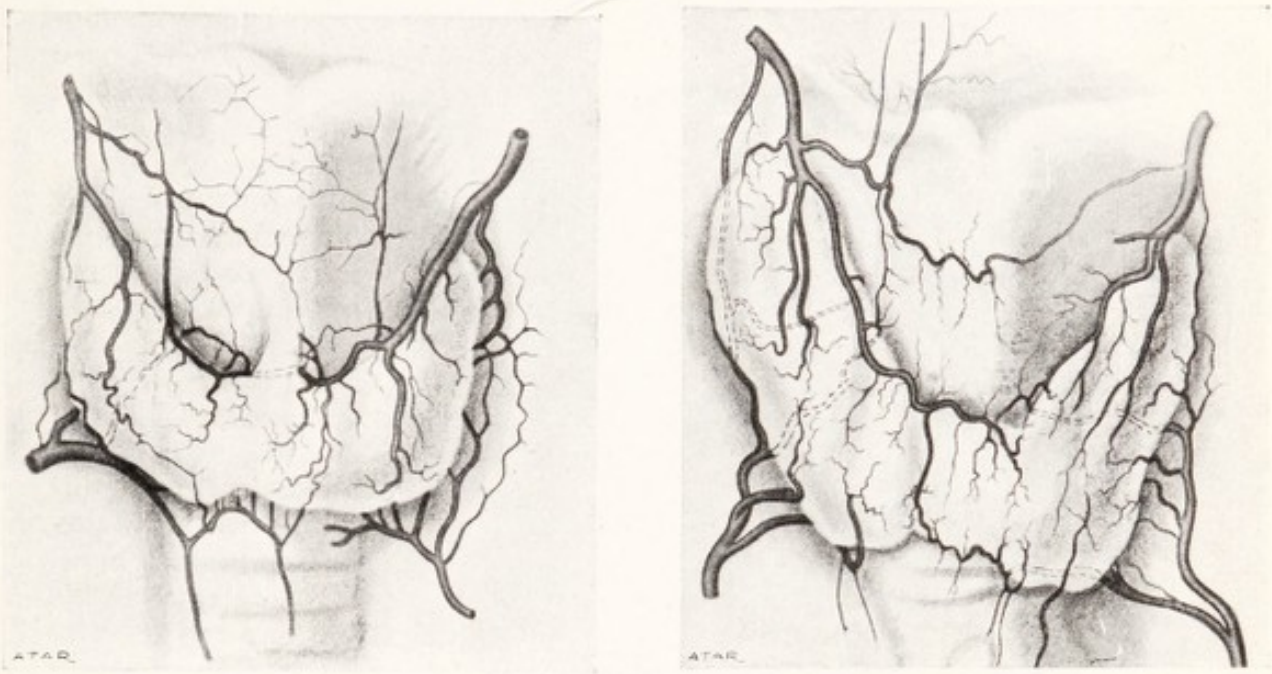
The anastomotic network is situated within the true capsule; no anastomosis of any importance is to be found in the interior of the gland. There is also an anastomosis external to the thyroid gland, which is derived from the indirect route of the laryngeal, pharyngeal and tracheal arteries.

The arrangement of this anastomosis is very variable, but it is well illustrated in figs. 5 and 6, taken from Landstroem.

The effect of these anastomoses is to ensure a good blood supply to the two arteries on the same side, but the blood supply between the two lobes themselves is not so well secured.

If both arteries of one lobe are tied, the circulation is obstructed considerably, but necrosis does not follow. The vitality of the tissues is ensured, partly by the flow of blood from the other side, and partly by collateral vessels outside the gland. Ligature of the four arteries at one time leads to necrosis, if the extrathyroid collateral vessels are also destroyed at the same time by completely isolating the gland. The result of the manifold communications of the gland is that the vitality of its glandular tissue is maintained, although its normal functioning may not be immediately preserved.

Fig. 7 was obtained after injecting, in the cadaver, the right inferior thyroid and the left superior thyroid, with an alcoholic suspension



FIGS. 5 and 6.—Arrangement of the thyroid arteries and their collaterals.

of oxide of mercury. This method demonstrates easily the arterial areas and the collateral network which connects the superior and inferior thyroids with each other, and with the extra-thyroid and laryngeal arteries.

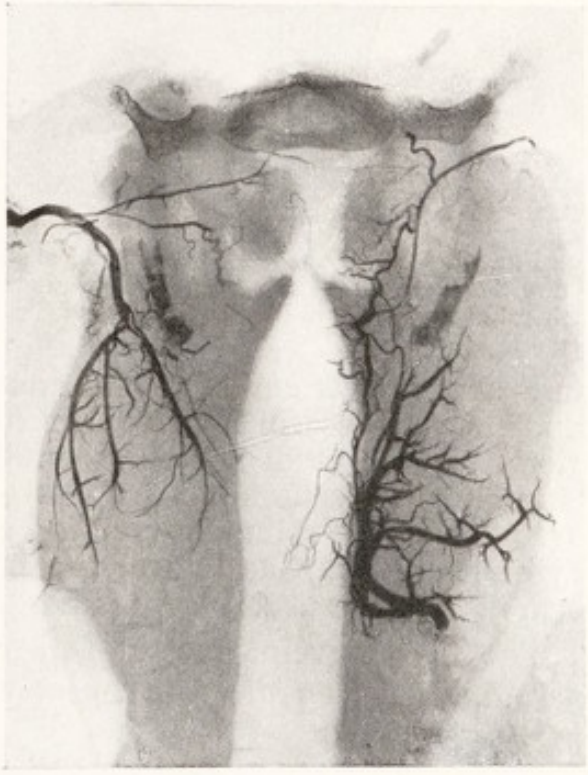


FIG. 7.—Showing areas supplied by superior thyroid artery (*a*) and inferior thyroid artery (*b*) after injection of oxide of mercury.

The blood supply of the parathyroids depends upon the retrothyroid arterial network, i.e., the branches which constitute the communication between the superior and inferior thyroid arteries. We shall see later on that, contrary to the prevalent view, the nutrition of the parathyroid is not affected by the ligature of the four main trunks, as long as the extrathyroid anastomotic network is not interfered with.

B.—VEINS.

The arrangement of the thyroid veins is less regular than that of the arteries; but it is convenient to differentiate three groupings.

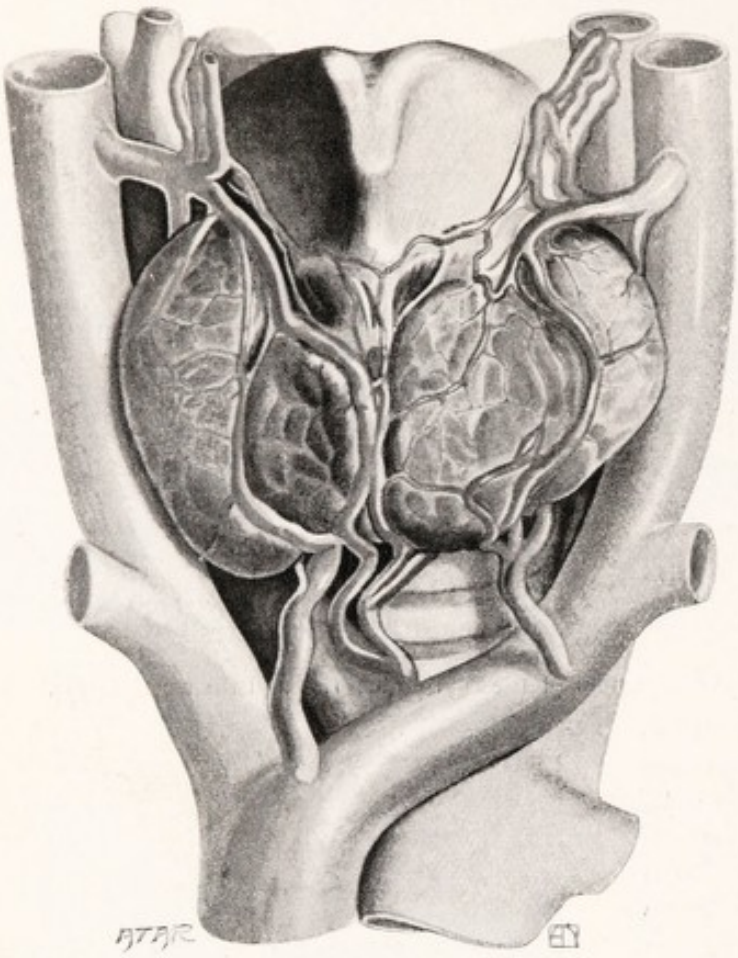


FIG. 8.—Arrangement of thyroid veins (original laboratory illustration). The retrothyroid position of the middle thyroid vein (absent in the illustration) is indicated by dots on the right.

(1) *Superior thyroid veins.*—These veins follow the course of the artery of the same name and they open by one or two branches into the internal jugular vein.

(2) *Middle thyroid vein.* — This vein arises at the lateral border of the lobe and runs directly into the internal jugular vein. It usually follows the course of the inferior thyroid artery, but at a more superficial level. We shall come across it again when discussing the ligature of this artery. Occasionally the vein is duplicated, and it is often missing.

(3) *Inferior thyroid veins.*—The inferior thyroid vein starts at the lower end of the lobe and opens into one of the brachiocephalic venous trunks. It thus follows the course of the lowest artery. At its origin it often has the character of a plexus, owing to its abundant anastomoses (subthyroid plexus). The two inferior thyroid veins are sometimes reinforced by a *lowest thyroid vein* (veine thyroidienne ima) starting at the isthmus, and also possessing the form of a plexus at its origin (see fig. 8).

The thyroid veins meet together and run mostly in the thyroid space, i.e., between the true capsule of the gland and the perithyroid sheath.

II.—NERVES OF THE THYROID REGION.

(1) The *recurrent nerve* is the one which incurs the greatest danger in operations for goitre. Its anatomical relations are too well known to require any lengthy description. The following points may be emphasized at this juncture; their importance will appear later on.

(*a*) The nerve penetrates the thyroid space at the level of the

inferior pole of each lobe, a little farther from the trachea on the right than on the left.

(*b*) It runs among the branches of the inferior thyroid artery; on the right side, most often in front of the principal branches, and on the left side generally behind them. At this level it is separated from the great cervical vessels by the perithyroid sheath. As the trunk of the inferior thyroid artery is situated outside this sheath, it is easy to reach it without coming into contact with the nerve, or even without exposing it, provided the space of the small muscles is followed.

(*c*) The recurrent nerve is again in danger at the level of the larynx where it passes beneath the crico-pharyngeal muscle. At this point it is very near the antero-internal branch of the superior thyroid artery, and can easily be injured by a hurried application of pressure forceps, or be included in a ligature "en masse."

(2) *The vagus nerve.*—This nerve runs in the sheath of the great vessels behind the carotid artery and internal jugular vein. It is well out of the way in operations for innocent goitre, but it is necessary to sacrifice it occasionally in operations for malignant goitre. This nerve is easily reached by the liquid injected at the time of the paravertebral local anæsthesia.

(3) *The sympathetic nerve.*—The cervical sympathetic trunk, like the vagus, runs behind the large vessels, but it is situated in a plane posterior to that of the vagus. It is separated from the latter by layers of connective tissue which form the vascular sheath and the anterior layer of the deep cervical aponeurosis. It runs slightly to the outer side of the vagus, behind the jugular vein, and like the vagus it is affected by the local paravertebral anæsthesia.

It is the section of the cervical sympathetic trunk between the middle and lower cervical ganglia which comes into relation with the thyroid region. The branches which connect these two ganglia embrace the trunk of the inferior thyroid artery. This nerve is therefore endangered by all the procedures which involve the first portion of this artery. The sympathetic nerve is very sensitive to traumatic lesions, and researches on this subject are now being conducted by Dr. Wölflin. Transverse traction applied to the nerve in a rabbit, by a weight of 10 grm., caused temporary paralysis, and traction by a weight of 20 grm. caused a decided paralysis. The prognosis of paralysis of the sympathetic is bad if return of function does not occur within the first few weeks.

(4) *The nerves of the thyroid gland proper.*—The nerves distributed to the gland accompany the main arteries. They are derived from the cervical sympathetic, and from the superior and inferior laryngeal nerves. The fibres of the sympathetic reach the gland along the two arterial trunks, but the superior trunk is also accompanied by the fibres which come from the superior laryngeal nerve. The thyroid fibres of the recurrent laryngeal pierce the gland either directly, or they run along the course of the inferior thyroid artery. According

to Cyon the former fibres are vasodilator, and the latter are vaso-constrictor. This last statement is however contradicted by the recent experiments of Frank and Hallion. The question of the vaso-constrictor nerves of the thyroid is still under discussion.

The secretory fibres exist in the superior laryngeal nerve, and therefore are in the upper pole of the gland (Asher and Flack). According to Missiroli, section of the cervical sympathetic causes both hypersecretion and hyperexcretion.

CHAPTER II.

THE PHYSIOLOGY OF THE THYROID GLAND.

We have been aware of the importance of the thyroid gland in the adequate discharge of the functions of the organism since 1883, owing to the work of J. Reverdin and of Kocher. These observers were impressed by the disastrous results of total thyroidectomy, which was practised then as the operation of choice in the treatment of goitre. Kocher formulated at that time the classical description of the cachexia which follows the total deprivation of the thyroid gland —and it holds good until now. At first he was inclined to attribute the symptoms to an atrophy of the trachea and to a defect of respiration which resulted in a severe anæmia and thus produced a cachexia; while Reverdin thought that there was an intrathyroid vasomotor centre. Schiff and Wagner, and subsequently P. von Bruns and Grundler (1884), appear to have been the first to attribute the symptoms which follow total removal of the gland to the loss of its functions. The similarity of the symptoms to idiopathic myxœdema soon became very noticeable, and the condition was therefore termed operative myxœdema. The experimental investigations, which were undertaken in great number, led to erroneous conclusions for some ten years owing to ignorance of the functions of the parathyroids. As the organs are, in many animals, partially included in the thyroid gland itself, it is difficult to distinguish experimentally the individual effects of the removal of the one or the other.

The definite facts hitherto established in this matter may be summarized as follows :—

(1) The complete or even incomplete removal of the thyroid causes nutritive disturbances and anomalies of growth. These derangements are more striking in carnivorous animals than in herbivorous, and are more marked among young than adult subjects. The symptoms are similar to idiopathic myxœdema in human beings, and to the principal characteristics of endemic cretinism.

(2) The effects of the removal of the gland are prevented if accessary glands are present, and they are diminished by the administration of preparations of thyroid.

(3) The mode of action of the thyroid is complicated. Blum holds that the action takes place within the thyroid itself by the contact of the blood with the glandular tissue. But it is the view of most authorities that the action of the thyroid is carried out by the products of the cellular secretion which is poured into the blood-vessels and lymphatics. These products are of a varied character. Some pass directly into the capillary network surrounding the acinus (vascular pole of the cell); others constitute the colloidal material and they flow into the lymphatic vessels (Garnier). It is mainly owing to this that the accumulation of the colloid material in the gland prevents a proper estimate of its secretory activity. Indeed it prevents a proper estimate of the amount of the colloidal secretion. The quantity of colloid stored up in the gland and rendered visible in a histological section depends not only upon the activity of its production, but also on the rate of its excretion. The colloid material contained in the vesicles represents, so to say, the "ready money" of the thyroid production, and the "total turnover" cannot be estimated from it.

The colloid material produced during the last months of fœtal life disappears at the moment of birth. The store is replenished during the course of the early weeks of extra-uterine life and remains fairly constant until old age, a period which is again characterized by a certain diminution of the colloid material. This constancy of the store—which is not interrupted in man as it is in animals such as the bat and hedgehog (Adler) by a winter sleep—suggests some intraglandular regulating mechanism, by which the relation of absorption to secretion is maintained. The thyroid gland is the only gland—with the exception of the pituitary—wherein the mechanism of the "threshold" is so plainly evident. It is unnecessary to add that those substances which are secreted directly into the circulatory vessels without making a detour of the vesicle have no threshold of absorption.

The glandular extracts employed for physiological experiments usually contain, not only the colloid material, but the total products of the gland, and possibly some foreign substance also. Since Baumann's discovery, a primary importance has been assigned to the presence of iodine among these products (iodothyrine or thyroiodine of Baumann; iodized thyreoglobuline of Oswald). But identical physiological reactions have been obtained by Asher and his pupils with a thyroid extract—thyreoglandol—which is almost free from albumin and from iodine. We shall refer later on to the part played by iodine in the mechanism of thyroid function.

The following are the usual functions ascribed to the thyroid gland, based upon clinical experience and physiological experiment:—

(1) Control and stimulation of tissue growth in general.

(2) Control and stimulation of the functional processes of tissues.

(3) Neutralization of toxic substances produced in the normal metabolism of the tissues.

(4) Assistance in the defensive action of the organism against bacterial toxins.

We propose to speak of the thyroid secretion as if it were one consistent entity, although this is not scientifically accurate. Its first function is *morphogenetic*. This term was introduced by Gley, in his work on endocrine glands, and it designates the building up of the body in the course of its intra-uterine and extra-uterine development and the acquisition of its complete structure. Gley has suggested the name *harmozones* for the morphogenetic substances, to differentiate them from the hormones. This morphogenetic action is so well demonstrated by clinical observation and by experiment that it is quite unnecessary to dwell upon it here. The thyroid shares this duty with the pituitary, the thymus, the suprarenal cortex and the testicle. This action is not exerted to the same extent on all the tissues and on all organs. On the contrary, it would appear from the experiments of Champy on the embryos of frogs, that certain areas are very sensitive, while others are more or less insensitive. These areas must not be confused with the different classes of tissue; they depend upon the stage of development which the organism has attained. Thus, an excessive action of thyroid substance does not by any means produce an indefinite increase of tissue, but only a sudden metamorphosis which, in the species referred to, results in a decrease of the general proportions of the organism.

This fact is not at all in conflict with the well-attested observation in human pathology that the athyroidic subject remains a dwarf, whereas the stature of the hyperthyroidic person exceeds the average. The normal growth of the skeleton is determined by the co-ordinated morphogenetic influence of the thyroid, pituitary, testicle and thymus, and this also applies to the adipose tissue and to the growth of hair. Any deficiency or excess in one or other of these glands interferes with the development of these structures in quite a definite manner.

This morphogenetic action also has a salutary effect on the development of the nervous system. Thyroid inadequacy interferes with the proper development of the nervous system, much more than inadequacy of any of the other glands which possess a morphogenetic action.

It goes without saying that this action does not terminate with the

completion of growth, but it continues throughout life maintaining the anatomical and physiological constitution in a normal state. It is true that this action becomes less evident as age advances, and possibly this is one of the reasons which explain the greater sensitiveness of the adult than of the adolescent to thyroid.

The second function of the thyroid gland is to *regulate the normal processes of the various physiological mechanisms.* This action is exerted by a stimulating substance, which, according to Gley, is the only one entitled to receive the designation of *hormone.* This substance is the most powerful excitant of nitrogenous and respiratory exchanges. This action is essentially katabolic, and is therefore antagonistic to the morphogenetic action, which is essentially anabolic. This divergence also exists in other organs, such as the pituitary, and Gley looks upon this as an argument in favour of the view of the multiplicity of the secretory products.

In this connection must be mentioned the hyperglycæmia and the glycosuria which occur in connection with experimental thyroid work, although no clear explanation can be yet given for these observations. Thyroid intoxication, produced experimentally, has the effect on metabolism of increasing the excretion of phosphorus.

The action of the thyroid hormone reveals itself in the *acceleration of the cardiac rate* and a slight *diminution of arterial pressure.* De Cyon, Asher, Flack and Oswald have proved experimentally that the depressor nerve of the heart is stimulated, and Asher's pupils have established the fact of the *sensitization of the sympathetic system towards adrenalin.*

The third function of the thyroid is its *power of neutralizing certain toxic products of normal metabolism.* According to Blum this action takes place in the gland itself, but most authorities who support the theory of neutralization, such as Moebius, consider that this action is exerted by the secretion of the gland. This theory of neutralization has, however, been discarded recently in favour of the theory of its stimulant action, although it forms the basis of the thyroid therapy which is so extensively employed at the present time. If such a function really exists, the blood of an athyroidic subject should be loaded with injurious substances which have not been neutralized. The experiments performed in our laboratory by Messrs. Hara and Branovacki, to which we shall refer subsequently, suggest that this is really the case. There is indeed a temptation to attribute to these products an inhibitory action on growth agreeing with the recent experiments of Carrel and Ebeling, who have been comparing the serum of adult subjects with the serum of young subjects. It seems to us probable that both processes, that of stimulation and that of neutralization, go on together and that the dwarfism of the athyroidic

subject is the result, simultaneously, of a failure of stimulation and an excess of inhibition.

A fourth function attributed to the thyroid gland is that of *defence against bacterial invasion*. This view is very theoretical, though of course the thyroid necessarily plays an indirect part in the struggle against infection, because its secretion participates in most of the vital functions. Our own researches and those of Roger and Garnier show that certain histological changes occur in the thyroid in the course of certain infective diseases, but these observations cannot be regarded as a conclusive proof of this view. We do not know whether these changes, which are absent in many forms of infection, indicate any strengthening of the defence against infection. In our own experience, cretins do not appear to be more sensitive to infection than normal individuals. Definite experimental proof of an antibacterial action has not yet been forthcoming.

Houssaye and Sordelli state that if the thyroid is removed from a guinea-pig, the operation does not affect its sensitiveness towards the diphtheria bacillus or its toxins, or towards cobra toxin. Fleckseder finds that typhoid fever runs a milder course in goitrous subjects than in normal persons, but that the disease is not modified by the administration of thyroidin. Bassenger's experiments on the dog showed that the thyroid had no action on the toxins of the diphtheria or tetanus bacillus.

According to Banus antithyroid serum increases the resistance towards the toxins of the diphtheria bacillus, and Garibaldi states that the removal of the thyroid gland favours the formation of antibody; but the conclusions of Launoy and Lévy are opposed to this statement. Tuberculosis appears to be more common among sufferers from Graves' disease than among patients with ordinary small goitres.

The rapid survey which we have just made of the functions of the thyroid clearly suggests that there are a number of secretory products formed therein, and if so, it will explain the existence of functions which are diametrically opposed to one another. There is, however, another explanation which is based upon the inter-relation of the entire endocrine system, and which sees in the thyroid secretion a general stimulant which activates the mechanisms of opposite functions—anabolism and katabolism, to give only one example. The evidence of pathology is rather in favour of the view that there are numerous secretory products. The chemistry of the thyroid also suggests this multiplicity. The following are the principal substances whose actions have hitherto been studied.

(*a*) *Albuminoid substances.*

(1) Iodothyrine of Baumann.

(2) Iodothyreoglobuline of Oswald (containing 0·15 per cent. of iodine).

(3) Nucleoprotein of Oswald (containing no iodine).

(*b*) *Non-albuminoid substances.*

(1) Thyreoglandol of Hoffmann and Laroche (iodine practically absent).

(2) Thyroxine of Kendall. This substance is crystallizable and contains 65 per cent. of iodine and represents the active principle of a weight one thousand times greater than the dry gland. Chemically, thyroxin is an oxybeta-indolpropionic trihydric triiodic acid.

In the following chapter we shall enter more fully into the question of multiple secretion.

It is necessary now to say something about the rôle of iodine in the thyroid secretion.

The importance of this metalloid in the normal physiology of the body was first recognized by Prévost in 1849, and was investigated more fully by Chatin in 1850. Those interested in the historical development of this important problem are referred to a monograph of Monéry, which, although published in 1903, has lost nothing of its value. Since the time that iodine was discovered in the thyroid by Baumann, it has become increasingly evident that this substance is indispensable for the adequate discharge of the functions of the gland, and the absence of iodine in the new-born is no valid objection to this view.

In 1905, Aeschbacher made some investigations, at our suggestion, on the iodine content of the gland in relation to its histological state. His conclusions confirm and complete the researches of Baumann, Roos, Notkine, Oswald, &c., and hold good up to the present time. The following is a brief résumé of his work :—

(1) The iodine occurs mainly in the colloid material.

(2) The content of iodine in this latter is variable. The very liquid, vacuolated, eosinophile colloid material appears to contain more of it than the concentrated colloid material holding the hæmatoxylin.

(3) The epithelial cells of the gland also appear to contain a certain quantity of iodine.

(4) The phosphorus content of the gland depends primarily on the amount of cell nuclei, and secondarily on the phosphorus content of the colloid material. The antagonism between the iodine and phosphorus, demonstrated by Kocher, depends upon the fact that the glands which have much colloid material are poor in cells, and vice versa.

(5) The iodine content is distinctly less in the infant than in the adult, and it decreases again in old age.

(6) As a rule the gland is richer in iodine in the female than in the male, but richer in phosphorus in the male than in the female.

(7) The iodine content of the gland is increased by drugs containing iodine.

The average amount of iodine contained in a normal thyroid gland is 5 to 6 mg. Zunz found that this amount was considerably increased in soldiers wounded during the war—about 15 mg.; but this figure obtained from robust subjects in full vigour cannot be regarded as the normal average. The precise situation of the iodine in the gland continues to be a subject of discussion. Recent researches made from sections of frozen gland have led Gatum to the conclusion that iodine is usually absent from the cells themselves, whereas van Dyke states that there is a more or less constant relation between the iodine content of the colloid substance and that of the cellular elements. The proportions vary in different species of animals.

The investigations of Marine and Rogoff show that the iodine introduced artificially into the body is seized, so to say, instantly by the epithelial cells of the thyroid.

Analyses made by Seidell and Fenger on the cattle killed in Chicago show that the iodine is stored up in the gland, especially in the winter months.

According to Swingle the only function of the thyroid is that of a reservoir for iodine, and in his opinion iodine is itself the hormone. In biological experiments preparations of thyroid can be replaced by inorganic preparations of iodine. We may say forthwith that this view is opposed to the experience of almost all investigators. Inorganic iodides cannot replace preparations of thyroid (Abelin, Cameron, Carmichael, Jenssen, &c.), but the combination of iodine with certain albuminoid derivatives (tyrosine, tyramine, &c.), does produce, to a small extent, effects similar to thyroid preparations (Abelin, Booth, Janssen, Romeis).

The main point is whether the action of thyroid preparations varies as their iodine content. Among others, Oswald states that this relationship holds for iodothyroglobuline, while experimenters with goitrous thyroids (Graham, Wegelin and Abelin) are forced to agree upon a general dependence, which presents certain exceptions.

These differences of opinion can be reconciled, if we agree with those investigators who state that iodine exists in the gland in two distinct forms, one biologically active (a compound of iodine with protein-forming material) and one inactive. This latter according to some is ionic, and according to others is a compound with albuminoid or protein-forming substances. The latter theory is held by Wilson and Kendall, who believe in the existence of a product A, affecting the metabolism, and a substance B, regulating principally the nutrition of the skin. Iodine is present in both of these.

Asher and Flack have obtained the typical reactions of iodine-containing thyroidine, with a preparation practically free from iodine—thyreoglandol. The problem is far from being solved. Our own experiments made in collaboration with Messrs. Hara and Branovacky have led us to conclusions which may be summarized as follows :

(1) There is a general interdependence between the biological activity of the glandular tissue and its relative iodine content, but there are striking exceptions.

(2) Iodine ions are incapable of replacing the products of the thyroid secretion in the general circulation, and therefore iodine is not to be identified with the thyroid hormone.

(3) The biological activity of substances extracted from the thyroid gland does not depend upon their iodine content, although chemical combination with iodine increases the very feeble biological activity of the amino-acids (tyrosine, tyramine).

(4) The main action of the iodine seems to take place within the gland itself and not in the circulation, whereas the actual thyroid secretion exerts its activity through the medium of the circulation.

These results only refer to the effect of the thyroid on the respiratory exchange, and have no bearing on its action on other mechanisms.

The functions of the **parathyroids** are even more doubtful than those of the thyroid. There are definite data from which we conclude that the parathyroids influence the nervous system (tetany), the growth of ectodermal structures and the metabolism of calcium and magnesium (McCallum).

It may be taken for granted that tetany is the reaction to a state of acute intoxication. Thirty years ago we demonstrated the effect of a protein diet on the development of attacks of tetany, and there is to-day no doubt on the matter. According to Koch and Noël Paton, tetany is an intoxication which corresponds to that caused by guanidine. The substance is neutralized or destroyed by the intrinsic cells of the parathyroid, or by a product secreted by the cells. But it is necessary to add that experimental poisoning by guanidine is not influenced by the administration of calcium salts, whereas they do exert an influence on tetany (Farner and Klinger).

Some authors have cast doubt upon this neutralizing action, and they claim a hormone function for the parathyroids. This function is said to harmonize with that of the thymus, pancreas, suprarenal cortex and genital glands, and to antagonize the functions of the thyroid, pituitary and the chromaffine system. But this view is imaginative, and not firmly based on scientific theory, and hardly demands discussion.

CHAPTER III.

THE CAUSES OF GOITRE.

THE problem of the ætiology of goitre is very obscure, and it is not within the purpose of this book to discuss it in detail. We need only briefly summarize here the actual position of the subject as it stands at present.

There are four classes of theory on the matter.

(1) *The earth and water theory* (hydro-tellurique). This theory ascribes the origin of goitre to inorganic or organic chemical substances contained in the water, and which are derived from the geological character of the soil through which the water percolates. This is a very old view, and has found advocates up to the present time among numerous authorities, particularly Bircher and Kocher.

(2) *Toxic-infective theory.* This assumes the existence of a specific infective agent (Kutschera) or, at any rate, a specific intestinal flora, the toxic products of which exert their mischief in the thyroid gland. (Gaylord, McCarrison, Galli-Valerio, Messerli).

(3) *The theory of the absence of iodine from the food* was formulated by Prévost in 1849, and by Chatin in 1851. The works of Hunziker and Bayard have conferred upon it a belated credibility.

Klinger suggests a combination of the two latter theories, and he assumes that in certain districts the iodine contained in foodstuff is seized upon by certain intestinal flora and retained in the bowel, thus preventing its utilization by the organism.

(4) *The theory of multiple causation in relation to general hygiene.* This theory has obtained adherents during the last century among the greatest authorities in the study of goitre (Lebert, Demme, the Sardinian commission on goitre, Troxler and recently Grassi).

Clinical and epidemiological observations stand to the credit of all these theories, but not one of them is established by irrefutable evidence. Certain very striking clinical and epidemiological observations, as well as the experiments of Gaylord and McCarrison, appear to us to support strongly the toxic-infective theory, but we must repeat that it is not absolutely proved. The theory of deficient iodine in the food, as the cause of goitre, seems very plausible at first sight. The comparative incidence of iodine in goitrous and non-goitrous countries has not been ascertained with sufficient accuracy to constitute definite evidence, notwithstanding the painstaking investigations of Chatin and others. The state of the thyroid varies in a striking manner from village to village, between one family and another,

although the food conditions are identical, so that this cannot be explained merely by the absence or presence of iodine. There is the old view of Baillarger, to the effect that goitre is caused by certain undefined alimentary and other poisons, but that an excess of iodine beyond the strict needs of the organism is capable of neutralizing the goitre-producing power of these poisons. This view cannot, however, be accepted in its entirety.

In concluding this brief résumé of the subject, we must emphasize the consideration that the term goitre merely expresses under one designation the various modes of reaction of the thyroid gland. We do not know whether there is one uniform cause which produces both the colloid goitre of the sea-coast, and the parenchymatous and nodular goitre of mountainous districts. It is possible that we shall one day be able to explain the diversity of clinical symptoms and epidemiological observations, by the discovery of diverse causes for the different forms of goitre.

We may add here that St. Lager's very original treatise (1867) contains the most comprehensive general review which we possess of the numerous ætiological theories of goitre. During the half century which has elapsed, many of these theories have been discredited and others have been more clearly defined, but a true solution of the problem has, however, not been found.

It is possible, nevertheless, to make the following statement without fear of contradiction.

Endemic goitre is a reaction of the thyroid gland, partially hyperplastic and partially neoplastic. It usually begins in intra-uterine life, and develops particularly during the second or third decade. This reaction occurs more frequently in the female than in the male, and is probably caused by auto-intoxication from the intestine. The precise form of the goitre appears to depend, to some extent, on hereditary influences. The geographical differences in the histological type of the goitre are probably due to ætiological differences on the one hand, and hereditary or racial factors on the other hand. The introduction of iodine into the organism, in physiological quantities, is capable of arresting this reaction without doing any evident harm to the general economy of the organism.

CHAPTER IV.

PATHOLOGICAL ANATOMY OF GOITRE.

I.—HISTOLOGY OF SIMPLE GOITRE.

It would be difficult to discuss the operative treatment of goitre without first casting a brief glance at the pathological anatomy of this disorder.

We shall commence by referring to the *histological lesions*, as they give the clue to the macroscopic changes in the organ.

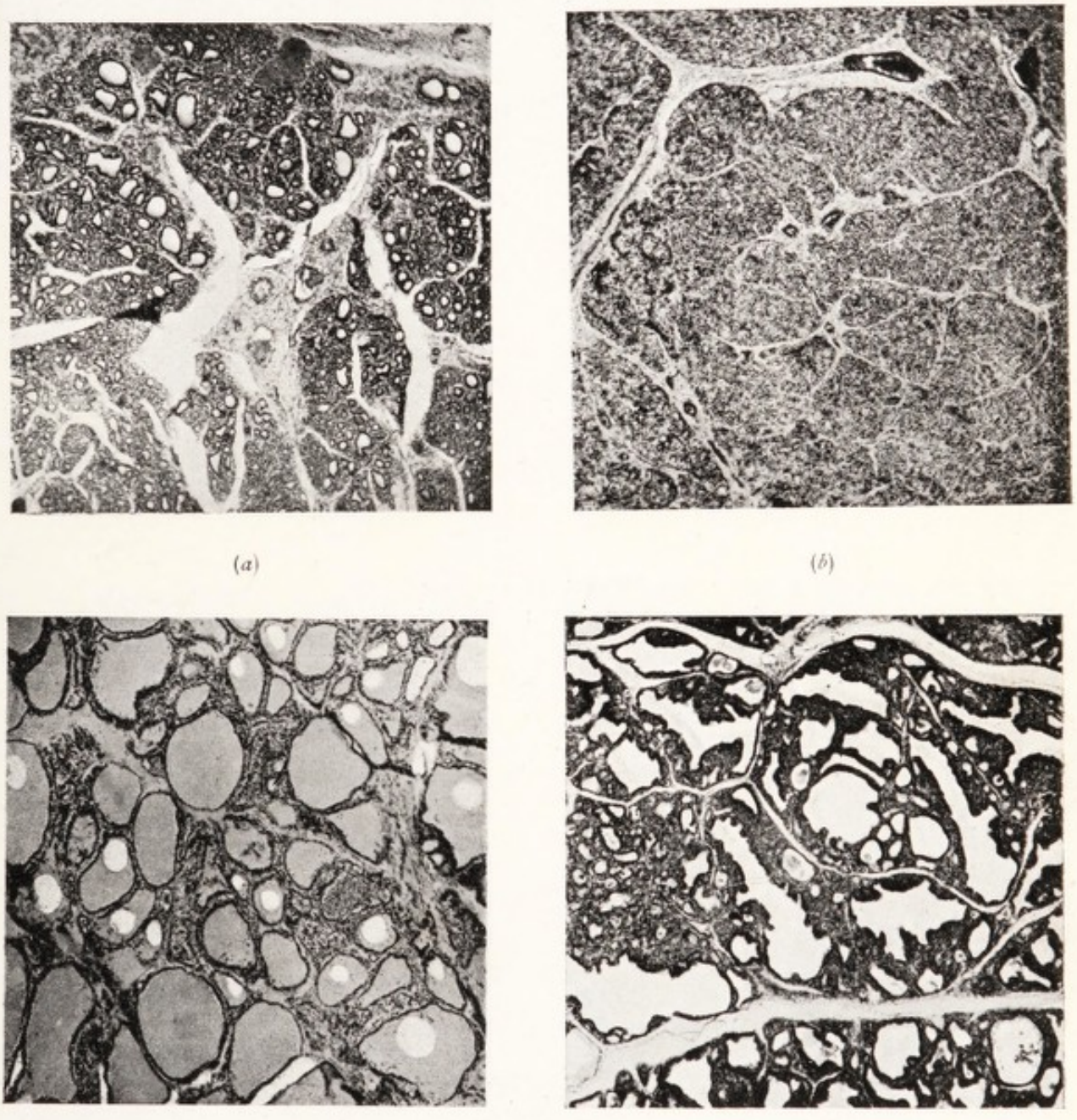
The thyroid gland in the *new-born child* (fig. 9 *b*) is characterized by the absence of colloid material, by an abundant desquamation of epithelial cells and by a considerable development of blood channels. After a few weeks it reassumes its classical acinous structure which it first obtains at the fourth month of intra-uterine life (fig. 9 *a*) and loses only temporarily at the period of birth. The vesicles are much more irregular in shape at this time than either before or after. Goitre in the new-born, which is very frequent in those districts where goitre is endemic, presents the same histological appearance, and differs from the normal gland only in its larger size. Thus the normal gland weighs but 1·55 gr. at Kiel, while at Berne it weighs from 4 to 6 gr., not including real goitres which may weigh as much as 40 gr. (C. Hesselberg).

Goitre in children up to about twelve years of age is generally diffuse and only microscopic nodular lesions are present. From the histological standpoint it represents what may be called a neutral type, characterized by increase in number of the vesicles. This increase is accompanied by a decrease in the volume of the vesicles compared with those found in subjects of the same age hailing from non-goitrous districts (Isenschmid). It is easy to recognize in this change a tendency towards excessive proliferation of the epithelial cells, i.e., a condition of excitation. This condition can eventually develop in one of two directions :—

In the *first case* the colloid substance gradually disappears and the thyroid finally consists of tubes and irregular follicles which are either empty or contain desquamated epithelial cells. This is **parenchymatous goitre** in the strict sense of the term (figs. 9 *d*, &c.).

The vesicles assume an irregular shape and the epithelium shows the characteristic signs of exaggerated activity : more or less cylindrical in type, with desquamation, formation of papillæ, occasionally many-layered proliferation, scarcity or more or less complete absence

of colloid material. The goitre thus recalls that of Graves' disease in its most aggravated form. This type is so frequent between the ages of 12 and 16 that it may be called the goitre of puberty. The body is making a very heavy demand on the thyroid secretion at this time



(*a*) (*b*)

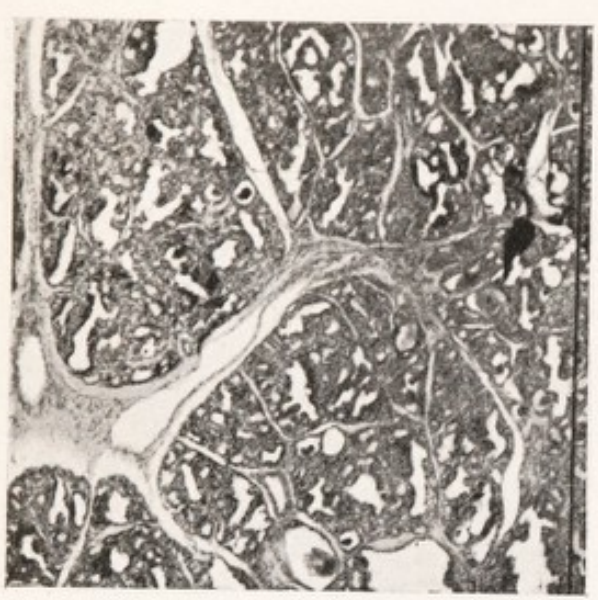
(*c*) (*d*)

FIG. 9.—Histological appearances of the normal thyroid and of goitre. Magnified 40. (*a*) Thyroid from a 7 months' fœtus; (*b*) thyroid of a new-born child; (*c*) normal adult thyroid; (*d*) diffuse goitre of puberty.

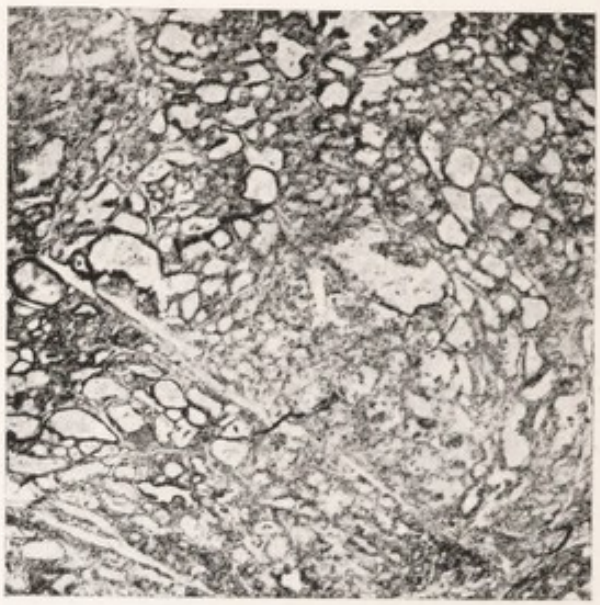
and the coincidence of this activity of the gland with the awakening of sexual life need occasion no surprise.

In certain cases the cylindrical cells are defective, and the collec-

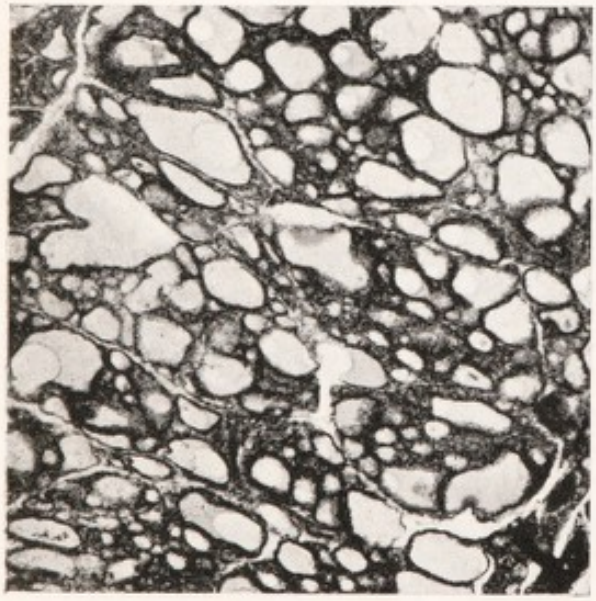
tions of colloid material stain in their centre with hæmatoxylin. This type gives the impression of less activity than in those forms with papillæ and abundant desquamation. We shall see later that the



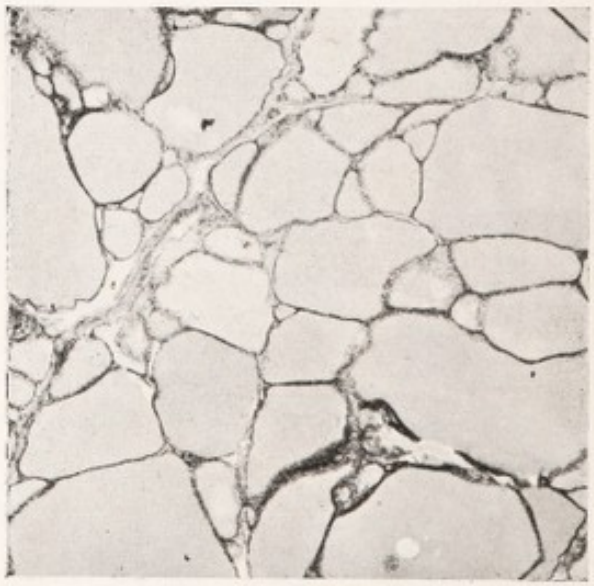
(*e*)



(*f*)



(*g*)



(*h*)

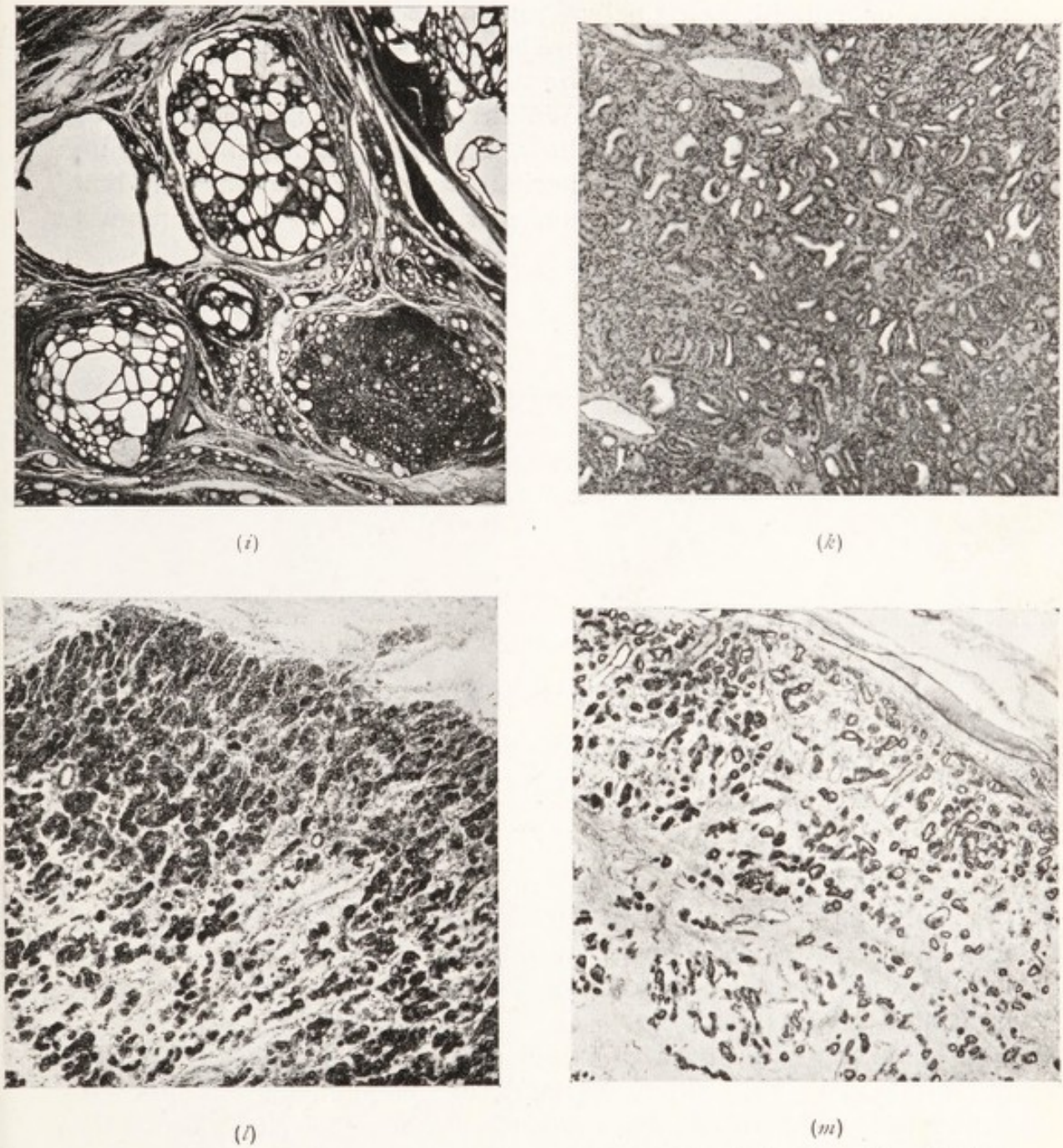
FIG. 9.—Histological appearances of the normal thyroid and of goitre. Magnified 40. (*e*) Diffuse goitre of puberty; (*f*) Graves' disease; (*g*) colloid goitre, small follicles; (*h*) colloid goitre, large follicles.

goitre of puberty produces occasionally what appears to be a mixture of hyper- and hypothyroid symptoms.

The colloid material which is penetrated by the hæmatoxylin appears to correspond approximately to the tannic-resistant colloid

material of Kraus. The latter, after having been stained blue by a methylene polychrome stain, is not decolorized by tannic acid.

In the *second case* the goitre proceeds towards an increase in



(*i*) (*k*)

(*l*) (*m*)

FIG. 9.—Histological appearances of the normal thyroid and of goitre. Magnified 40. (*i*) Nodular goitre, partly adenomatous, partly colloid; (*k*) nodular parenchymatous (adenomatous) goitre from a cretin; (*l*) nodular parenchymatous goitre (microfollicular); (*m*) nodular parenchymatous goitre (microfollicular) from a cretin.

volume of the vesicles. The latter assume a more and more irregular shape. Groups of large follicles enclose collections of follicles which have remained small. Masses of colloid substance, and not the

cellular element, now form the great bulk of the substance of the goitre. This is the type known as **colloid goitre** (fig. 9 *h*).

The lesions which have just been described involve, at first, the gland in its entirety. They are **diffuse goitres,** either parenchymatous or colloid. Gradually some of the follicles or groups of follicles in a parenchymatous goitre become **adenomata.** It is impossible to enter here on a discussion as to the function played by the fœtal cell masses described by Wölffler (fœtal adenomata). Suffice it to say that we agree with Virchow, Langhans, Hitzig and Wegelin, that there is no proof of such an origin for thyroid adenoma, but that it is derived from pre-existing vesicles or tubules. In the commonest

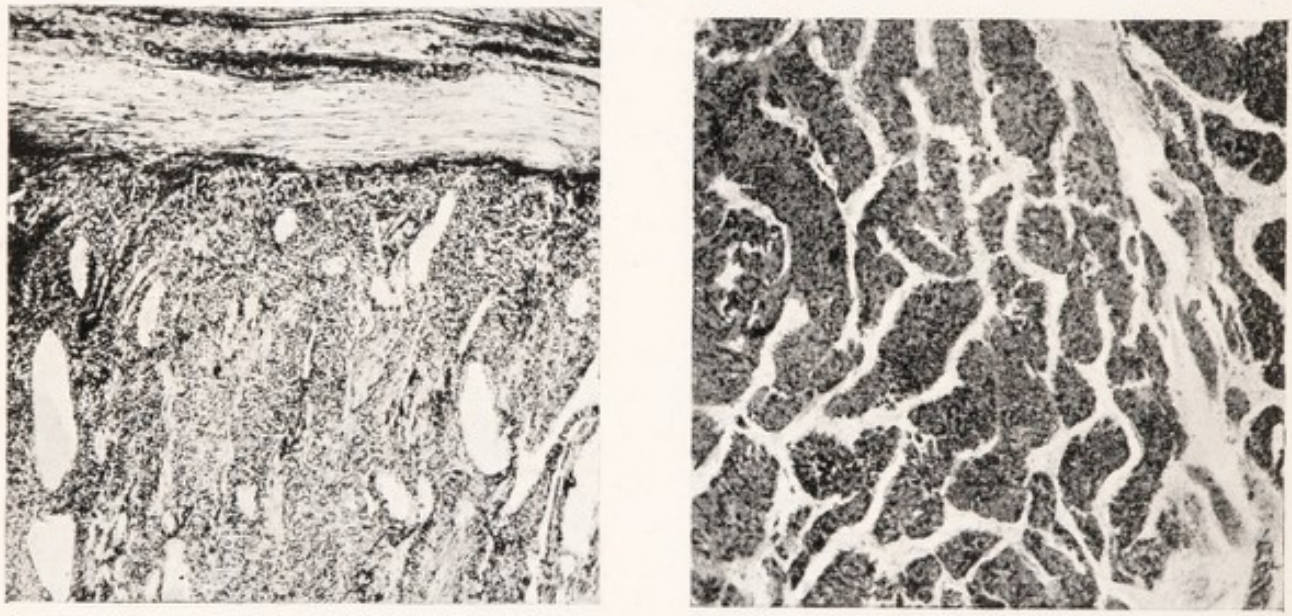


FIG. 9A.—Malignant adenomatous goitre ("proliferating goitre" type of Langhans).

type the periphery of the nodule consists of parallel tubules arranged perpendicularly to the capsule, while the interior of the nodule is formed by an irregular network of tubules, and, towards the centre, by isolated vesicles often composed of a small group of cells and having no central lumen (fig. 9 *k-m*).

Follicular goitre of early infancy generally develops towards the microfollicular type, or towards the diffuse parenchymatous goitre of adolescence which resembles Graves' disease histologically. But as the patient approaches the twenties the goitre assumes a nodular form, so that the latter is the rule in the adult. The goitre then consists of a mass of adenomata, more or less separated from one another and surrounded by multilobulated tissue showing hyperplasia of small follicles.

A similar development takes place in colloid goitre. The diffuse follicular goitre of infancy is transformed during adolescence to diffuse colloid goitre, and then gradually assumes the form of **nodular**

colloid goitre. Thus one meets diffuse colloid goitre more often before the second decade than after, and the majority of apparently diffuse colloid goitres in adults are really collections of small colloid tubules varying in size from a small pea to a nut (figs. 15 and 16) (pudding goitre), which may or may not be surrounded by general colloid tissue. This is also the type of the goitre of pregnancy. In about a third of nodular goitres one can demonstrate the presence of follicular and colloid tubules side by side.

The relative frequency of nodular goitre varies with the nature of the locality. At Berne, in the centre of an endemic district, we find nodules from the size of a nut upwards in about 15 per cent. of goitres in patients of 16 years.

Colloid goitre remains diffuse till after the third decade in certain regions far from the mountains (for example, the Norwegian sea-coast).

It is convenient to refer here to the *diffuse adenomatosis* of American authors (Goetsch). This is a kind of diffuse parenchymatous goitre due not to abnormal development of pre-existing vesicles but to the fœtal cell masses of Wölffler. We again reserve our opinion as to the function attributed to them by Goetsch.

So far we have spoken of the fundamental lesions which form the basis of all goitres. The *secondary lesions* must now be considered .—

In **diffuse goitres** these *secondary lesions* are :—

(*a*) Excessive *vascularity* of the gland (vascular goitre) independent of the histological type of the parenchyma.

(*b*) *Fibrous degeneration*—diminution of epithelial tissue and preponderance of connective tissue, following on pathological affections, general (tuberculosis), local (thyroiditis), atoxic (iodism), or on senile atrophy (fibrous goitre).

(*c*) *Amyloid degeneration*, forming part of a general amyloid disease.

In **nodular goitres** the *secondary lesions* are much more important. They are :—

(*a*) *Gelatinoid, hyaline or mucoid change* in the interstitial substance. These lesions commence in the centre of the nodule. The microfollicular nodule is seen to change into a tubular and follicular mucoid adenoma ; the colloid nodule becomes a more or less uniform hyaline mass.

(*b*) *Cystic Change in the Centre of the Nodule.*—This change by commencing in the centre of the nodule transforms it into a cyst at first with irregular and then with smooth walls. The cysts which exceed several millimetres in size are not due to the extension of the thyroid vesicles but to a destructive process affecting both the interstitial tissue and the follicular epithelium.

(*c*) *Vascular Lesions.*—Degeneration of the vessel walls is very frequent in goitre. C. Hesselberg observed atheromatous plaques in the thyroid arteries of a new-born child, and Isenschmid reports

numerous cases of arteriosclerosis of the thyroid arteries in infants. This arteriosclerosis, like the hyaline degeneration of the vessels, plays an important part in the formation of cysts and the calcification of the nodules. One wonders whether it may not have something to do with the change of diffuse goitre to nodular goitre.

(*d*) *Hæmorrhages.*—The vascular lesions lead to the formation of hæmorrhagic areas in the wall of the nodules, in their substance and in the cysts. These hæmorrhagic areas are accompanied by the histological changes common to any blood effusion.

(*e*) *Calcification.*—The necrosed centre of either a microfollicular or a colloid nodule changes in the course of time into a calcified mass, irregularly spherical in shape. The wall of a cyst may become impregnated with phosphates or carbonates of lime, thus forming a calcareous shell.

To complete the picture it may be added that one meets with the most varied combinations of the different forms of goitre that have been described. Thus diffuse goitre is associated with nodular goitre as its owner advances in age. In a nodular goitre one finds follicular or microfollicular nodules in one part and colloid nodules in another. The nodules of the same goitre may be partly solid and partly cystic. Cystic change begins in some nodules as soon as they are a few millimetres in diameter, whereas others undergo liquefaction only after they have reached the size of a tangerine orange.

II.—MORBID ANATOMY OF GOITRE.

The morbid anatomy follows in large measure from what has been said about the histological structure of goitre. The goitre of a new-born child is always, and the goitre of an infant often, diffuse and homogeneous, retaining the horseshoe shape of the normal thyroid (fig. 22). There is a very marked tendency for the gland to become intrathoracic. In endemic goitrous regions it may remain diffuse until thirty years of age, although diffuse goitre is usually at its maximum during the second decade. It retains this tendency longer in places remote from endemic districts. Diffuse parenchymatous (follicular) goitre represents a less

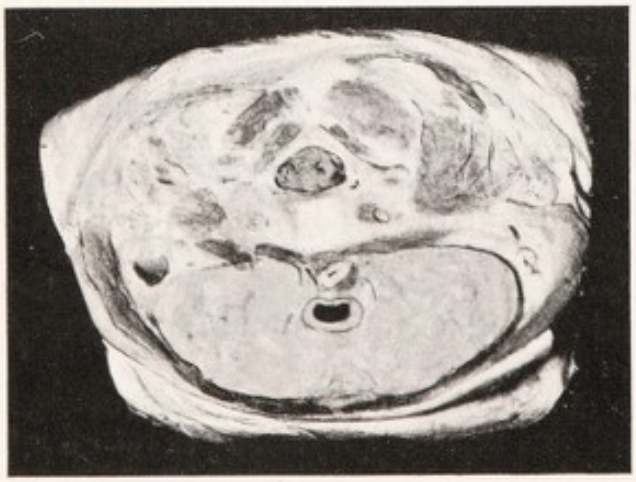


FIG. 10.—Section across the neck of a new-born child at the level of the isthmus. Diffuse parenchymatous goitre. (From the Berne Pathological Institute.)

advanced stage than diffuse colloid goitre. The following figures have an important bearing on this matter: in our statistics, out of 951 cases examined microscopically (Mlle. Woelz) there were twenty-six ordinary diffuse follicular goitres and of these twenty-four were from patients under 20 years of age. Ordinary diffuse colloid goitres numbered forty-four: twenty-three from patients under 20 and thirty-nine from patients under 30. Reference to figures from schools shows that goitre is much more frequent among children than these figures would lead one to suppose. Goitres in patients of school age rarely attain such a size as necessitates surgical treatment. The diagram 26*b* comprises the results of an inquiry into goitre conducted by the primary schools in Berne (over 7,700 children). If one is precise in estimating the size of the thyroid it is found that 74 per cent. of the children entering school have a mild hypertrophy of the gland, and 94 per cent. show this increase in size from 15 years of age. The development of goitrous nodules either in the normal thyroid or in a gland showing slight general hyperplasia commences at puberty. We demonstrated the presence of nodules as big as a nut in at least 15 per cent. of the children in our series. The character of the nodules (follicular or colloid) does not at first sight appear to follow any rule, because one frequently finds both types present in the same goitre. The comparison of goitres from Berne with those from Bâle enables one to draw the conclusion that nodular parenchymatous (follicular) goitres predominate in the cases from Berne, and the nodular colloid type in those from Bâle. If we restrict ourselves to four types then follicular nodular goitre comprises 14·6 per cent. of all the cases from Berne and 5 per cent. of those from Bâle,

FIG. 11.—Diffuse parenchymatous goitre in an adult.

FIG. 12.—Parenchymatous and nodular (adenomatous) goitre in an adult.

whereas the colloid nodular type is represented by only 7·3 per cent. of cases from Berne, but by 26·4 per cent. of cases from Bâle. This confirms the observations of M. Isenschmid mentioned above, namely, that at Berne in goitres of children up to fifteen years microfollicular forms exceed thyroids having normal follicles. The influence of the goitrous neighbourhood thus asserts itself again by a premature change in the histology of the gland towards the adenomatous type.

FIG. 13.—The same, showing great compression of the trachea.

A nodule, the centre of which has not degenerated, rarely attains a diameter of 5 cm. The central degeneration may take the form of hyaline necrosis, cystic or fibrous change, or calcification. It is found in about one-third of the cases which come to operation, and in most of them the degeneration is of the cystic form. The cysts are surrounded by

FIG. 14.—Section of a diffuse colloid goitre with nodule formation commencing.

FIG. 15.—Section of a diffuse multinodular goitre.

a rather thick fibrous capsule formed of the interstitial tissue of the gland. This capsule often contains within it elements of thyroid tissue which are practically normal but which have been enclosed mechanically, and it represents the so-called intraglandular capsule of the nodule. The cyst is sometimes lined by a smooth wall and sometimes by necrotic tissue undergoing hyaline degeneration and containing traces of hæmorrhages and calcified portions. The cyst contents may vary from a transparent serous fluid to a chocolate-brown hæmorrhagic mixture. Crystals of cholesterin are often to be found therein.

Nodular goitre exists in four more or less distinct varieties.

The first is seen in a normal or hypertrophied thyroid containing somewhere in its substance a small-sized nodule. The recognition of this form presents no difficulty.

The second type is that of the thyroid which has been entirely transformed into a mass of small-sized nodules, none much larger than the rest, and which gives the impression of a diffuse goitre. It is what is called the "pudding" goitre. The presence of this form will be suspected when one comes across an apparently diffuse goitre with an uneven surface in a patient over 30.

16.—Section of a goitre; diffuse colloid m at upper pole, nodular form elsewhere.

FIG. 17.—Section o. a nodular colloid goitre, with large nodules.

FIG. 18.—Nodular colloid goitre showing compresion of healthy tissue at upper pole. Central necrosis.

FIG. 19.—Malignant adenoma. Central necrosis.

FIG. 20.—Cystic goitre.

The third type is represented by the nodular goitre consisting of a solitary large nodule. The soft nodules which are not larger than a small tangerine are generally adenomatous. Colloid nodules are as a rule of firmer consistence than adenomata. Cysts vary considerably, being soft, elastic or sometimes hard. A nodule which is larger than an orange is probably cystic, the more so as it is more tense. The older a cyst is the more likely is it to have a fibrous capsule and calcareous deposits in its walls. Large cysts generally cause a very marked lateral displacement of the trachea, whereas in diffuse or diffuse nodular goitre the trachea retains its normal position but is compressed on either side or completely surrounded.

The cyst may become pendulous if neglected by the patient.

The fourth type is represented by the multinodular goitre with large nodules. Each lobe consists of several relatively big nodules. The whole may form one of the enormous trilobed goitres seen in very endemic regions, especially among cretins.

FIG. 21.—Hæmorrhagic cystic goitre, with malignant change (endotheliomatous) in the wall at the upper pole (x).

III.—DISTRIBUTION OF THE DIFFERENT FORMS OF GOITRE.

It will be interesting to give an account of the relative frequency of the different types of goitre in Switzerland, basing the results on the last thousand cases operated on by me or under my direction. The centre of activity was first at Bâle and then at Berne, and as the two clinics were supplied with material from the surrounding cantons the statistics will afford a fairly accurate picture of goitre in Switzerland. In these figures account has been taken of the clinical examination, appearances at operation, results of microscopic examination and, finally, of operative methods employed. These are the results as tabulated by Mlle. Woelz :—

FIG. 22.—Horseshoe-shaped diffuse goitre from a new-born child.
(From the Berne Pathological Institute.)

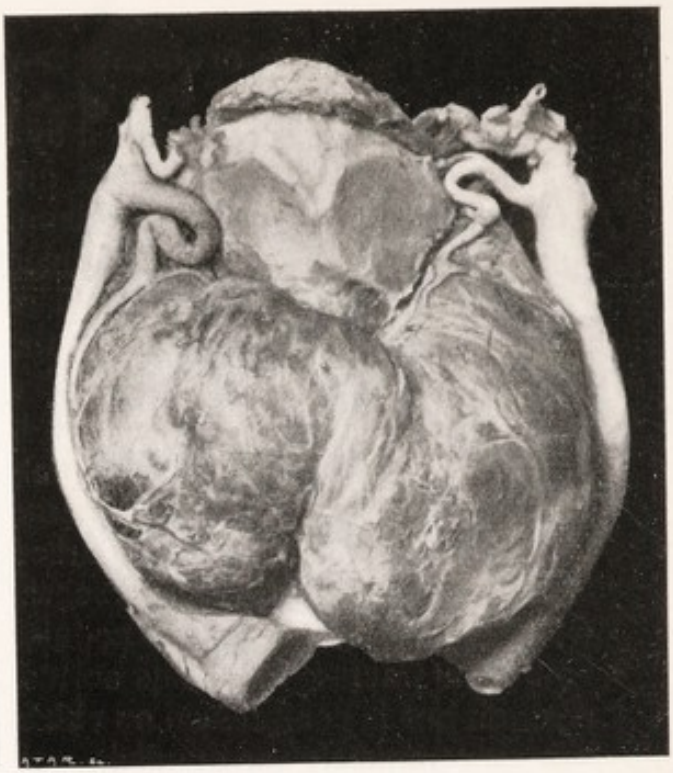


FIG. 23.—To show displacement of the carotids by a diffuse nodular goitre in an adult.

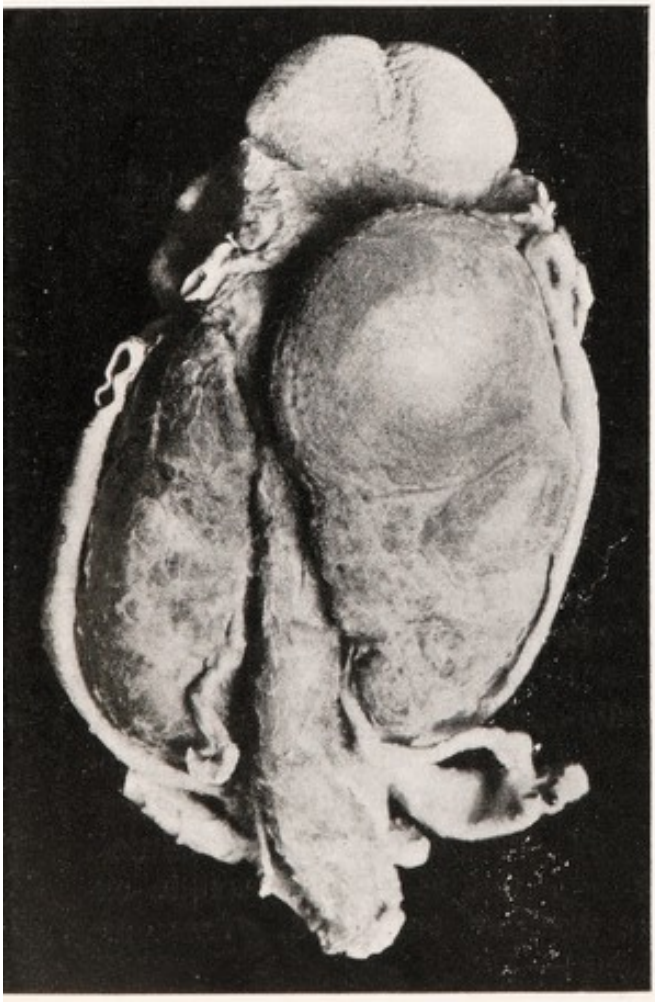


FIG. 24.—Retrovisceral goitre.
(From the Berne Pathological Institute.)

FIG. 25.—Small intrathoracic goitre (X).
(From the Berne Pathological Institute.)

	Diffuse goitre	Nodular goitre, including mixed cases
I. Result of clinical examination (980 available cases) ...	13·77 per cent.	86·23 per cent.
II. Macroscopic appearance at operation (884 available cases)	12·9 ,,	87 ,,
III. Result of microscopic examination (951 available cases)	7·7 ,,	92·3 ,,
IV. Operative procedure (1,000 available cases)		
For diffuse goitres (resection, ligature)	17·9 ,,	
For nodular goitres and mixed forms (enucleation, resection-enucleation)		81·7 ,,

Examination of these figures shows a close agreement between the clinical results and those of the naked-eye examination at operation. The discrepancy between the results of clinical and microscopical examination is due to the fact that the histologically transitional forms are reckoned as nodular goitres. They are essentially diffuse goitres but contain small-sized nodules which escape notice at the clinical examination and even on inspection at operation. If they were included with the diffuse goitres the figure for the latter would be 17·1 per cent.

FIG. 25A.—Goitre, partly extrathoracic (*a*), partly intrathoracic (*b*). Removed at operation (half natural size).

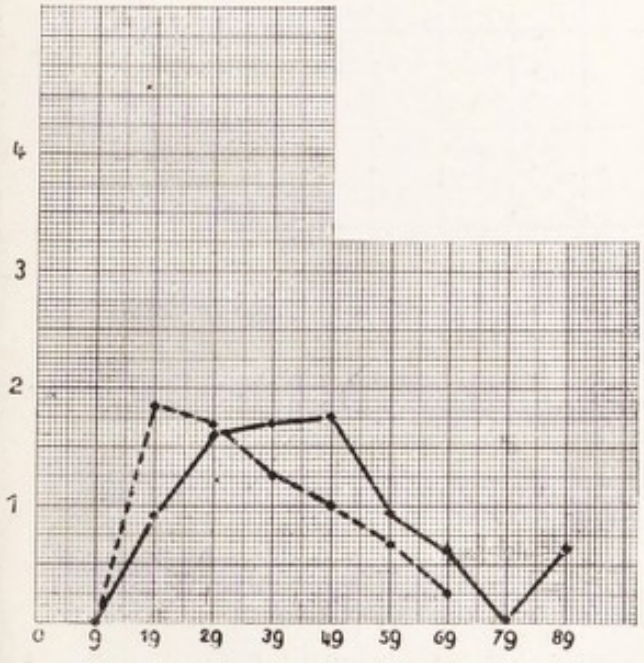


FIG. 26.—Morbidity rate of goitre in relation to age, from the operative statistics of the surgical clinic at Bâle.

..... men; ——— women.

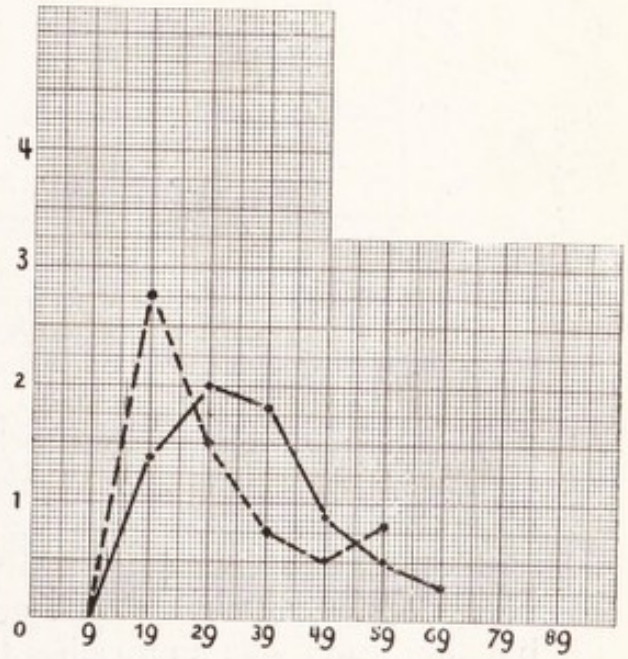


FIG. 26A.—*Idem.* From the surgical clinic at Berne.

The statistics for the operative procedures tally with this last figure. Diffuse goitres, the transitional forms and the diffuse goitres with small nodules have to be resected, while the forms with fairly distinct nodules are effectively dealt with by enucleation or enucleation combined with resection. It may be said in general that one-sixth of the goitres which present themselves for operation in Switzerland are

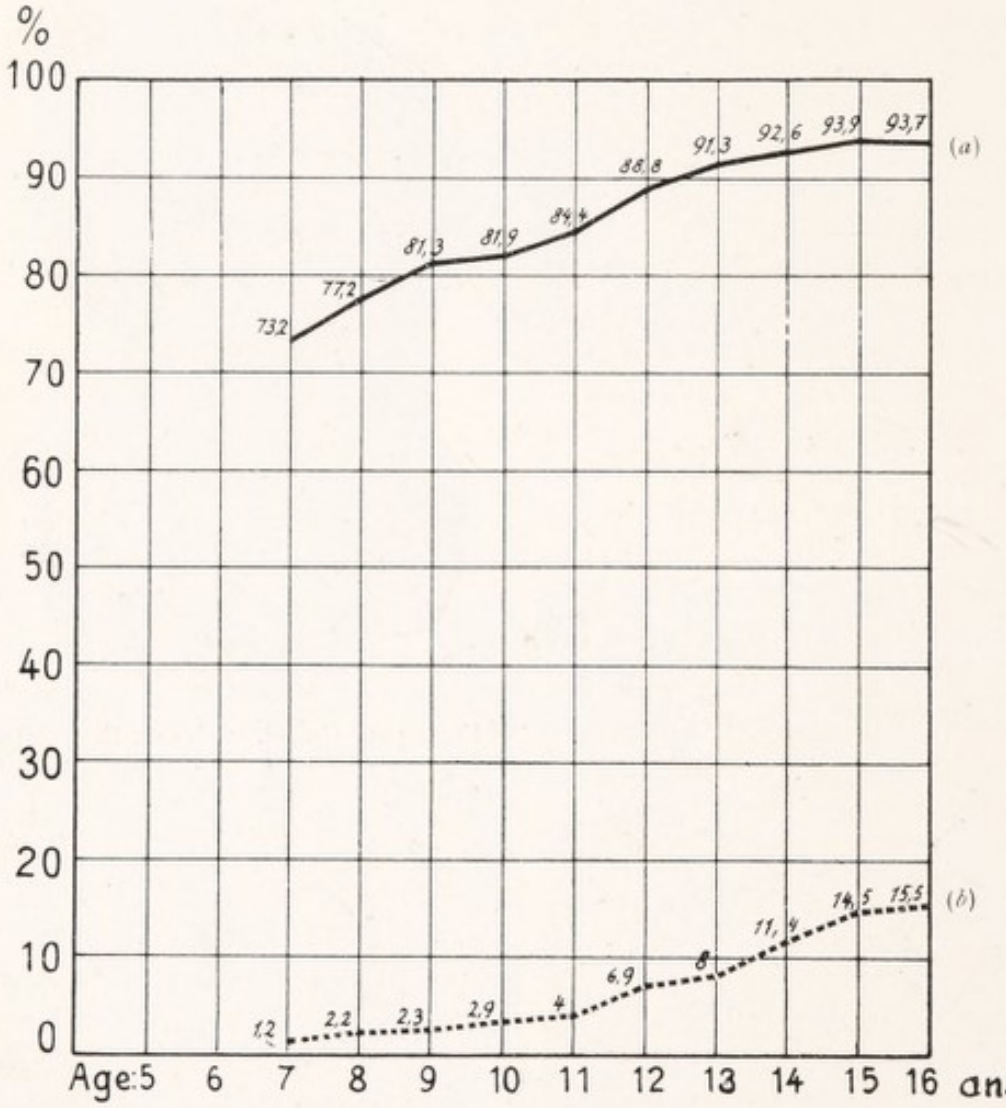


FIG. 26B.—Frequency of goitre of puberty at Berne, from observations on 7,500 children. (*a*) Total showing hypertrophy of the gland. Types II-IV. (*b*) Nodular forms.

essentially diffuse and demand resection, while the remainder are nodular and are relieved by enucleation or a combined method.

The *distribution of goitre between the sexes* affords some interesting observations :—

Females are considered to be more affected than males in the proportion of 3 to 1. This figure agrees with what is found at Bâle, but the nearer one approaches the centre of an endemic region the more the proportion increases on the male side. This observation was

made some time ago by Baillarger for France, and more recently by McCarrison for India. It is confirmed by our observations, for at Berne in the immediate neighbourhood of the centre of an endemic area the proportion is 1·6 to 1.

We have thus established by systematic classification proceeding by decades the morbidity rate not of goitre in general but of those *forms necessitating operative treatment* (figs. 26 and 26A). This morbidity rate is determined by the percentage of goitres, operated on in each decade in proportion to all operations for goitre, divided by the percentage of people of that decade in proportion to the whole population. Among males the rate is at its highest about the twentieth year, among females about the thirtieth year. This difference is accounted for by the influence of pregnancy on the development of goitre in the female sex.

It must be emphasized that this diagram shows the frequency only of those goitres which come to operation. The total morbidity rate can only be established at present for those of school age. In this case the curves for the two sexes are approximately the same, the males being somewhat less affected in regions where endemic goitre is not very prevalent.

IV.—PATHOLOGY OF EXOPHTHALMIC GOITRE.

Exophthalmic goitre in the widest sense of the term exists in two distinct types :—

The diffuse goitre of Graves' disease and the adenomatous goitre accompanied by hyperthyroidism.

The *diffuse goitre of Graves' disease* is characterized in the living subject by its rich arterial vascular supply. This excessive vascularity is not limited to the thyroid gland but extends to the surrounding tissues as far as the subcutaneous fasciæ. This type of goitre is sometimes soft or elastic, more often firm and slightly granular. It is peculiar too for its close adhesion to its outer capsule—the thyroid fascia.

Histologically it is intermediate in form between the parenchymatous goitre in the new-born child and colloid goitre. Its epithelial cells are often cylindrical and show considerable desquamation. They tend to form papillæ. The vesicles are of medium size or larger, more or less irregular, and colloid material is either absent or considerably vacuolated, staining poorly, and very suggestive of a spider's web. This collection of signs is so characteristic that in the adult one can make a certain diagnosis of exophthalmic goitre by a mere glance at a microscopic section. Transitional forms of all degrees are found between this classic type and a practically normal gland and even

simple colloid goitre. Masses of lymphocytes are frequently present in the goitre of Graves' disease but are not characteristic of it, as they are also to be found in simple goitre (von Werdt).

The nodular or *adenomatous goitre of Graves' disease* shows a combination of one of the various types of adenoma with the lesions which have just been described. The surrounding thyroid tissue may be quite normal. Thus, in toxic adenoma the histological evidence of perverted activity is very poor. Clinical symptoms and histological changes do not always go hand in hand.

Most authors recognize no difference in principle between these two types of Graves' disease, but we must bear in mind that Charles Mayo and his colleagues Plummer, Boothby and Wilson emphasize the different symptomatology of these two forms of the disease. The classic syndrome with exophthalmos is produced only by the diffuse goitre of Graves' disease, while the toxic adenomatous goitre gives rise to less marked symptoms which do not include exophthalmos. According to these writers there is a true hyperthyroidism in this latter form, while the classic Graves' syndrome is probably the result of dysthyroidism.

These observations and the particular type of goitre occurring in the United States determined Plummer and Wilson to base their classification of goitre on its degree of toxicity as established principally by the respiratory exchange. Viewing the problem as a whole and taking into account the experiments performed in countries where real goitres abound it is obvious that the subject is much more complex. If one is going to take the functional element into account in making a classification one must include both decreased and perverted function. This method would be quite justifiable if one knew the physiological value of the different forms of goitre, including cretinism. Any biological classification would be premature at present, when our ideas on the subject are so rudimentary. We are obliged to keep for the moment to an anatomical classification and to relegate the physiological element to the second place. Our classification, based on the histological examination of a large number of goitres from different countries, does not depart on its main lines from that made by our teacher, Langhans, and his school. The following is a summary of it :—

V.—CLASSIFICATION OF INNOCENT GOITRES.

(i) Diffuse Goitre.

The whole gland is diseased but retains its normal shape.

A.—*Forms Deficient in Colloid Material.*

(1) Parenchymatous goitre in the new-born.
(2) Parenchymatous goitre of childhood and puberty (school-

childrens' goitre). Function normal, hypothyroidism, hyperthyroidism or combination of both.

(3) Parenchymatous goitre of adults, without marked hyperthyroidism, rare after the twenties (including the diffuse adenomatosis of Goetsch).

(4) Graves' disease.

Parenchymatous goitre is either microfollicular, or has irregular follicles, with or without excessive proliferation of epithelium.

B.—*Forms with Normal Amount of Colloid Material.*

(1) Hyperplasia of the gland, with normal structure. Chiefly found in children or adolescents. Does not exceed three times the volume of the normal gland and rarely necessitates operation.

C.—*Forms Rich in Colloid.*

(1) Diffuse colloid goitre without clinical symptoms of hyperthyroidism.

(2) The same with symptoms of hyperthyroidism.

(ii) Nodular Goitre.

A.—*Forms Deficient in Colloid Material.*

(1) Adenoma with flat cells, small vesicles or narrow tubules, practically free from colloid.

(2) Adenoma with cylindrical cells, formation of papillæ, vesicles or tubules of very irregular shape, reminiscent of Graves' disease.

(3) Adenoma with tubules or solid columns of cells, rather large, parallel with the edge of the tumour, forming a network at the centre of the nodule, approaching the "proliferating goitre" type of Langhans.

It is not always easy to differentiate between these three types because transitional and compound forms exist. Clinical symptoms are sometimes more important than histological characters in the diagnosis of the malignant form of "proliferating goitre."

B.—*Forms containing a Normal Amount of Colloid* are practically non-existent, most goitrous nodules showing histological changes.

C.—*Forms Rich in Colloid.*

(1) Nodular colloid goitre; corresponds to diffuse colloid goitre; enlarged vesicles, often irregular in shape.

The different types of goitre summarized according to the naked-eye anatomy are :—

(I) *Homogeneous or lobulated diffuse goitre.*

(II) *Normal thyroid,* or hypertrophied and contained adenomatous or colloid nodules.

(III) *Diffuse multi-nodular goitre* (pudding goitre). The gland is entirely transformed into a mass of microfollicular or colloid nodules, the volume of which may vary from that of a pea to that of a nut.

The following are the *secondary changes* found in different goitres :—

(i) **Diffuse Goitre.**

(1) Excessive vascularity, with or without symptoms of Graves' disease.

(2) Diffuse sclerosis. (Tuberculosis of other organs; chronic thyroiditis; senile change.)

(3) Amyloid degeneration.

(ii) **Nodular Goitre.**

(1) Colloid, hyaline or myxomatous degeneration of the interstitial tissue.

(2) Cystic degeneration of the centre of the nodule.

(3) Hæmorrhage.

(4) Fibrosis.

(5) Calcification.

VI.—TOPOGRAPHICAL ANATOMY OF GOITRE.

The structures enclosing a goitre correspond to those of a normal thyroid but they are more dense. One must distinguish between the *external capsule* formed by the cervical connective tissue known as the thyroid fascia and the *specific capsule of the goitre* formed by the connective tissue of the thyroid. The diffuse goitre has two envelopes separated by the extrathyroid space, while the nodular goitre is surrounded by three capsules: the thyroid fascia, the capsule proper of the goitre, and the intraglandular capsule of the nodule. The planes of cleavage, which are generally clearly indicated, may be obliterated as a result of inflammatory processes.

A goitre lies, as a rule, on both sides of the trachea, but we have seen cases in which it surrounds it completely (retrovisceral goitre) (fig. 24). The lower poles of both lobes extend down to the upper aperture of the thorax, but may pass into the thorax and develop there as a tumour or nodules practically independent of the original goitre (fig. 25). These intrathoracic goitres are formed sometimes by a single lower pole, sometimes by both. They may reach almost to the auricles of the heart.

The *displacement of the great cervical vessels* is of interest from the operative standpoint. They may be pushed right away to one side (fig. 23) or covered over by the mass of the goitre. The same applies to the cervical nerve trunks, especially the vagus and the sympathetic. The subject of the displacement and deformity of the trachea will be discussed later with the X-ray appearances.

CHAPTER V.

PATHOLOGICAL PHYSIOLOGY OF THE THYROID GLAND, WITH SPECIAL REFERENCE TO GOITRE.

ONE of the most important of the practical considerations in the operative treatment of goitre is raised by problems in the pathological physiology of the thyroid. Surgery is indeed responsible for the original discoveries in this branch of knowledge, and clinical observation, supplemented by histological examination and laboratory experiment, remains one of the principal factors—if not the principal factor—in all discussions on this subject.

In Chapter III we enumerated the main functions of the thyroid gland, as far as they have hitherto been ascertained. We now have to consider how these functions may be disturbed; but before doing this we shall tabulate the various states of thyroid activity, which in themselves constitute the chief problems for our present discussion.

(i) Euthyroidism.

In this state the various functions of the gland are in a condition of equilibrium, and the secretion is normal.

(ii) Athyroidism.

Complete abeyance of function owing to

(1) Absence of gland.
(2) Pathological destruction of gland.
(3) Temporary loss of function (inflammation).

(iii) Hypothyroidism.

Diminution of function of thyroid, owing to

(1) A *quantitative decrease* in all the secretory products, due to

- (*a*) quantitative decrease of glandular tissue.
- (*b*) a diffuse lesion of the parenchyma.
- (*c*) a limitation of the blood supply.
- (*d*) nervous causes.

(2) *Suppression of a part only of the thyroid functions:*

- (*a*) Partial or relative hypothyroidism owing to parenchymatous lesions.
- (*b*) Or to nervous causes.

(iv) Hyperthyroidism.

Theoretically, increase in the function of the thyroid may occur under analogous conditions to those which have been enumerated as the causes for hyperthyroidism.

(1) *Quantitative increase* in the essential functions of the gland, i.e., of its normal secretion, due to

(*a*) a simple increase in normal parenchyma.
(*b*) a state of irritation, caused by histological lesions.
(*c*) an increased blood supply.
(*d*) nervous causes.

(2) An increased production, only of one portion of the glandular secretion ; *partial hyperthyroidism*.

(3) The formation of an abnormal secretion, *dysthyroidic hyperthyroidism*.

(A) Consideration of the Purely Thyroid Factors.

The study of the pathological physiology of the thyroid turns upon the solution of certain fundamental questions, viz. :—

(1) Is the secretion of the thyroid gland one single entity, or is it composed of several different constituents ?

(2) Does a true increase in function (hyperthyroidism) of the gland really occur, and a true decrease in function (hypothyroidism) ?

(3) Does a perversion of function occur, and this being the case, what relation does this bear to states of hyper- and hypothyroidism ?

The problem of *single or multiple secretion* has been under discussion for some few years. Most theories which have been advanced, until within quite a recent time, start with the assumption that there is only one secretion, and most physiologists appear, even now, to adhere to this view. But, in addition to *iodothyreoglobuline* and *nucleoprotein* extracted by Oswald, we are acquainted with *thyreoglaudol*, which contains practically no iodine or albumin and which has been investigated by Asher and his pupils ; and also with *thyroxine*, a crystallizable substance extracted by Kendall. Thus we have four different substances, three of which, according to laboratory experiments, possess a clearly defined and practically identical action. It would therefore appear that it is quite certain that there are several active substances, but it is quite possible that there is only one active principle common to them all. Kendall's experiments have inclined him to think that this is not the case. To quote one experiment only —he obtained different physiological results with the substances which were insoluble in acid (group A) from those obtained with substances soluble in acid (group B).

The clinical fact of the dissociation of the symptoms of cretinism

is, in our opinion, an additional argument in favour of the plurality of functions. The various types of cretin exhibit very striking differences. The morbid changes in the skeleton do not, by any means, keep pace with the mental defects. Besides, we are acquainted with cases wherein certain symptoms of thyroid deficiency are associated with symptoms which indicate hyperthyroidism. But all difficulties of explanation vanish if we adopt the view of multiple products of secretion. There is, however, another explanation which is based upon the theory that the various organs possess different degrees of sensitiveness towards functional disturbances of the thyroid. An analogous state of affairs exists in regard to bacterial infections. The pathological condition represents the end result of the action and reaction. There is no doubt that this explanation contains part of the truth. It is quite probable that in some subjects the osseous system is particularly sensitive to endocrine influences, whereas in others the nervous system is the more susceptible. The diversity of clinical types cannot always be explained by dissociation in a chronological sense, or by diversity in predisposition; but this is a problem to which we shall return later on.

We shall now resume our consideration of the functional conditions enumerated in our scheme.

The two opposing conditions, *euthyroidism* and *athyroidism* require no comment. The normal function of the gland appears to us to be one single whole despite its numerous phases, and physiology is not yet in a position, on its own merits, to distinguish the different elements which contribute to the totality of the function.

The conceptions of a simply *deficient function* or an *excessive function*, without any qualitative change in the secretion, form one of the foundations of present-day pathology of the thyroid, although these ideas are not quite in accord with what we know of glandular secretions in general. It is true that all glands exhibit variations in their functional activity, according to the time of the day, the season, or dependent upon the age of the individual. Other variations are accidental and are due to the conditions of the environment, or to some general pathological cause. All these alterations are subject to a somewhat automatic form of control. Gley is, therefore, quite right in objecting to the use of the terms hypo and hyper in a derogatory sense, as applied to glands with an internal secretion. He states that he has no wish to extend his criticism to the field of pathology, but we are of opinion that a little more discretion is also required in this department. What are the facts?

Firstly.—A very small amount of healthy thyroid tissue is enough to maintain its essential function and to prevent hypothyroidism (certainly much less than the quarter which is usually said to be

necessary). What inference is to be deduced from this fact? Simply that the body possesses a considerable reserve of thyroid tissue, and is able to adapt itself to very varying amounts of secretion without either hypothyroidism or hyperthyroidism resulting. This power is necessarily limited and its lower limit is very near athyroidism. But if a small fragment of healthy tissue is preserved in the body, the function of the gland is discharged normally. If, however, nothing is left the clinical picture of athyroidism is obtained. The same observation has been made in regard to other glands, the pancreas, liver and testicle among others. This is in very close agreement with the law which Pézard formulated in regard to the internal secretion of the testicle, "the whole or anything." The margin between the whole of the secretion and anything of it, is apparently much greater for the thyroid than for the testicle, hypothyroidism implies a very narrow margin of reserve.

Secondly.—The body is able to neutralize much larger amounts of thyroid secretion than is strictly required. It must be admitted that in Graves' disease the gland supplies an amount of secretion which is more than the body can tolerate, or it may be that the tolerance is diminished in this condition—an abnormal sensitiveness to thyroid secretion. The very frequent disproportion between the amount of secreting tissue and the severity of the symptoms suggests that the latter of these two possibilities is the true explanation, or at any rate that both factors are concerned. It may be that in some cases of Graves' disease the symptoms are due to a change in the character of the secretion, but this is not an indispensable condition, because all the symptoms can be evoked in a patient, apparently cured from the disease, by the administration of normal thyroid extract.

It follows from what we have just said that *thyroid instability*, the existence of which is admitted by Lévi and Rothschild, cannot occur in persons with normal thyroid sensitiveness. The normal individual has such great powers of adaptation in regard to "hypo" and "hyper," that he will not oscillate between the two groups of symptoms. If this instability exists—and we have no doubt of it—it presupposes an abnormal sensitiveness of the nervous system. In regard to the term "dysthyroidism" applied by Lévi and Rothschild to these conditions, we prefer to reserve it for genuine alterations in the secretion, which we will describe later on.

The question also arises as to the exact consequences of the histological lesions which are encountered in idiopathic myxœdema, and in Graves' disease. Do these lesions cause a mere *decrease* in the secretion—a simple *quantitative* alteration therein—without affecting the *quality* of the secretion? The only analogous condition known in this regard concerns the glands with an external secretion, but no

absolutely definite conclusions can be drawn from this consideration. It is, however, quite certain that specific secretory products can be manufactured by a gland which has undergone pathological change (cirrhosis of the liver). The simpler the secretion and the more defined its chemical constitution, the more likely is it to maintain its normal character despite changes in the organ which produces it; but the more complex it is the more likely is it to undergo qualitative alteration. The argument from the liver does not solve the question.

Is the active principle of the thyroid secretion a body with a definite chemical constitution? Is there only one active principle or are there many substances chemically different and possessing different actions?

We have already replied to these questions. It is probably true that there is one predominant substance—the thyroxine of Kendall—but it is quite certain this is not the only active principle concerned in the thyroid function. In our view we must discard the idea of simple hypo- or hyperthyroidism, and must look upon thyroid disorders as more complex. We may assume, for example, that the content of one active principle may be quite normal, but that there may be an increase or decrease of another, giving rise to a relative or partial hypo- or hyperthyroidism. It is possible to conceive a condition wherein one group of functions is diminished, whereas another group of functions is increased. Indeed this corresponds to actual clinical conditions, which manifest a combination of symptoms of hypo- and hyperthyroidism, as seen in some cases. We shall have something further to say on this particular matter. The problem of functional disturbance of the thyroid thus becomes much more complicated than we could possibly apprehend until recently.

Again, can the thyroid secretion be deranged, not merely in regard to the proportions of its components, but in the sense that *it may contain substances foreign to the normal secretion?* In other words does *a genuine qualitative dysthyroidism* exist? This question has been the subject of much discussion, and the existence of a true dysthyroidism can neither be affirmed nor disproved. In support of the theory of dysthyroidism Gley adduces the observations made by Garnier on changes in the thyroid during infections—observations which we have been able to confirm and to complete in a work which appeared in 1907. In 1902 we called attention to the fact that the colloid substance underwent some alteration from the normal, in certain infective conditions (when a true thyroiditis occurred) and in exophthalmic goitre. It is much more fluid in consistence, and stains better with hæmatoxylin than with eosin. We may agree with Gley in this type of case and regard it as indicative of a certain amount of dysthyroidism; but we will not go so far as to

assume the presence of foreign substances in the normal secretion, on the basis of these microscopical and physical changes. This histological change can well be explained by a slight alteration in the proportions of the albuminoid substances and other constituents, and these albuminoid substances themselves may merely be the vehicle or excipient for the really active principle.

The problem is still unsolved, and although histological examination demonstrates the alteration in the colloid substance, this is no justification for concluding that an absolute dysthyroidism exists. We have endeavoured to estimate the effect of histological lesions on the function of the gland, and for this purpose our pupil, Aeschbacher, calculated in 1905 the relative and absolute iodine content in glands obtained from individuals who had died of various maladies. This iodine content was found to be diminished in most cases of acute infectious disease. The considerable difference both in iodine and in phosphorus content noted in different glands seemed to depend partially on their varying content of colloid substance, and this suggests that the iodine and phosphorus content of the colloid substance is very variable. Sometimes the histological condition seems to influence the chemical constitution of the glands, at other times there is some chemical variation without any evident histological cause to explain it. We are, therefore, not justified in speaking of dysthyroidism, except in a relative sense. Possibly there is a true dysthyroidism, but its existence has yet to be proved. We must also remember that chemical analysis of the thyroid gland gives no absolutely definite information about the secretion of the gland, and that thyroid extract must no longer be confused with the internal secretion which circulates in the blood.

How do the clinical facts accord with one or other of the theories considered above? Let us take the questions in detail.

It is quite certain that the conditions commonly called *hypothyroidism* and *hyperthyroidism* are not due to mere quantitative differences in the amount of thyroid tissue. Let us consider, for example, the most common type of hypothyroidism, viz., cretinism, putting aside the possible hypothetical influence of an extra-thyroid factor in its pathogenesis. Although the gland may not be quite normal, it is very far from being atrophied in all cases. Often enough its histological appearance would suggest that its secretion was quite abundant. Among cretins, moreover, there is a remarkable dissociation of the cardinal symptoms of cretinism, which are skeletal changes, intellectual defects and deaf-mutism. Thus we may get the most severe degrees of cretinoid dwarfism (with or without deaf-mutism) in subjects whose intelligence is but slightly affected; whereas we come across cretins who are complete idiots, but whose

skeletons are normal. We cannot deny the importance of the age at which the thyroid disturbance begins to appear, nor that of the part played by the individual predisposition of any special organ or tissue. Observation shows that most cretins who are dwarfed have an atrophied thyroid, whereas those whose skeletons are normal or only slightly diminished have an obvious goitre. The same parallelism holds good in regard to the development of the genital organs and the growth of hair, which is defective in the dwarfed cretin, but is more or less normal in the cretin of good stature.

These observations would tend to show that the thyroid secretion in the cretin of normal stature, is not only insufficient quantitatively, but is also defective qualitatively.

Let us now pass on to hyperthyroidism. Here also the histological lesions are not merely quantitative. Exophthalmic goitre does not present a simple numerical increase in the components of the gland, but it exhibits a very characteristic histological change. According to the view of Plummer and Wilson, the true syndrome of exophthalmic goitre is due to a combination of hyperthyroidism and dysthyroidism, whereas the symptoms of "toxic adenoma" are due exclusively to hyperthyroidism. Kendall and Wilson hold that iodine exists in the thyroid gland in two different combinations, one of which, only, possesses a toxic character. The symptoms of Graves' disease are not due to an over-production of this substance, but to its excessive diffusion throughout the body. This view seems plausible at first sight, but obviously an excessive diffusion and continuous flow is impossible without an over-production, in the absence of which the gland would be rapidly exhausted.

Another interesting point is the fact that iodine medication causes artificial Graves' disease only in patients who are already goitrous, i.e., who have a diseased thyroid. We have never seen symptoms of Graves' disease supervene after iodine in a person with a normal thyroid gland. At this juncture one may well ask whether the quality of the secretory product does not play an important part, as well as its quantity. This is a difficult problem to solve because the severity of the symptoms of Graves' disease is not strictly proportional to the amount of glandular tissue involved, and moreover, the influence of individual predisposition and family history is very great. Indeed this latter point was elucidated by Lebert as long ago as 1861.

(B) Polyglandular Influences.

Our discussion of this problem has been conducted exclusively from the point of view of the thyroid function, but there is no doubt that *other glands* are also concerned, although we do not know in what manner or in what degree. According to Kendall increased activity

of the cortical substance of the suprarenals is just as important in the production of hyperthyroidism as increased activity of the thyroid itself. According to von Haberer, the presence of an enlarged thymus is of more importance in the causation of recurrences of the syndrome of Graves' disease than a recurrence of the goitre itself. Capelle, von Haberer, Bircher and other authors, hold that there is a close relationship between the persistence or enlargement of the thymus and exophthalmic goitre, although very little is known of the mechanism.

(C) Influence of the Nervous System.

We have hitherto left out of consideration the question of the effect of *functional disturbance of the nervous system* upon the functions of the thyroid gland.

It is undeniable that there is a close association between the nervous system and the symptoms of Graves' disease, but this association can be explained in various ways.

(*a*) There may possibly be some primary functional disturbance of the great sympathetic, producing, simultaneously, histological changes in the thyroid gland and derangement of its functions. This hypothesis is, however, the least probable. Wilson himself, who has demonstrated the frequency of the pigmentation of the superior cervical ganglion in exophthalmic goitre, looks upon it as a secondary manifestation.

(*b*) There may be a fundamental lesion associated with a peculiar and individual predisposition of the nervous system. This explanation, which is accepted by most authorities, appears to be supported by the existence of cases of goitre with the histological characters of Graves' disease but without any corresponding clinical symptoms. These goitres occur in adolescents, but we have not met with them in adults, a fact which can be explained by the very great tolerance which exists at the age of puberty in regard to the thyroid secretion.

(*c*) On the other hand the essential pathological condition may be a disorder of the thyroid, producing a clinical picture which is quite definite. The pre-existing state of the nervous system may have no influence as a causative factor, but may have some effect on the severity of the symptoms.

In favour of this view one may refer to the well-attested fact that the syndrome of Graves' disease may follow an acute thyroiditis; but the comparative rarity of this mode of origin is rather an argument for the preceding hypothesis.

(D) Threshold of Absorption.

In a previous chapter reference has been made to the "threshold of absorption" of the normal thyroid, and its temporary lowering

immediately after birth has been noted. It is now necessary to consider certain facts in the pathological physiology of the gland from this point of view.

The disappearance of the colloid substance in certain acute diseases, notably in scarlet fever, in alcoholic poisoning, and in extensive burns is obviously due to a lowering of the threshold, but we do not know whether it is due to an increased consumption or to an insufficient production of the colloid substance. In all these pathological conditions, as well as in the goitre of Graves' disease, the lowering of the threshold is associated with an abnormally fluid consistence of the colloid substance.

There is a lowering of the threshold in diffuse parenchymatous goitre, particularly in the goitre of adolescence ; but in diffuse colloid goitre there is a raising of the threshold. Nodular goitres of a simple type, parenchymatous (microfollicular) or colloid, behave like the corresponding diffuse goitres. There is no fixed rule in regard to the threshold in cases of mixed goitre.

All the evidence tends to show that the lowering of the threshold in cases of nodular microfollicular goitre is the result of diminished production, whether the patient be euthyroidic or hypothyroidic.

(E) The Effect of an Ordinary Goitre on the Organism.

One of the most obscure problems in the pathological physiology of goitre concerns the *influence of an ordinary goitre on the organism*. We are not, of course, referring to mechanical pressure on the vessels or on the trachea, but exclusively to the matter of the secretion of the gland. The lymphocytosis, which is so frequent in patients with goitre, is apparently an argument in favour of some such action. We will go into details when discussing the diagnosis of Graves' disease, but we may say at once that we are very sceptical as to the significance of this symptom in goitrous subjects. We attribute more importance to the fact established by Messrs. Hara and Branovacki in our laboratory, that the blood of the veins of the arm of certain goitrous individuals, who are free from symptoms of hyperthyroidism, increases the sensitiveness of the rat in regard to a deficiency of oxygen. In other words, this biological test reveals some partial hyperactivity before the appearance of any clinical symptoms, and in individuals who will never exhibit the true syndrome of Graves' disease. M. Hara performed an analogous experiment with the blood of four dwarf cretins, and he found that in three cases the blood diminished the sensitiveness of the rat towards deficiency of oxygen.

In this connection we may recall the statement of Asher and his pupils Streuli and Duran, to the effect that the rat always manifested an increased sensitiveness towards an oxygen deficiency after the introduction of thyroid extract into the stomach. The hyperthyroidic

rat requires a very large amount of oxygen, and is asphyxiated much more rapidly in an air pump than a normal rat. A hypothyroidic rat, on the other hand, accommodates itself better towards a deficiency of oxygen than a normal rat.

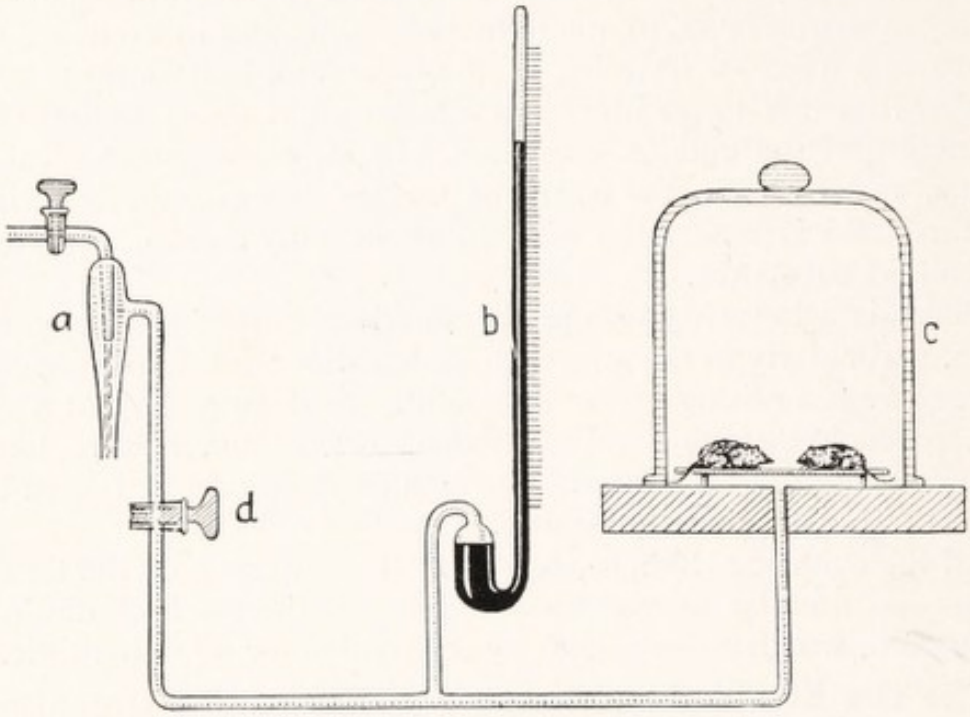


FIG. 27.—Experiment of Asher-Streuli. a-c, Air-pump ; b, Barometer.

Messrs. Hara and Branovacki have examined, independently of each other, some 120 cases in respect to the sensitiveness of the rat towards a deficiency of oxygen. The methods employed were as follows :—

(1) The injection of the serum of venous blood from the arm.

(2) The injection of the serum of venous blood taken from a goitre (withdrawn at the time of operation).

(3) The introduction of 60 grm. of goitrous material from the same case.

The point was to study the possible effect of different thyroid conditions upon the blood of the general circulation of the goitrous subject or of the cretin, the biological characters of the venous blood of different histological types of goitre, and finally the relative functional value of these various types of goitre. It had been established from the first by means of numerous controls that the subcutaneous injection of the same amount of serum (2 c.c. three times) from an individual who was free from goitre, did not modify the sensitiveness of the rat towards a deficiency of oxygen.

The agreement of the results of these two series of tests was so remarkable that we are compelled to ascribe a great importance to this experiment, conceived by Asher. We may add that the experimenter was unaware at the time of the experiment of both the clinical conditions of the case and of the result of the histological examination, in order to eliminate all possibility of auto-suggestion in judging of the state of the rats during the test.

ACTIVITY OF VENOUS BLOOD FROM THE ARM, VENOUS BLOOD FROM THE THYROID AND FROM THE GOITROUS MATERIAL.

Form of goitre	No. of cases	Venous blood from arm	Venous blood from goitre	Goitrous material
1. *Goitre of Graves' disease*	17	++	+++	+++++
2. *Ordinary goitre.*				
(*a*) Diffuse colloid goitre	9	+	++	++++
(*b*) Nodular colloid goitre	26	+	++	+++
(*c*) Diffuse parenchymatous goitre	5	+	++	+++
(*d*) Nodular parenchymatous goitre (adenoma)	19	0 to +	+	++
3. *Goitre with cretinism.*				
(*a*) Diffuse colloid goitre	4	0	0	+
(*b*) Nodular colloid goitre	5	0	0 to +	+
(*c*) Diffuse parenchymatous goitre	1	0	0	+
(*d*) Nodular parenchymatous goitre	27	0	0	+
4. *Dwarfed cretin without goitre*	6	−		
5. *Normal subject*	22	0		

0 = Sensitiveness of rat, normal.
+ = Sensitiveness of rat, increased (each + represents a difference in pressure of 40 mm. of mercury in comparison with a control test).
− = Sensitiveness of rat, diminished.

The accompanying table represents the mean of the two series of experiments.

The conclusion to be derived from this table is that the venous blood of the arm from a case of Graves' disease is the most active, that it is still definitely active in diffuse and nodular colloid goitre, but that there is no definitely marked activity in adenoma. There is no activity in the blood of goitrous cretins, whatever be the histological type of the goitre. The blood of the dwarf cretin, without a goitre, is also inactive.

The activity of the venous blood of the goitre diminishes progressively in the same manner, but in the goitre of Graves' disease, in ordinary goitre, and in the rare cases of colloid goitre in cretins, it is slightly more marked than that of the blood of the arm of the same case.

When the goitrous substance itself is administered a similar progressive diminution of activity is noted. It should be noted that all the histological varieties of goitre in cretins possess only a feeble activity.

These experiments, broadly speaking, confirm and extend the results obtained by Graham, Wegelin and Abelin, who employed the method of Gudernatsch—control of the effect of the goitrous material on tadpoles. They are new facts which tend to prove the slight activity of the goitres of cretins, but the undoubted activity of the blood of the arm, not only in cases of exophthalmic goitre, but also in certain cases of ordinary goitre in persons who are apparently euthyroidic. The activity of the venous blood of a goitre and that of the blood from the arm in exophthalmic goitre had already been

observed in some cases by Eiger in 1917, who was working in the laboratory of Professor Asher, adopting the method of Laewen-Trendelenburg.

We have been occupied in comparing the results of these examinations of blood and goitrous material with the respiratory exchange in the persons concerned. The results obtained in thirty cases seem to indicate that there is a close relationship between these two tests, but many more examinations are required before definite conclusions can be reached. Experiments on the rat appear to be more sensitive than tests of respiratory metabolism in the sense that the former yield a slightly positive result with the blood of a person with a harmless goitre and normal metabolism, and that the goitrous material of a cretin influences the rat, whether the metabolism of the cretin be normal or abnormal.

This leads us to the consideration of the subject of *respiratory exchange*.

The most accurate method of ascertaining the functional state of the thyroid gland is by determining the respiratory exchange or basal metabolism. The earliest information on this subject dates from 1893, and the observations were made by Friedrich Müller. Magnus-Lévy confirmed the work of this author in 1895, but it was not possible to apply this principle clinically on a large scale until manageable apparatus was designed, and until standard tables indicating normal metabolism in respect to age, sex, height and weight had been prepared. This latter work we owe to D. and E. Du Bois, Benedict, Means, Aub and Talbot.

We must preface with a word or two about apparatus.

The big pieces of apparatus designed by Jaquet and by Benedict, with a closed circuit, are limited to the purpose of research in laboratories. In Jaquet's apparatus the patient lies flat on a long couch in a hermetically closed cage. The air expired during a period of one to two hours is analysed by Haldane's apparatus.

In Benedict's large apparatus the subject inhales a given quantity of oxygen through a mask, in a closed circuit, the carbonic acid being absorbed by caustic soda. The analysis is made by the volumetric determination of the oxygen inspired and by the weight of the carbonic acid produced.

In Tissot's apparatus, made in Paris in 1904 and popularized in America, the air expired through a mask or a piece of india-rubber tubing introduced through the mouth, is collected in an open circuit during a given time. The air contained in the gasometer is afterwards analysed by Haldane's method.

In Benedict's smaller apparatus the subject breathes, in a closed circuit, into a small gasometer containing a given quantity of oxygen. The carbonic acid is absorbed by a mixture of quicklime and caustic soda. The analysis of the expired air is replaced here by the single

measurement of the volume of oxygen absorbed in a given time. This test is much simpler than the preceding one, but it deprives the experimenter of the very important control of the respiratory quotient ($CO_2 : O_2$) and of the exact knowledge of the volume expired per minute. This small apparatus in one of its numerous modifications

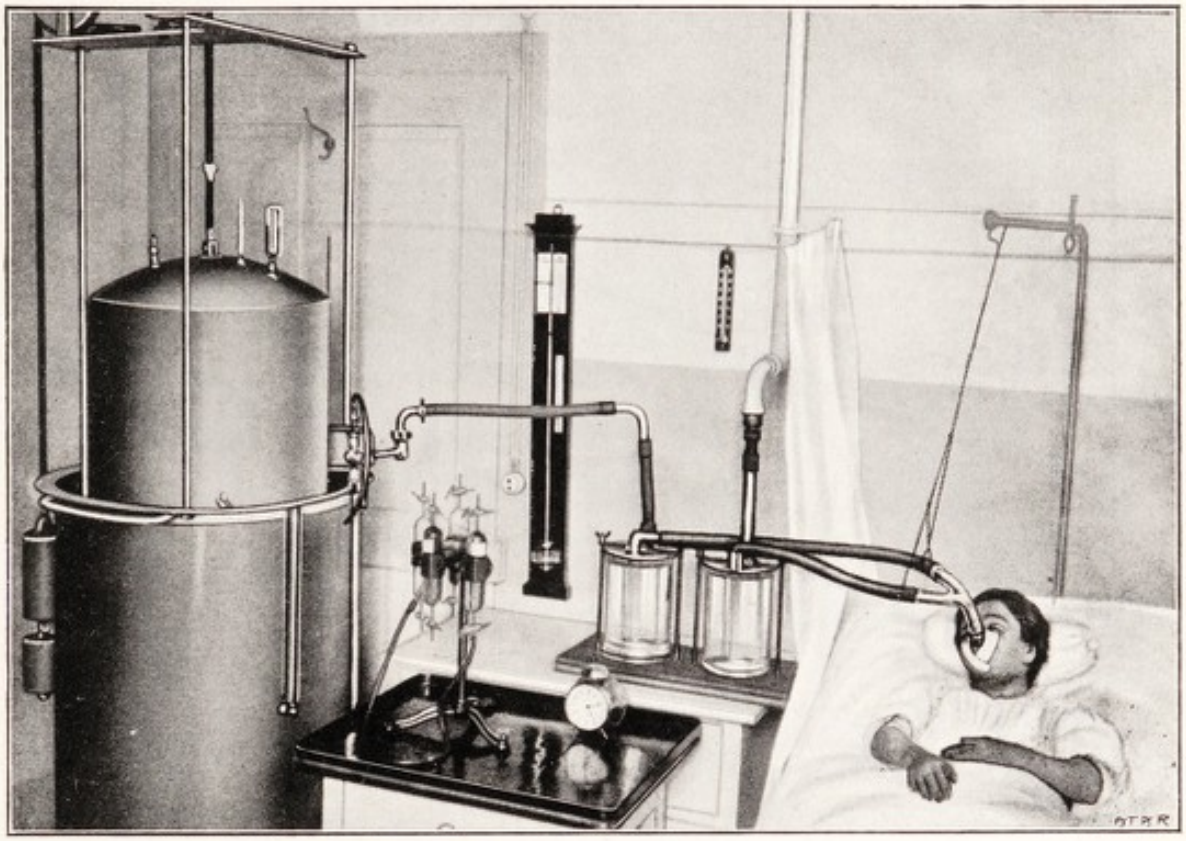


FIG. 28.—Tissot's apparatus, with water valves (laboratory for metabolic estimations in the Surgical Clinic of Berne).

appears to suffice for ordinary hospital requirements, but is unable to replace the more accurate apparatus of Tissot for scientific research (Boothby). The accuracy of this instrument is increased by the kymographic record of the movements of the bell-chamber (Roth).

Boothby has established the fact which has been confirmed by other workers that in 95 per cent. of the cases an increase of respiratory metabolism is due to thyroidic causes, and it is for this reason that the estimation of the respiratory exchange is so important.

The amount of oxygen absorbed in a definite period of time, or the corresponding caloric value, is compared either with the body weight of the subject or the superficial area. The latter is calculated according to Du Bois' modification of Rubner's formula, from the height and body weight. The tables and diagrams constructed on the basis of this formula give the superficial area, corresponding to any height and weight, without further calculation.

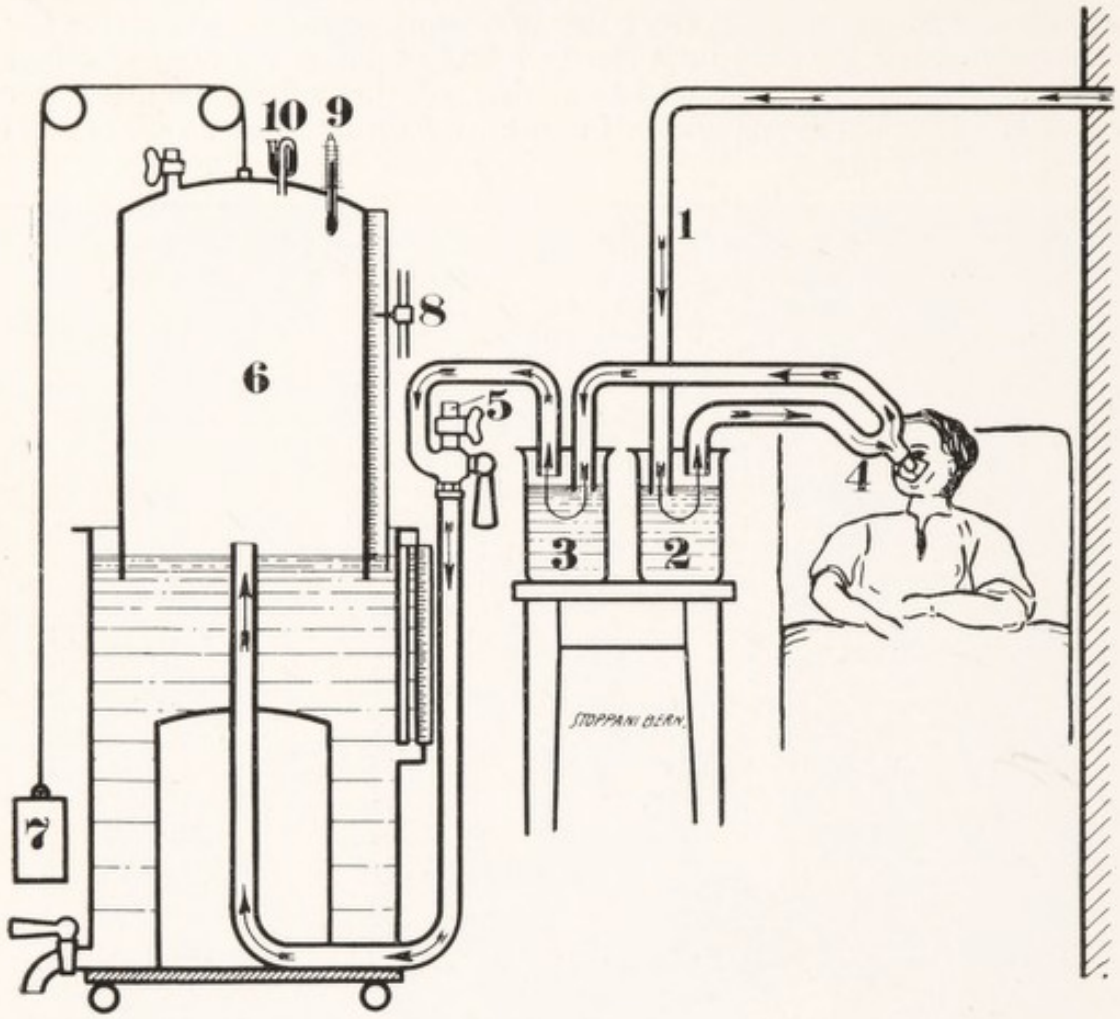


FIG. 29.—Diagram of Tissot's apparatus, with water valves.

1. Pipe for introducing fresh air. 2 and 3. Water valves. The valves are superior to any other system, because they cannot get out of order, and are always ready to act. 4. Y-shaped glass tube surmounted with an india-rubber mouth-piece which is fixed by bands of strapping after the occlusion of the nostrils. (This may be replaced by an air-tight mask.) 5. Evacuating tap. 6. Gasometer. 7. Counterpoise weights. 8. Scale indicating the contents of the gasometer in litres. 9. Thermometer. 10. Manometer.

(The counterpoise 7 is equilibrated by the aid of accessory counterweights, so as to guarantee that the difference in pressure should not exceed 3 mm. of water, whatever be the position of the gasometer. The column of water to rise in the water-valves does not exceed 3 mm.)

It is the second of these principles which is generally applied in practice, viz., the relation between the caloric value of the oxygen absorbed and the superficial area of the body. The number of calories usually absorbed per hour and per square millimetre of surface has been established for both sexes and for different ages by the above-mentioned authors, particularly by Du Bois, Benedict and Talbot. The main variations are found in the figures which have been ascertained for infancy and puberty. The figures given by Du Bois seem to be somewhat above the true average, especially for individuals less than 20 years old, and it is suggested by Means and Woodwell that 1·8 calories should be deducted from figures of Du Bois. In regard to persons under 14 years of age, the scale

of Benedict and Talbot, based exclusively upon the body weight and the age, appears to be the best hitherto available. In our opinion the formula of Rubner-Bois yields inaccurate results in extreme cases, such as in very short and very heavy persons and vice versa.

The tables now in our possession have already yielded most interesting results, quite apart from any further development this system of investigation may undergo. In hyperthyroidism there is always an increase in the respiratory exchange even up to 100 per cent., and in hypothyroidism there is usually a diminution to the extent of 20 to 40 per cent. below normal. We shall discuss these figures in greater detail in the chapters on hyperthyroidism and hypothyroidism.

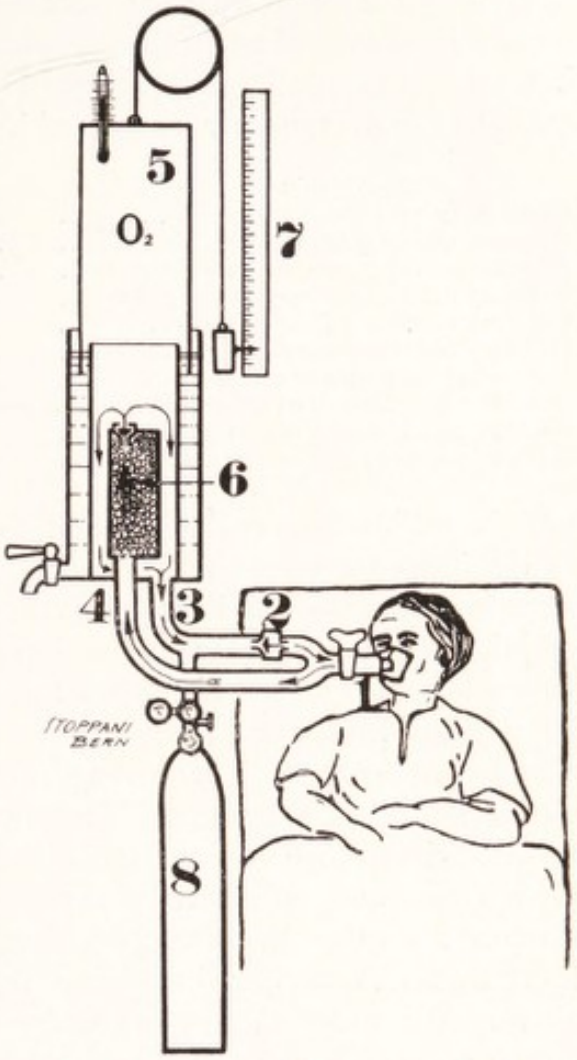


FIG. 30.—Diagram of Benedict's smaller apparatus.

1. Y-shaped piece with india-rubber attachment as in preceding figure. 2. Valve opening on inspiration. 3 and 4. Entrance and exit pipes for air. 5. Small gasometer containing oxygen. 6. Receptacle containing lime impregnated with caustic soda. 7. Scale indicating the contents of gasometer, by position of counterpoise. 8. Cylinder for oxygen.

(The gasometer is filled with oxygen at the beginning of the experiment and the cylinder is then closed. The patient then inspires oxygen through the pipe 3 and the valve 2. The expired air passes through the receptacle 6, arranged to absorb the carbonic acid, then through the valve fitted to the lid of the cylinder and finally into the gasometer. The whole constitutes a closed circuit in which the oxygen is gradually absorbed by the lungs of the person under examination. The quantity used up in the unit of time is calculated according to the duration of the test and the position of the gasometer at the beginning and end of the test.)

(F) The Rôle of Iodine.

We will conclude our account of the pathological physiology of goitre by a few remarks on the relations existing between the histological form, the biological activity, the iodine content of the gland and the clinical symptoms, in different conditions of the thyroid.

Our pupil, M. Aeschbacher, whose researches we have already mentioned, has observed a decrease in iodine content in most acute infectious diseases, in certain disorders of the circulatory system, as well as in certain cases of chronic alcoholism.

As far as *goitre* is concerned, he only examined mild cases, coming from a district where goitre is scarce (the highlands of the Jura).

He observed a slight relative decrease in the iodine content, and an increase in the absolute iodine content in cases of mild diffuse goitre. M. Branovacki analysed 60 cases of goitre, and the following figures represent the average percentage of iodine in the dried substance.

Type of goitre	Percentage of iodine	Biological activity
Classical exophthalmic goitre	0·417 ...	+++++
Ordinary diffuse colloid goitre	0·385 ...	++++
Nodular colloid goitre of Graves' disease	0·31 ...	++++
Ordinary diffuse parenchymatous goitre	0·209 ...	+++
Ordinary nodular colloid goitre	0·141 ...	+++
Ordinary nodular parenchymatous goitre	0·12 ...	++
Diffuse colloid goitre of cretin	0·088 ...	++
Nodular parenchymatous goitre of Graves' disease ...	0·063 ...	++++
Nodular colloid goitre of cretin	0·057 ...	++
Nodular parenchymatous goitre of cretin	0·052 ...	++

This table shows that although the relationship between the relative iodine content and clinical and biological characters of the goitre is not absolute, it is nevertheless a very close one. The one exception is the nodular parenchymatous goitre of Graves' disease (toxic adenoma) which is remarkable in having a low iodine content and a high biological activity. The table also shows that colloid goitres contain more iodine than nodular parenchymatous goitres in each of the clinical groups. The forms which contain much colloid are also richer in iodine than the adenomatous forms (nodular parenchymatous), whether the case be a goitre of Graves' disease, an ordinary goitre or a goitre of cretinism. The diffuse colloid goitre of cretinism is poorer in iodine than most ordinary adenomatous goitres. We must always remember that the *absolute iodine content* may be increased, even in the case of a cretin, owing to the great size of the goitre. Thus, the mean amount of diffuse colloid tissue removed from two cretins was 436 grammes, containing a mean of 5·9 grammes of iodine, i.e., an amount equal to that in a normal gland. But this is exceptional: in most cases of cretinism the total iodine content is 10 to 20 times less than that of a normal thyroid.

(G) Condition of Activity and Histological Characters.

We have now to consider how we may infer the functional condition of the gland from the facts ascertained by histological examination.

The following appearances would suggest a condition of activity.

(1) A cylindrical form of epithelial cells.
(2) A tendency to the formation of papillæ.
(3) Irregular vesicles, deficient in colloid substance.
(4) The colloid material badly stained, much vacuolated or reticulated, staining preferably but feebly with hæmatoxylin.
(5) Considerable desquamation.
(6) Great frequency of mitochondria (Goetsch).

The opposite appearances would suggest a condition of rest or inactivity.

(1) A squamous shape and flattening of epithelial cells.
(2) Absence of papillæ.
(3) Circular shaped vesicles.
(4) Colloid material homogeneous; intensely stained by eosin, by hæmatoxylin or by both at the same time. Complete absence of colloid material in other cases.
(5) No desquamation.
(6) Few or no mitochondria.

The value of these signs is not by any means uniform, and if the goitre has any tendency to malignancy, the above classification will not apply. A malignant goitre may exhibit an increase of mitochondria and of other signs of activity, while actually its function may be very deficient. The same remark applies in a lesser degree to all adenomatous enlargements. The signs which should indicate an absolute dysthyroidism are unknown.

CHAPTER VI.

THE DIAGNOSIS OF GOITRE.

To perform **palpation** of the gland the practitioner must stand behind the patient, rest the two thumbs on the nape of the neck and endeavour to grasp the two lobes of the thyroid between the index and middle fingers of both hands. Begin by determining the limits of the lower poles, making the patient swallow if necessary. If the outline of the gland is not clearly appreciable make the patient lie down flat with the head extended slightly but supported, and the sternomastoids relaxed. If the lower pole of one lobe can still not be reached it is because it is retrosternal and has entered the thorax. Palpation may lead one into error by what feels like a distinctly limited lower lobe, while there is really a narrow prolongation into the thorax which, once it has entered into that region, grows into a retrosternal goitre. This is the commonest type of intrathoracic goitre, and is much commoner than the true accessory goitre.

When the shape and position of the lower poles have been discovered the fingers should glide towards the upper poles, the limits of which are generally not difficult to determine, any more than those of the lateral borders or the shape of the isthmus.

Nevertheless if the gland is soft in consistency it may appear smaller than it really is.

FIG. 31.—Measuring the circumference of the root of the neck.

FIG. 32.—Measuring the anteroposterior diameter of the root of the neck.

Measurement of the gland includes :—

(*a*) Measurement of the circumference, the tape passing above the seventh cervical spine and across the suprasternal notch or the most prominent point of the goitre.

(*b*) Measurement of the anteroposterior diameter of the neck, from the seventh cervical spine to the suprasternal notch or to the most prominent point of the goitre.

(*c*) Measurement of the height of each lobe either from upper to lower pole, or if the latter is not palpable, from the upper pole to the suprasternal notch.

(*d*) Measurement of the total breadth of the gland, the points of the calipers being placed as a rule behind the sternomastoids.

FIG. 33.—Measuring the height of a lobe.

FIG. 33A.—Measuring the transverse diameter of the goitre.

FIG. 34.—Palpation of the thyroid.

FIG. 35.—Mensuration after Hunziker: a-b and a_1-b_1 = height of lateral lobes, c-d = total breadth of gland.

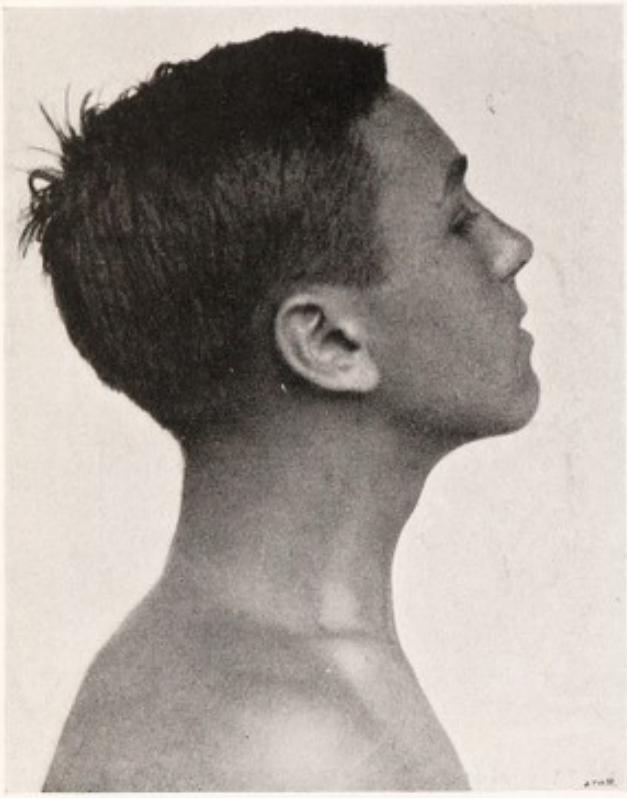


FIG. 36.—Class I. In profile.

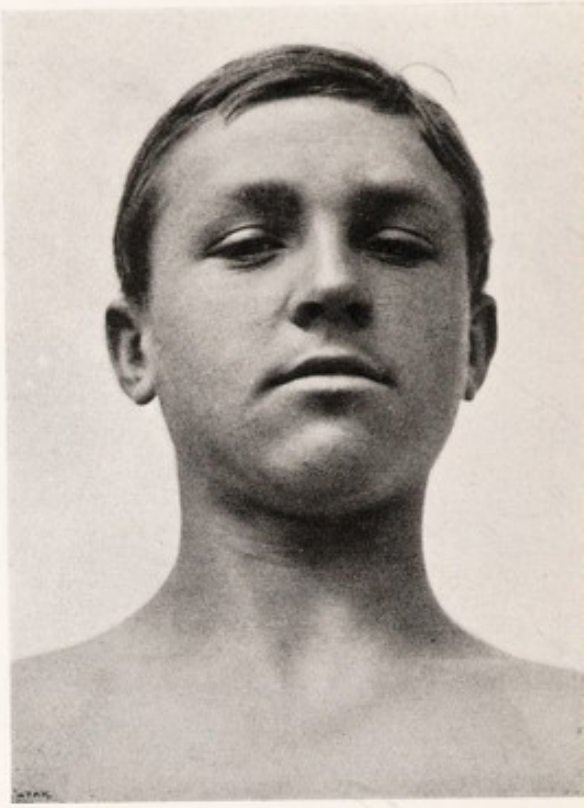


FIG. 37.—Class I. Full face.

FIG. 38.—Class II. In profile.

FIG. 39.—Class II. Full face.

FIG. 40.—Class III. In profile.

FIG. 41.—Class III. Full face.

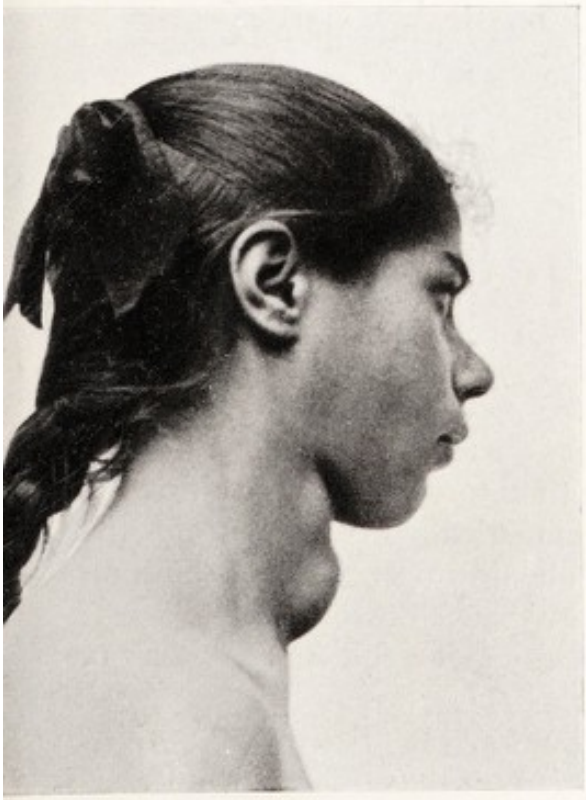


FIG. 42.—Class IV. In profile.

FIG. 43.—Class IV. Full face.

The figures obtained from (*a*) and (*b*) vary so much with the height of the patient that they are of comparative value only for the same subject and cannot be used to compare one patient with another.

The figures obtained from (*c*) and (*d*) afford more reliable values if one takes into account the source of error resulting from difference in consistency. It is true that they neglect the thickness of the gland and its intrathoracic portion. Hunziker uses them to calculate the rectangle occupied by the thyroid. This procedure, designed to control the results of prophylaxis, only gives figures which can be used on glands that are distinctly palpable and therefore appreciably increased in size. The normal gland, especially in children, does not lend itself to precise measurement.

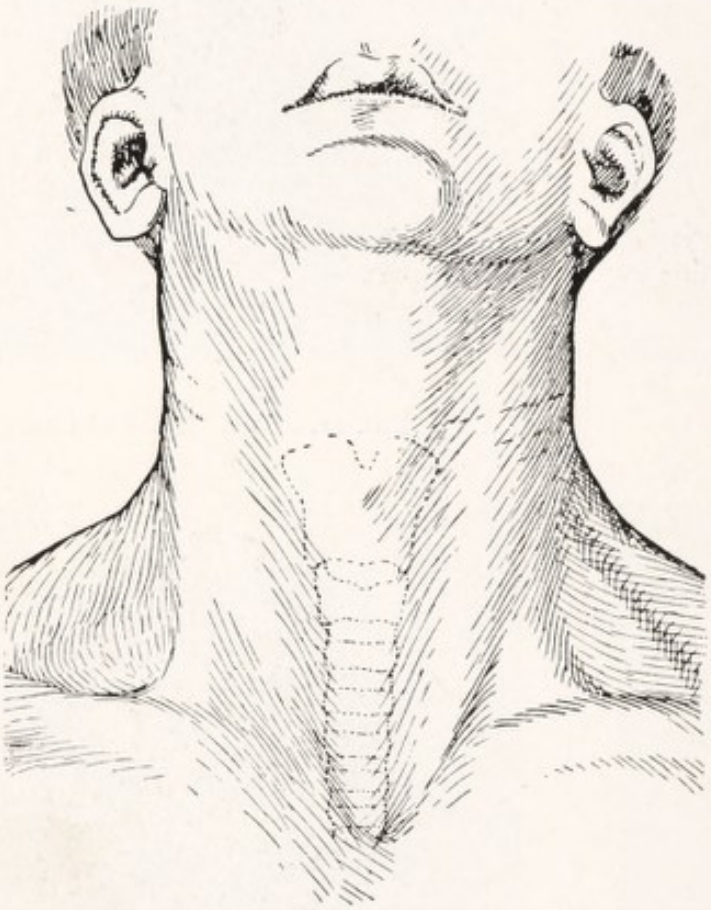


FIG. 43A.

Any inquiry, in schools or elsewhere, into the occurrence of goitre necessitates at least a minimum amount of classification. Neither the circumference nor the anteroposterior diameter of the neck can be used for this purpose. Estimation of the area according to Hunziker's method gives results much too arbitrary to be used in young subjects, not to mention the fact that we have no scale of comparison between the normal area and the age and height of the subject. The Swiss Goitre Commission therefore adopted the following classification which, although not mathematically accurate, fulfils the purposes of a summary inquiry. This classification, which is a modification of that proposed by Klinger, presupposes the following classes:

Class O.—Thyroid not felt. Trachea can be felt from the larynx to the suprasternal notch.

Class I.—Thyroid hardly felt on palpation. It fills the depressions on either side of the trachea, between it and the sternomastoids. It occupies the suprasternal hollow and is palpable as an elevation situated transversely on the trachea.

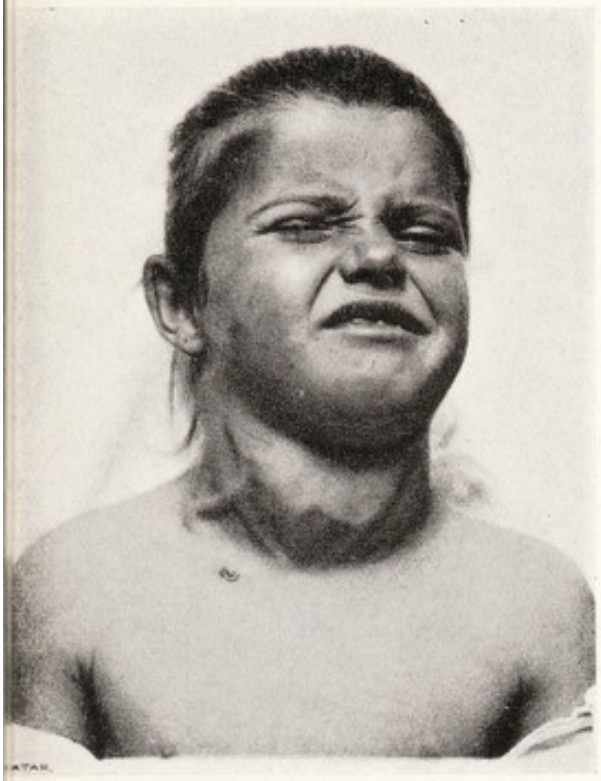


FIG. 44.—Diffuse vascular goitre in a girl of 5.

FIG. 45.—Diffuse goitre of puberty, girl of 15.

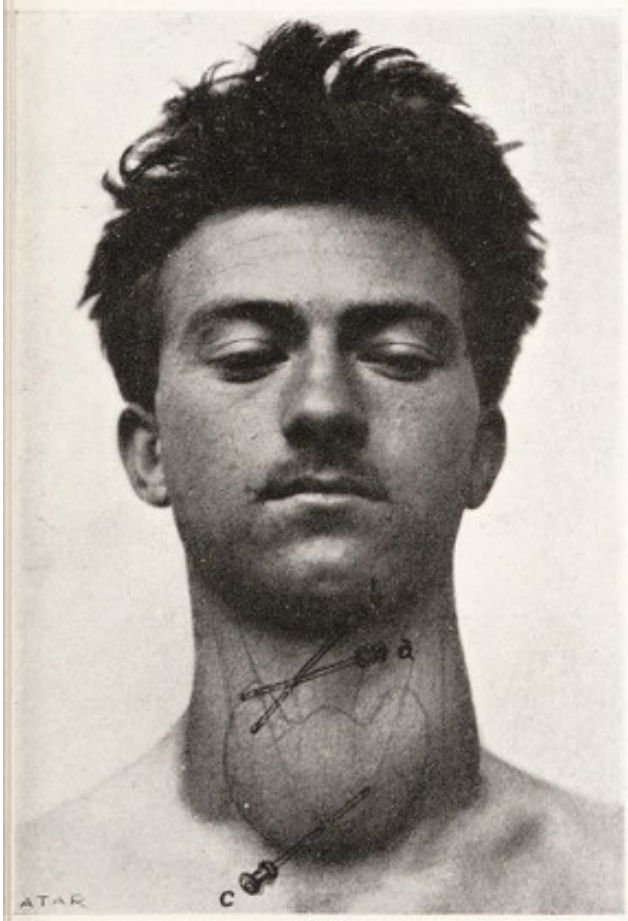


FIG. 46.—Diffuse colloid goitre in an adult.

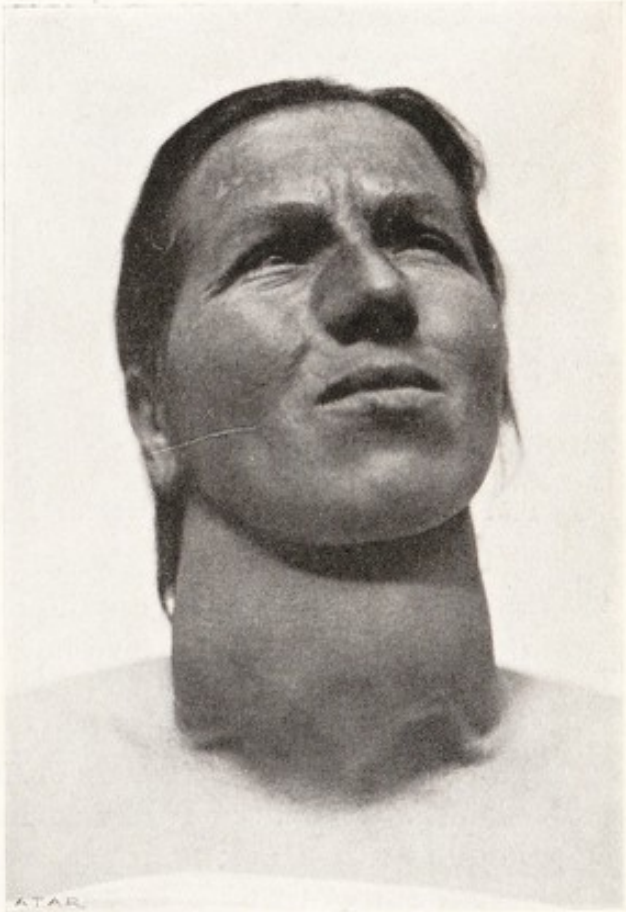


FIG. 47.—Diffuse multinodular parenchymatous goitre.

Class II.—Thyroid easily felt. The upper poles and, as a rule, the lower poles of both lobes can be made out, but the outline of the neck is not markedly affected.

Class III.—Thyroid easily felt and neck is obviously enlarged by it.

Class IV.—The shape of the neck is altered sufficiently to be called a "goitre."

Intermediate classes are labelled O-I, I-II, &c.

The presence of goitrous nodules is noted by addition of an N in brackets (N) after the number of the class The position and size of

FIG. 48.—Diffuse colloid goitre, multinodular.

FIG. 49.—Cystic goitre.

the nodule are written on the accompanying figure (43A) and reproduced on the scholar's own card. (See Chap. VII.)

In most cases it is easy to differentiate between a diffuse goitre and a nodular goitre. Diffuse goitre causes a uniform enlargement of the gland and adopts its horseshoe shape. Nodular goitre, on the other hand, is recognized by its asymmetrical form or by the presence of nodules which are of firmer consistency than the body of the gland and the size of which may vary from that of a small pea to that of an

adult's head. Mistakes are often made, however, in multinodular colloid goitres, in which the gland is changed into a collection of nodules no bigger than a small pea or a cherry. This type seems to merge into the diffuse colloid goitre of adolescence, as was seen in Chapter IV, and exists in adults only. It is the type of some very large goitres which are seen chiefly in mildly endemic districts. Thus in Switzerland this type is more common in Bâle than in Valais or the

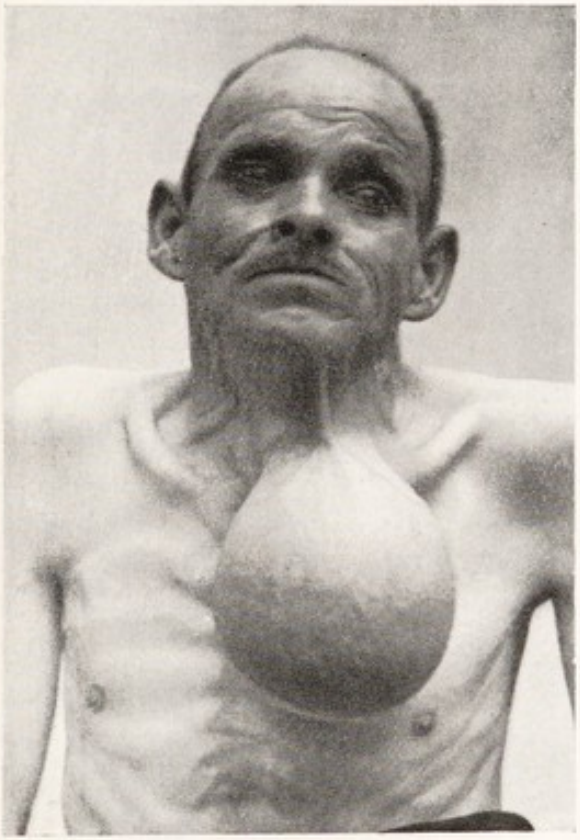


FIG. 50.—Pendulous cystic goitre.

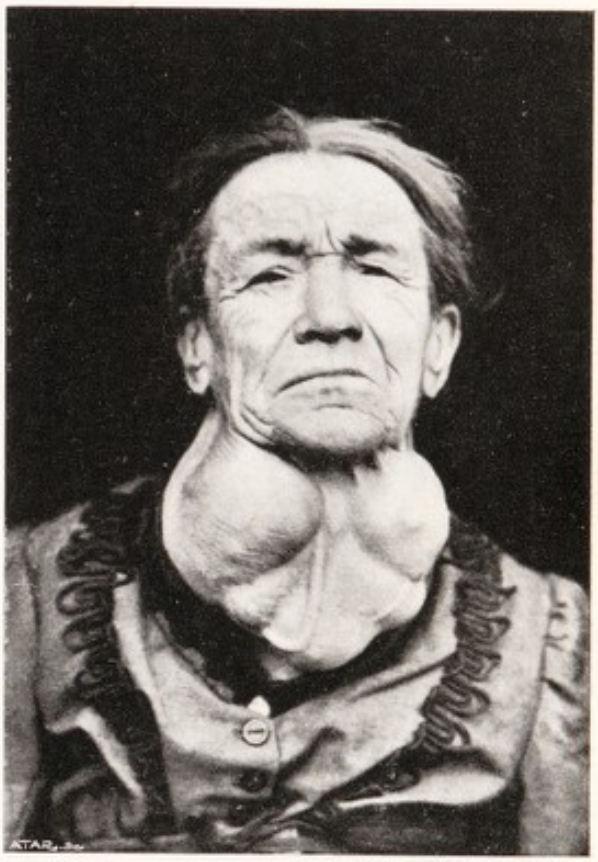


FIG. 50A.—Trilobed goitre.

Bernese Oberland. The age of the patient and the slightly nodular surface of the goitre disclose its nature immediately.

Multinodular (microfollicular) *adenomatous goitre* is also often confused with diffuse goitre. This type, as has been seen, merges into the *parenchymatous* goitre of adolescence.

True *diffuse goitre* feels homogeneous or slightly granular, being sometimes soft and sometimes hard. It is impossible to determine by palpation whether it is follicular, micro- or macrofollicular in type. From our observations made at Bâle it would appear that hard, granular goitres are generally macrofollicular and therefore colloid. But the records based upon the clinical material at Berne have failed

to confirm this impression. Microfollicular goitre, especially the adolescent type, is quite often hard and has a slightly granular surface. It is probable that local conditions play some part in the matter. We have already seen that, with the exception of Graves' disease, true diffuse goitre is rare after the third decade and that it is more often microfollicular or parenchymatous in highly endemic goitrous districts, and colloid in less endemic regions or near the sea.

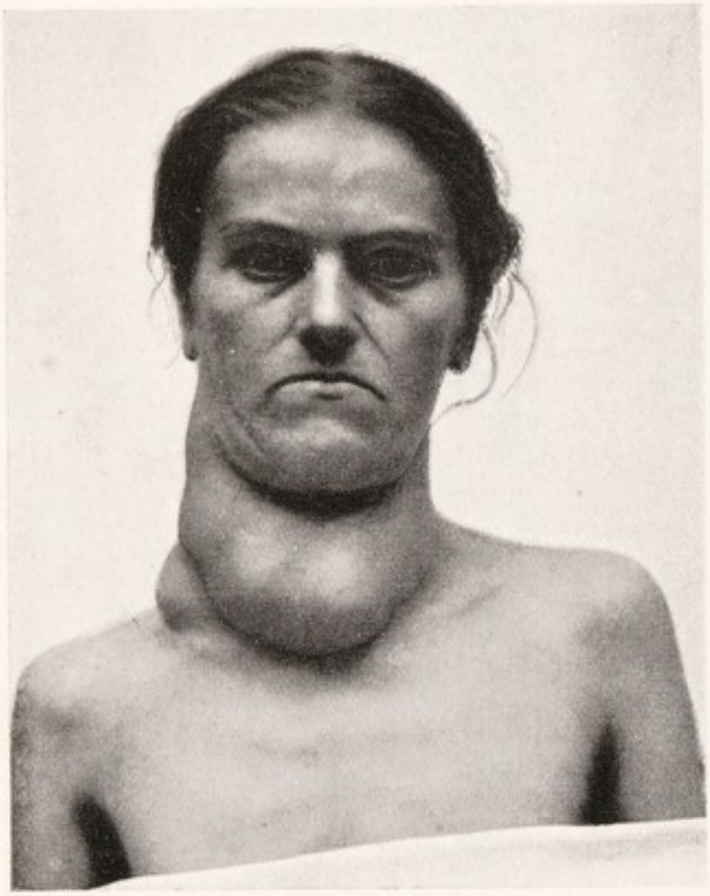


FIG. 51. – Malignant goitre.

The *increased arterial blood supply* which, of course, always presupposes an abnormal development of the venous system, is evidenced by the marked pulsation of the superior thyroids, often by an impulse at that level and, above all, by the expansile pulsation of the whole goitre together with the frequent presence of a systolic murmur. In some cases the venous system alone seems to be abnormally developed.

Venous blood, prevented from passing through the jugular veins, makes its way by thoracic collateral branches, and a caput medusæ is formed which in intrathoracic goitres sometimes extends out to the shoulders (fig. 54).

The patient can expand the goitre at will, even increasing the circumference of the neck by 2 cm. or more. These are the cases in which either or both internal jugular veins are compressed by the goitre. The venous network of the neck is abnormally developed and the face has the familiar bloated aspect characteristic of certain goitres. The change in the physiognomy of these cases after the great venous trunks have been freed by operation is very striking.

The nomenclature of the different types of goitre which are more

FIG. 53.—Same case with artificial congestion of the neck.

FIG. 52.—Diffuse goitre, partly retrosternal.

or less intrathoracic has given rise to some confusion. More especially has the term "goitre plongeant" (diving goitre) been applied to very different types. This point deserves brief consideration.

A *simple goitre* lies completely outside the thoracic cavity and its lower poles are easily defined. A goitre which develops in a thyroid

FIG. 54.—Goitre, most of which is retrosternal, showing caput medusæ.

situated low down (thyroptosis of Kocher) partly occupies the opening into the thorax without itself being very mobile. But it rises out of the thorax completely on swallowing.

A true "*diving*" *goitre* is recognized by its comparatively small size (about that of a large plum or at most of a small mandarin) and its great mobility. As a rule it is situated outside the thorax but it is sometimes aspirated towards the cavity by deep inspirations and pushed towards it by the simultaneous contraction of the pretracheal muscles and sternomastoids (figs. 56 and 57). This goitre is still termed "wandering goitre."

This type of goitre is peculiar in that it does not interfere with respiration while it is superficial, but dyspnœa increases with the depth of the goitre. Thus a vicious circle is established which may end in suffocation.

FIG. 55.—Marked exophthalmic goitre.

"*Deep goitre*," sometimes wrongly called "diving" goitre, is quite different. It develops partly outside the thorax, but the lower extremity of one or both of its lobes continues to grow down within the thorax. It thus affords a true example of retrosternal or intrathoracic goitre.

A goitre is called "*retrosternal*" or "*intrathoracic*" if the whole or a large part of it is confined within the thoracic cavity and cannot rise out of it.

It goes without saying that these terms represent types which are linked together by intermediate forms. Thus the distinction between a deep goitre and an intrathoracic goitre is merely a conventional one.

FIG. 56.—"Diving" goitre.

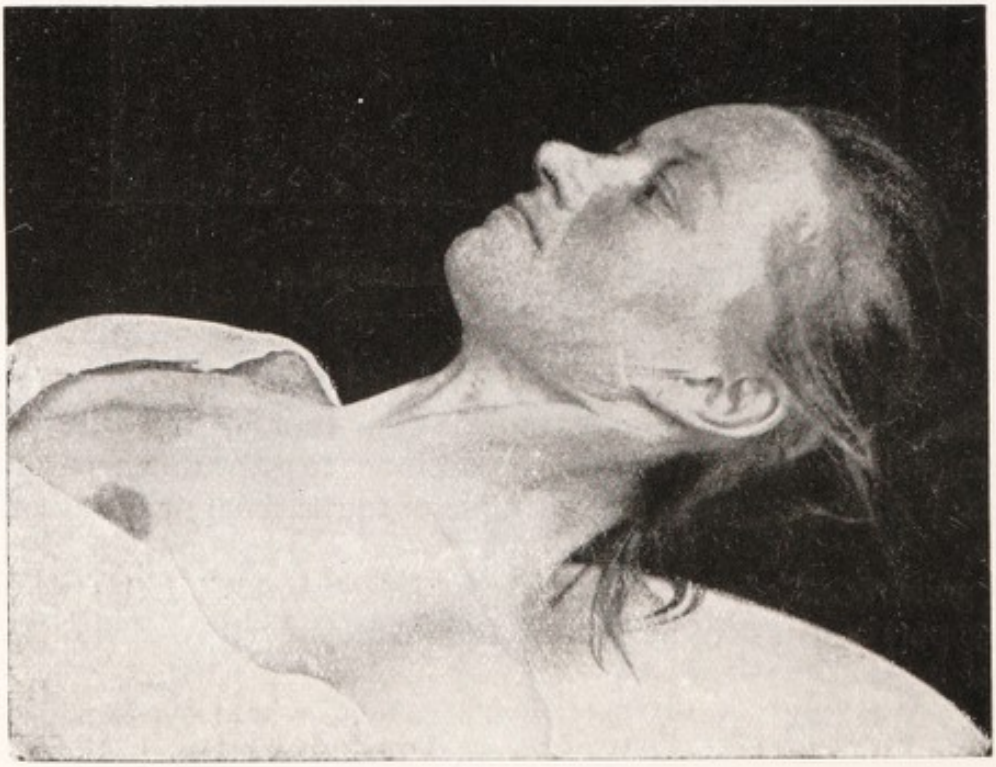


FIG. 57.—"Diving" goitre (with contraction of sternomastoids).

Nevertheless it is useful to understand the meaning of the various terms.

From the above account it will be seen that the symptoms caused by a true "diving" goitre are essentially variable and intermittent, whereas a goitre that permanently occupies the upper thoracic aperture gives rise to symptoms of constant compression. The patient gradually becomes accustomed to the lessened calibre of his trachea. He instinctively avoids any effort in excess of his powers and resigns himself to the exigencies of a sedentary life despite a goitre which may suffocate him at any moment. The diagnosis of a retrosternal goitre is suggested, as has been mentioned, by the bloated aspect of the patient, by the dilatation of the cervical and thoracic veins and by the very frequent occurrence of headaches. It is often confirmed by means of *percussion* and always by *screen examination* and a *skiagram*. The interpretation of a mediastinal shadow is easy when the shadow appears to be the prolongation of a goitre palpable in the neck. But it may be difficult if the whole goitre is intrathoracic. We have seen cases in which the shadow of the goitre was more suggestive of an aneurysm than anything else. In rare instances a cold abscess secondary to Pott's disease may simulate a deep goitre. The passage of the trachea between the mediastinal shadow and the sternum allowed of an exact diagnosis being made in one such case. The spinal disease itself had remained latent.

Inspection and palpation often give the clue to respiratory disorders, but they give no indication of the particular form or degree of compression or of tracheal deviation. Palpation must be followed by a *laryngoscopic examination* which may disclose a lesion of the recurrent laryngeal nerve: complete paralysis (cadaveric position of the corresponding cord) or partial lesion (adduction of the cord). It will show any torsion of the larynx and deformities of the upper part of the lumen of the trachea.

The frequent S-shaped deviations may completely escape notice by this method. This omission may be remedied by tracheoscopy, the tube of the instrument being introduced through the larynx into the trachea. This method of examination is not to be advised because not only does it irritate the mucous membrane of the trachea —especially harmful as the operation is generally performed a few days after the examination—but is sometimes a fertile source of error. The very introduction of the tube of the instrument into the trachea straightens it and obliterates the deformity it was designed to observe.

It is by means of **X-ray examination** that we can obtain some precise indications as to the condition of the trachea. The first view

taken is that from the anterior aspect of the neck and thorax which demonstrates any deviation or lateral compression of the trachea and also the presence of a retrosternal goitre. It is easy to detect single or double constrictions of the trachea, whether localized or widespread; ordinary lateral displacement, C or S-shaped curvature, &c. The accompanying figures show some of the commonest types.

At times one is struck by the lack of definition or even the complete absence of the shadow of the trachea in a perfectly successful

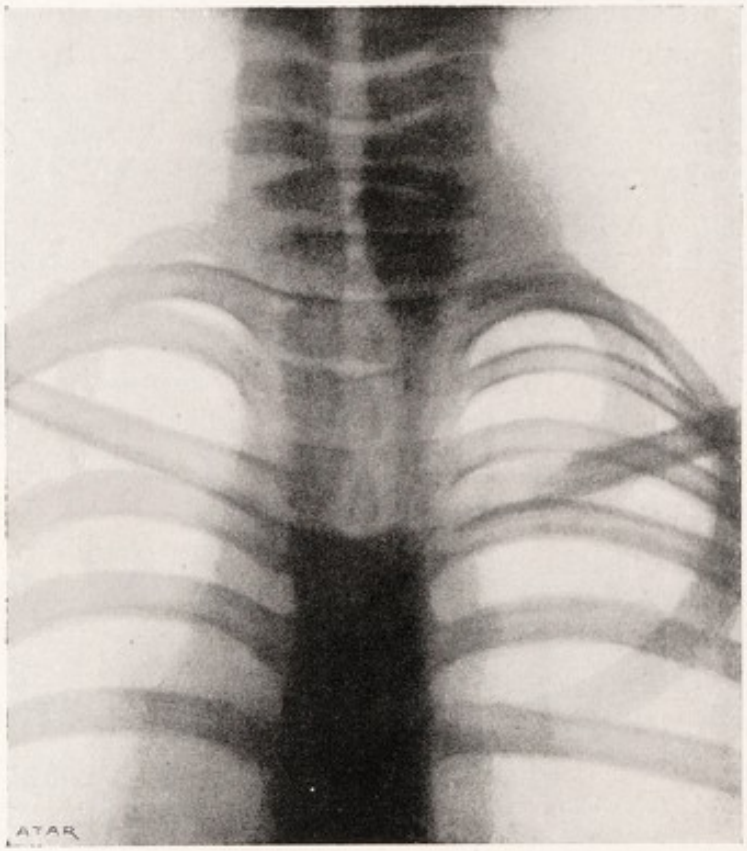


FIG. 58.—Bilateral compression of the trachea.

skiagram. This absence has been looked upon as a characteristic sign of malignant goitre. We have been able to confirm this observation in certain cases. Nevertheless, it would be wrong to generalize from this; it is not the malignancy of the goitre but the anteroposterior compression of the trachea which causes the absence of the tracheal shadow. Now this anteroposterior compression is not at all rare in innocent goitre. It is sufficient to take a side view to prove the decrease in the anteroposterior diameter of the trachea. The maximum compression, however, can be appreciated neither by front

nor side view, but only when the skiagram is taken obliquely (oblique compression). This oblique compression may be suspected when the tracheal shadow appears abnormally narrow both in front and side views. The side view also indicates whether a limited portion of the goitre has become insinuated between the trachea and the vertebral column: retrovisceral goitre, circumscribed retrotracheal goitre; or

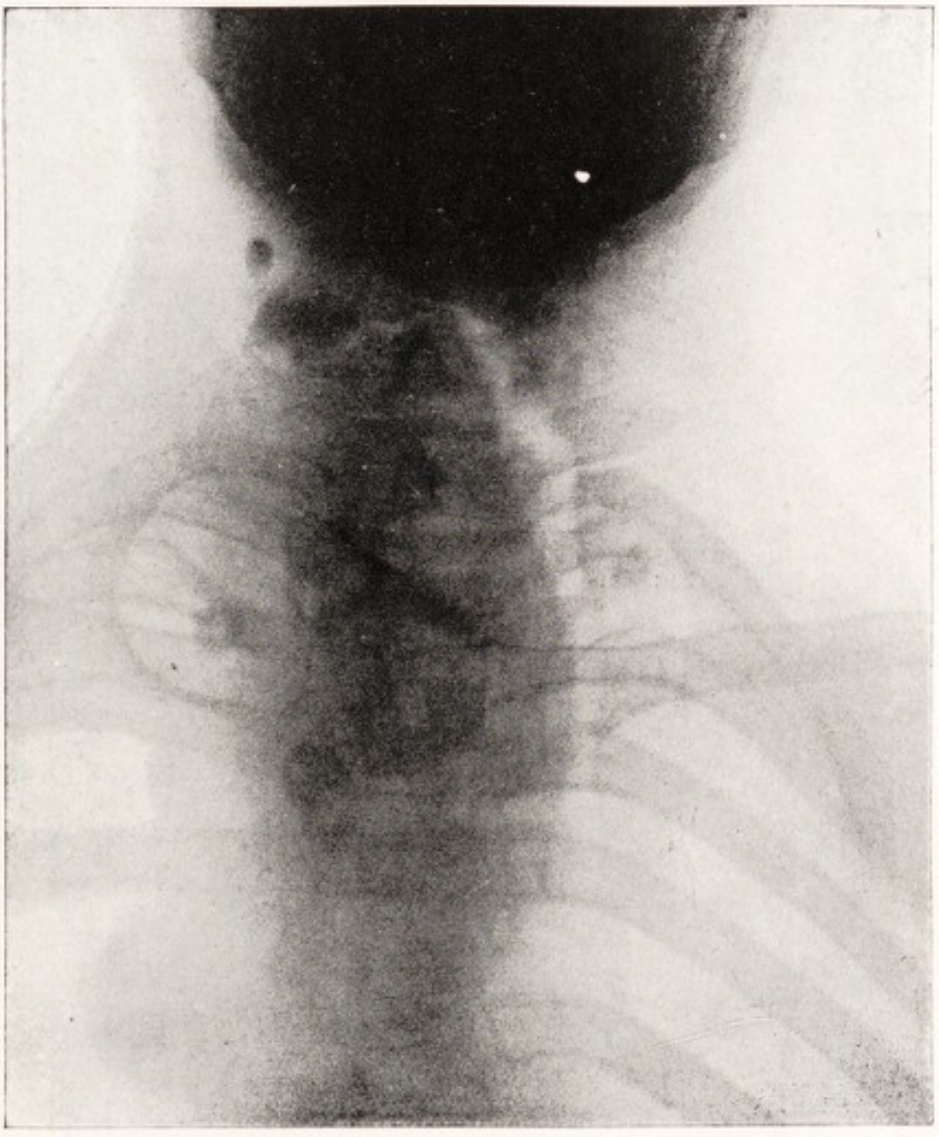


FIG. 59.—Unilateral compression and deviation of the trachea (anteroposterior view).

whether the trachea has become completely enveloped by a large goitrous mass.

The information afforded by an intelligent X-ray examination is much more precise and complete than that obtained by any other method. A skiagram has also this great advantage over the ordinary inspection of the trachea during operation, namely, it shows the actual

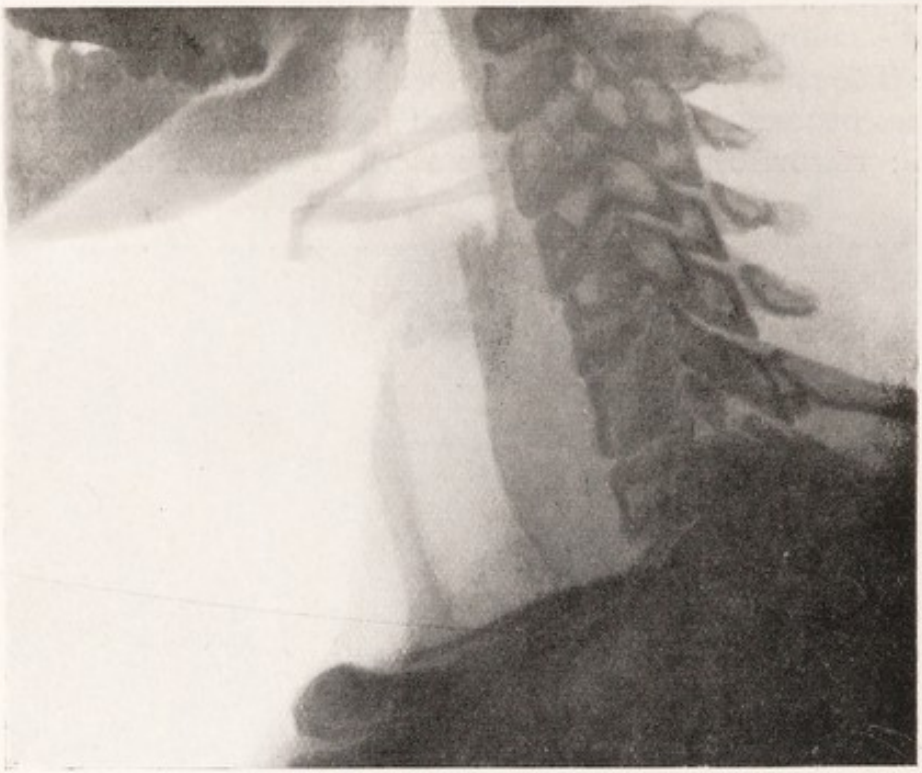


FIG. 60.—Small retrovisceral goitre.

FIG. 61.—Anteroposterior compression of the trachea.

FIG. 62.—Retrovisceral goitre (S = shadow of the goitre).

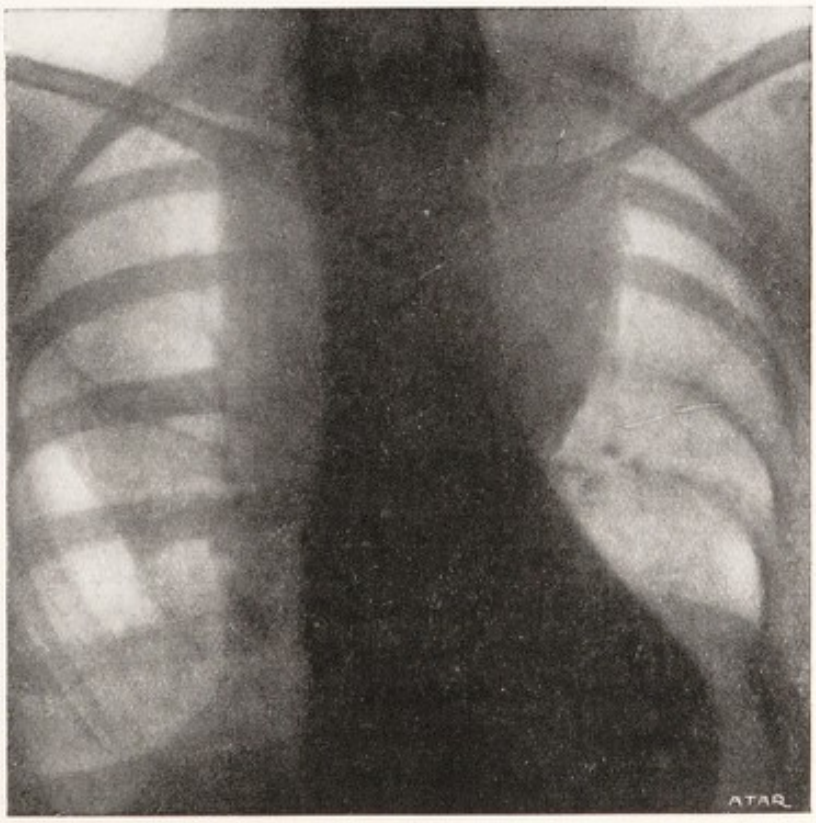


FIG. 63.—Intrathoracic goitre.

condition of the lumen of the trachea, that is to say the resultant of the various physiological and pathological forces at work: compression by the tissue of the goitre and by the muscular coats. Reference will be made later to the bearings of the X-ray appearances on the operative technique.

The examination of the heart, lungs and renal function must precede any therapeutic measures. In certain cases it will absolve the goitre from the blame of having caused any shortness of breath

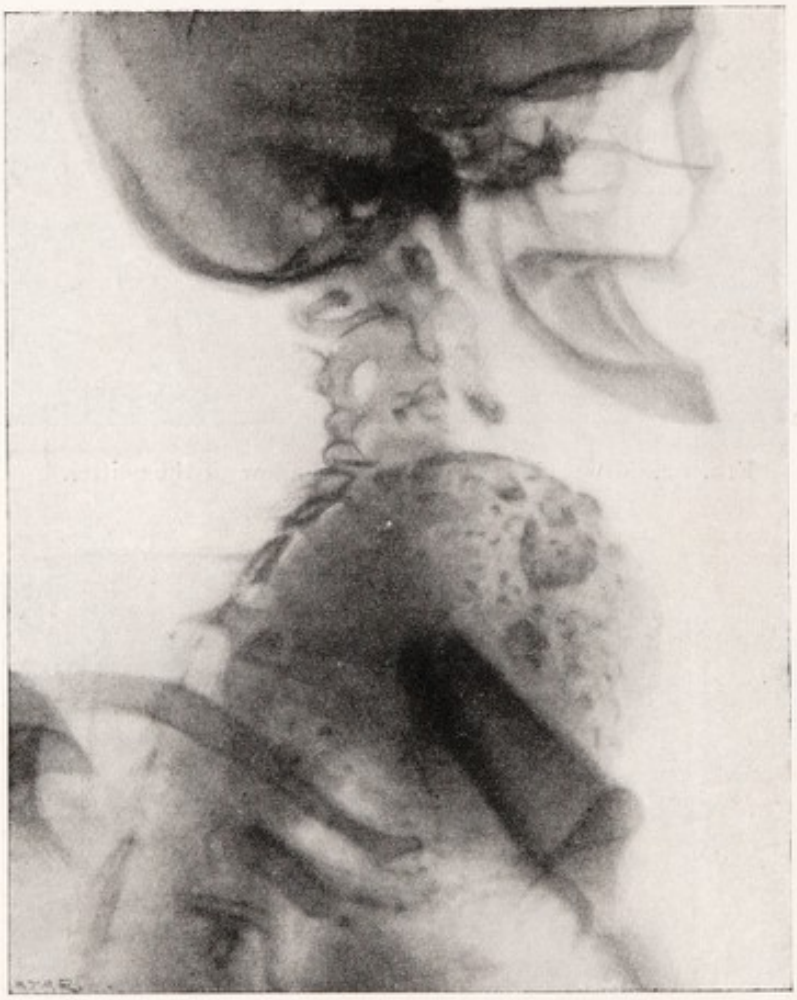


FIG. 64.—Cystic goitre, with considerable calcification of its capsule.

observed in the patient. The type of respiration is in itself generally characteristic. The classic dyspnœa of goitre is inspiratory. It is wheezy in character and respiration is slow. In emphysema and asthma the dyspnœa is expiratory and its hissing sound is quite different from the wheezing of tracheal compression. Cardiac and renal dyspnœa generally co-exist and are of the hurried type. It may be very difficult to establish the chief cause of the respiratory troubles in cases of goitre which are bronchitic, cardiac and perhaps nephritic

into the bargain. A patient who is brought into the hospital in this state must first be carefully examined, and the surgeon must be very sure of his diagnosis before he decides on an urgent operation in such a case.

Examination of the blood in anomalous conditions of the thyroid gland is of interest from several aspects. We shall consider the red and white cell counts and the hæmoglobin percentage.

FIG. 65.—Cold abscess in Pott's disease which has compressed the trachea from behind forwards.

The following are the results obtained by one of our pupils, M. Niederberger, from 250 cases in our clinic.

The *erythrocytes* are practically normal in number (4·7 millions) in simple goitre and in Graves' disease, and total 4·4 millions in cases of hypothyroidism. The maximum and minimum figures are fairly evenly distributed among simple and hyperthyroid goitres, while in hypothyroid forms the smaller numbers definitely predominate. The extreme figures are so common in the three groups that it is

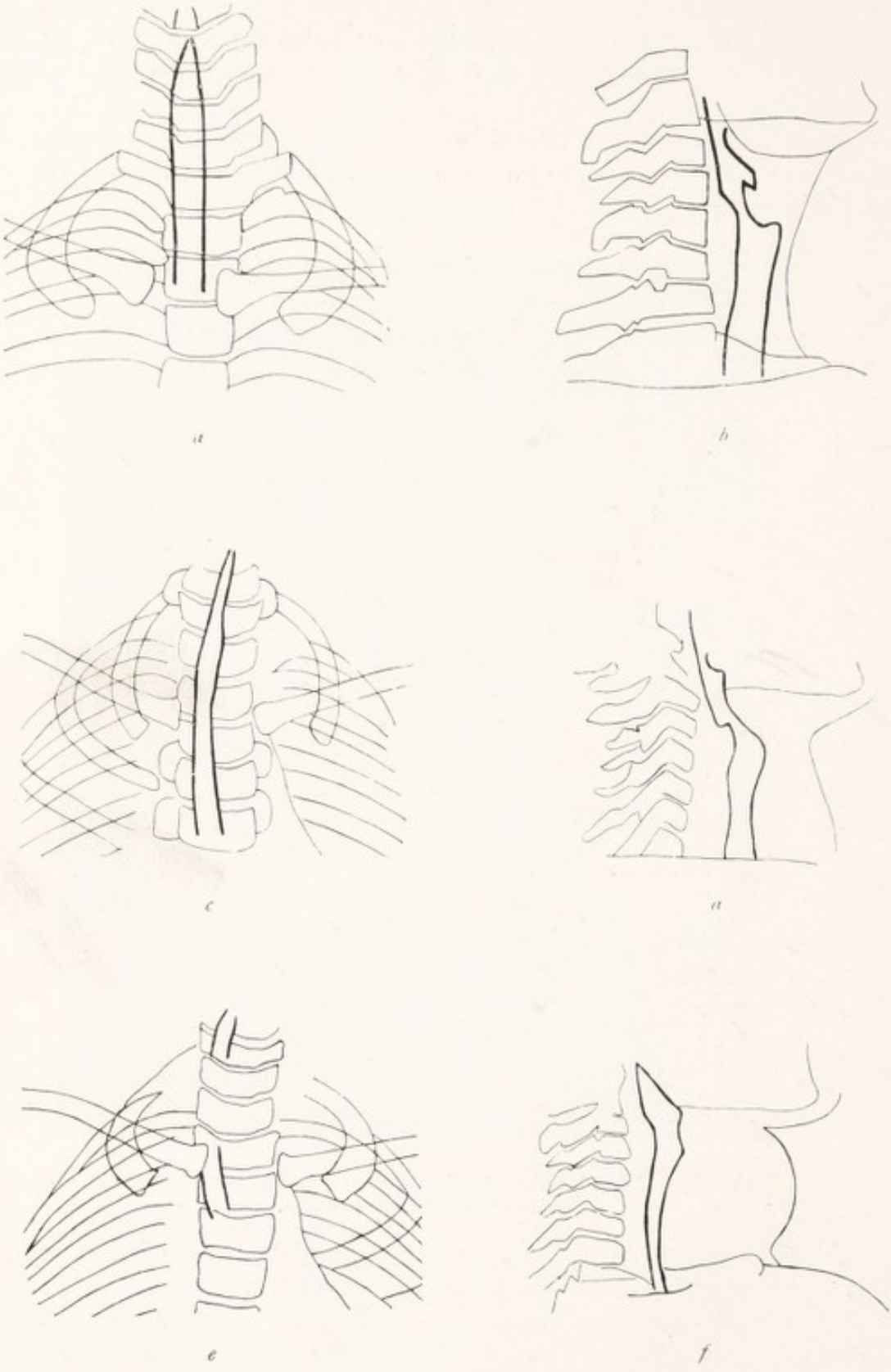


FIG. 66.—*a-b* Normal trachea ; *c-d* Slight deviation and compression, partly lateral, partly anteroposterior (partial torsion of the trachea) ; *e-f* Considerable anteroposterior compression with partial obliteration of the tracheal shadow in front view.

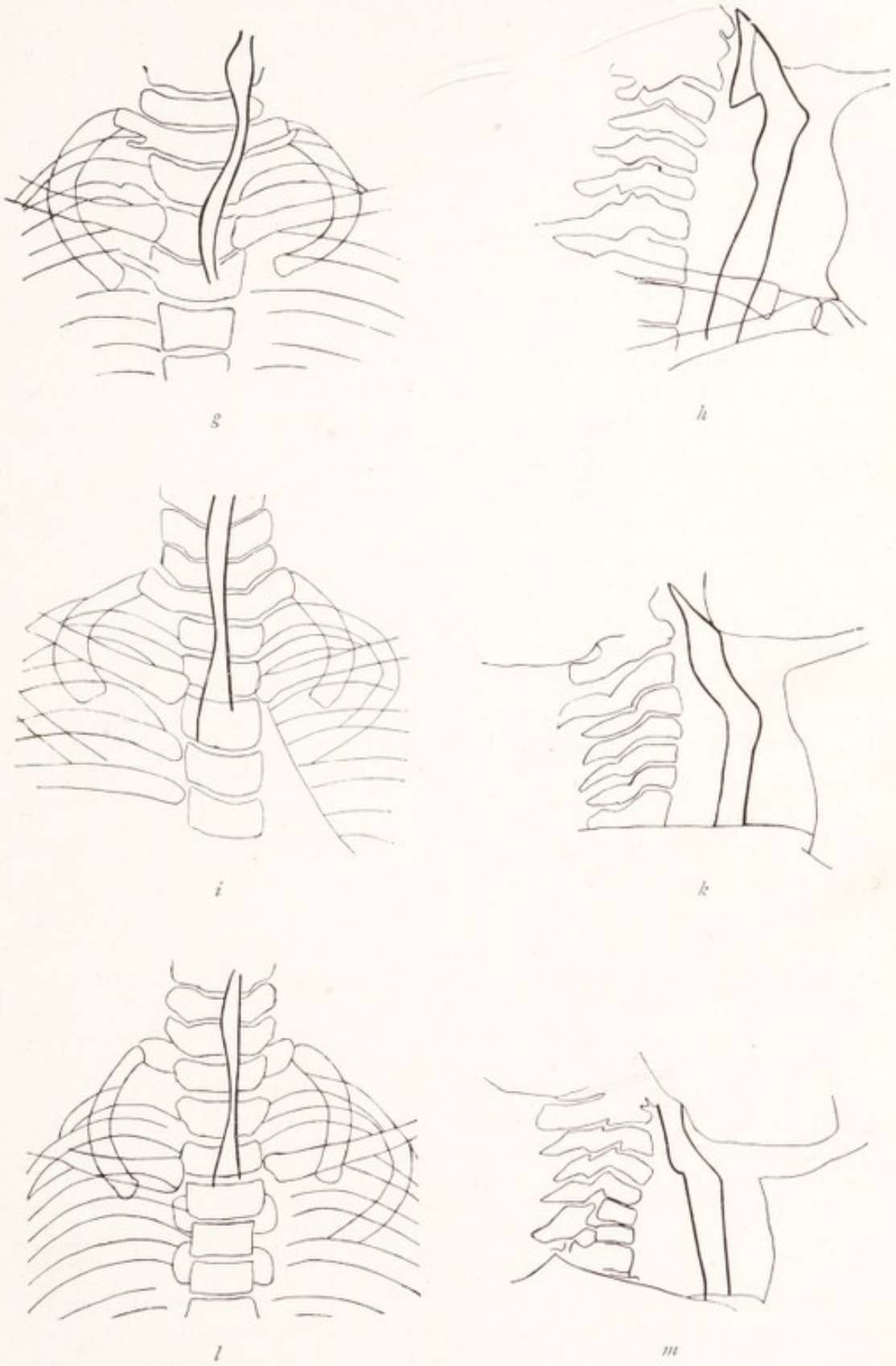


FIG. 66.—*g-h* S-shaped trachea with lateral and anteroposterior compression ; *i-k* Bilateral compression ; *l-m* Bilateral compression and partly anteroposterior.

impossible to assign any symptomatic importance to the red cell count. The same applies to the percentage of hæmoglobin. The most that can be noted is a slight decrease, somewhat more appreciable in hyperthyroidism. In none of the groups has there been observed an effect characteristic of the histological type of the goitre.

The results of the *white cell estimation* are also practically negative. The average values lie between 6,000 and 8,000 for the three groups mentioned above. As a rule the lowest values, leucopenias of 3,000 to 4,000, are more frequent in hypothyroidism than in the other two groups.

The white cell estimation is thus no more reliable for differential diagnosis of thyroid conditions than is the red cell count or the hæmoglobin estimation.

Since the work of Kocher, published in 1908, the interest of surgeons has been focused on the *differential leucocyte count* in various thyroid conditions.

According to Kocher and his school this should be normal in simple goitre, while exophthalmic goitre should be characterized by a more or less marked lymphocytosis together with a general leucopenia in two-thirds of the cases. The ingestion of thyroid products should produce in man and animals a relative, or more often an absolute increase of lymphocytes at the expense of the polymorphonuclears.

These conclusions, which are of undoubted importance from the point of view of diagnosis and indication for operation, have since been confirmed by some and denied by others. We shall not enter into the details of this discussion, but summarize our own conclusions bearing on the different functional thyroid states and on the different types of goitre, drawn from the findings of M. Niederberger in a total of 250 cases.

The average percentage of polymorphs is 64 in normal goitre, 61 in hyperthyroid goitre and 65 in hypothyroid goitre. The lymphocytes range about 28 per cent. in simple goitre, 30 per cent. in hyperthyroid goitre and 29 per cent. in hypothyroid goitre. The comparative frequency of extremes in the three classes is set out in the accompanying table. It appears that the maximum and minimum figures approximately balance in the three classes, and the only point that can be brought out is the occurrence of a slightly greater lymphocytosis in Graves' disease than in other thyroid conditions.

CHART OF LYMPHOCYTOSIS IN VARIOUS THYROID CONDITIONS.

	Patients with simple goitre (160 cases)	Patients with hyperthyroid goitre (57 cases)	Cretins (33 cases)
Average number of lymphocytes ...	**28** per cent.	**33** per cent.	**29** per cent.
Within limits of ± 0 to 25 per cent.	62 ,,	68 ,,	64 ,,
,, ,, ,, + 26 to 50 ,,	16 ,,	12 ,,	9 ,,
,, ,, ,, + 51 to x ,,	4 ,,	4 ,,	9 ,,
,, ,, ,, − 26 to 50 ,,	14 ,,	12 ,,	15 ,,
,, ,, ,, − 51 to x ,,	4 ,,	4 ,,	3 ,,

Our results tally with those of Ch. Muller, Bielajew, Bauer, Lampé and others as to the non-specificity of the leucocyte formula for the different thyroid conditions.

These conclusions in no way invalidate the observations made by Peillon, H. Courvoisier, W. Lanz, A. Kocher, on the modifications in the differential leucocyte count caused by thyroid preparations *in a given case*. It appears that the composition of the blood is influenced without a doubt, all things being equal, by alterations in the state of the thyroid.

The difference between the blood of a patient suffering from Graves' disease and that of a cretin can be established, according to Kocher and Kottmann, by observations on the coagulation time.

Kottmann showed in the cases supplied to him by Kocher an increase in coagulation time in 78 per cent. of cases of Graves' disease, while there was a decrease in the hypothyroid conditions.

The problem of coagulation has been studied in detail by Fonio, late principal of Kocher's clinic. This is the actual result of his researches which were conducted with great care :—

Goitre in subjects with normal thyroid secretion has no characteristic influence on the coagulation of the blood. At most the coagulation time is slightly increased. Patients suffering from *endemic cretinism* show quicker coagulation than normal, and this phenomenon is even more marked in *myxœdema*. *Exophthalmic goitre* causes an increase in coagulation time in some cases, but generally shows normal or sometimes a decreased time.

It is therefore necessary to be cautious in using increase in coagulation time as a sign of conditions of hyperthyroidism.

The examination of the blood can be brought to bear on other points. Kolle sought to discover in goitrous subjects a *serological reaction* based on the principle of the formation of an antibody, but his researches gave an absolutely negative result.

M. Waelly has been able to demonstrate in our laboratory that the serum of most cases of Graves' disease shows a marked *antitryptic reaction*. It is probably due to considerable destruction of the white cells. It has no specific character and is too complicated to be introduced into general use.

According to Schmidt the *freezing-point* of the blood is lowered in hyperthyroidism, but it is unnecessary to add that this reaction is in no way specific.

Kottmann conceived a kind of *photochemical process* which would enable one to discover differences in the state of *dispersion of the blood serum* in various thyroid conditions. This test, which is still under investigation, will perhaps afford in the future a practical means of

estimating increased and decreased function of the gland. A series of observations made by M. Doubler has confirmed the findings of M. Kottmann in 56 out of 57 cases.

In concluding this chapter mention must be made of the physiological test devised by Goetsch and based on the fact, established by Asher and Oswald, that the sensitiveness of the accelerator nerve of the heart to adrenalin is increased by the thyroid secretion.

A subcutaneous injection of 0·5 c.c. of a 1 in 1,000 solution of adrenalin accentuates the cardinal symptoms even of a slight case of hyperthyroidism. An increased pulse-rate of 10 beats per minute is considered by Goetsch to be a feebly positive reaction. Further observations will be needed to establish the practical value of this reaction, which it is inadvisable to use except in mild cases.

The importance of the respiratory exchange has been dealt with in Chapter V and we shall return to it in the chapters devoted to hypo- and hyperthyroidism.

CHAPTER VII.

THE PROPHYLAXIS OF GOITRE.

THE prophylaxis of a morbid condition would appear to be based upon its ætiology. However, there have always been exceptions to this rule. For instance we have an effective preventive for small-pox, although we do not know the agent causing the disease. The prophylactic action of quinine was put to good use before the discovery of the plasmodium. The therapeutic action of iodine, even in small doses, gave rise some time back to the idea of general prophylaxis, with the help of a small addition of potassium iodide to ordinary cooking salt, and also to prophylactic measures in schools through the distribution of iodine pastilles to the pupils. The cause of this movement was Prévost's theory—chiefly expounded about 1851 by Chatin, according to whom goitre is produced by the absence of iodine in the air, water, and in food. Thus the prophylaxis besides having an empiric aspect would for those holding this theory have also an ætiological aspect. The experiments made in this direction in France in three departments between 1860 and 1870 (*vide* Baillarger) were not continued, although excellent results had been obtained in certain schools. Any considerably increased addition of iodine to cooking salt (10 to 50 cg. in a kilogram of salt) produces symptoms of thyroid intoxication in adults. The strength of the pastille used in schools (1 cg. daily) was also too great.

This prophylaxis was not general enough. It was tried in the more goitrous districts, and in the schools, on children who were already attacked. The use of prophylaxis is better established to-day for the following reasons :—

(1) We know the actual function of the thyroid in the physiology of the organism, and in particular the importance of iodine for the proper activity of the gland.

(2) We know by the experiments of Gaylord, Lenhard and Marine that very small quantities of iodine prevent the development of goitre in trout and sheep.

(3) We are indebted to Marine and Kimball, Klinger, Hunziker and Bayard and others for their experiments showing the approximate quantities of the doses.

The movement in favour of prophylaxis inaugurated in Switzerland by Kocher, Roux, Galli-Valerio, Silberschmidt, Klinger, Hunziker, Bayard, Messerli, Steinlin, Weith, and others, is equipped with a much more definite programme than was formerly the case.

To obtain an efficient prophylactic, experiments must be made comprising the factors :—

(*a*) An automatic *general prophylactic* consisting of the addition of an infinitesimal quantity of iodine to cooking salt. This practice should be as widespread as possible. Most infants in the countries where goitre is endemic are born with a hypertrophied thyroid, and so it is necessary to influence the infant through its mother's milk. The quantity of iodine added to cooking salt should be kept within definite physiological limits, that is to say it should not exceed 5 mg. of potassium iodide in a kilogram of salt. This dose corresponds to the consumption of 15 mg. per annum on the part of the individual.

We must notice that according to M. de Fellenberg's recent analyses the average quantity of iodine taken in with water and food is 11·4 mg. per annum in Chaux de Fonds (a district where goitre is comparatively rare) and 4·7 mg. in Emmenthal (where goitre is frequent). The cooking salt used in Bordeaux contains 5-13 mg. of iodine per kilogramme (corresponding to an annual consumption of 25-65 mg.) and where this amount is not available undesirable results have been noted.

(*b*) A *prophylactic for use in schools*, consisting of a weekly dose of 1-2 mg. of iodine administered in the form of a pastille. This dose has proved sufficient and harmless in numerous cases treated up till the present in Switzerland. The iodine should be given regularly for about a year, and afterwards whenever required.

This latter prophylaxis—and as far as children are concerned it must be regarded as treatment—is an indispensable complement of

general prophylaxis, because this latter cannot cure goitre until school age. Probably it has to play this part for an additional number of years. The general prophylaxis by means of cooking salt, so as not to be harmful to goitre in adults, should be restricted to a minimum dose, even though it be insufficient for an infant already affected.

It is only the regular use on a large scale of this prophylactic that enables us to see the real importance of iodine for the health of the human race. It is hardly necessary to say that the problem of the ætiology of goitre remains unsolved, even though prophylaxis has had satisfactory results.

The scheme which we have just sketched raises certain objections worthy of discussion.

We are not considering the problem of *individual liberty* here. It is not difficult to allow the individual the right of having goitrous offspring or even to produce cretins. The principal objection is the danger of *hyperthyroidism* or *Graves' disease* in the adult and also a *harmful action on the other glands of the body*.

Prophylaxis by means of cooking salt containing from a decigram to half a gram of potassium iodide per kilogram, has had grievous results, and for this reason has been abandoned. The problem of what was then thought to be "constitutional iodism" was brought before the Academy of Medicine by Rillet in 1860, and gave rise to a lively discussion. It was impossible to deny the reality of the facts, but their true interpretation discovered about 1844 by Rœser, Prévost, Lebert and later by Virchow, that hyperthyroidism was caused by the softening of the goitrous tissue and not by iodine intoxication, was not accepted at once. Lebert himself had an intuition that in the future his researches would throw light on the physiology of the thyroid. The syndrome of thyroid intoxication comes on most generally in cases treated for a long time with very small doses (d'Espine). It cannot therefore be the sole result of *rapid* softening of the goitre, but follows a *comparatively slow* degeneration in those subjects which have an inherited tendency towards goitre (Lebert). This is a very important point since it makes us cautious regarding the quantity of iodine sufficient to produce gradual softening in the goitre of an adult. It is only observation of individual cases that will show whether the iodine administered can be dealt with or not. If it can be, then the iodine-containing salt should be continued, but if not, the salt should be replaced for the case under treatment by some that is iodine-free. Since salt is consumed chiefly in soup and bread, it is usually sufficient in such cases to prepare these foods with iodine-free salt. The patient who is sensitive to iodine will thus find himself in an environment more favourable than that of the seaside, because, though he has not moved his residence, he is able to avoid the iodine which his

system cannot tolerate. The risk of an infant acquiring Graves' disease through iodine is infinitesimal. This subject will be treated later.

We have already suggested that even if it were possible to prevent goitre altogether all diseases of the thyroid would not be abolished, because it is just in those countries which are free from goitre that the worst cases of Graves' disease are found. In placing before the public the two kinds of salt the opportunity is afforded of obtaining the maximum results with minimum inconvenience, i.e., Graves' disease due to iodine.

If we bear in mind the risk of Graves' disease due to iodine and try to compare the consequences of prophylaxis with the results of haphazard iodine administration, there seems to me to be no cause for anxiety. It may well be that prophylaxis accentuates the importance of iodine, since this is not realized at all by the general public, and quite insufficiently by the medical profession.

The problem of iodine administration is most difficult to deal with at *puberty*, where young people exhibit symptoms of slight hyperthyroidism, together with diffuse goitre. These are cases where one thinks it might be better to leave iodine treatment entirely alone. The question can only be solved by a study of the physiology of the case, chiefly by measurement of respiratory exchange. This is now being tried and we hope for some solution in the near future.

The experiments carried out at our clinic by M. Doubler in four cases of prepubertal diffuse vascular goitre (aged 13) showed us that the metabolism was normal, or even slightly diminished. We therefore hold, until there is a proof to the contrary, that a weekly dose of 1 to 2 mg. can be given safely in cases where there are no signs of marked hyperthyroidism.

Oswald has observed some cases of thyroid intoxication following treatment of goitre by iodine before puberty. The symptoms are transitory and consist of striking nervousness and inability to sleep soundly. These same symptoms are often found at puberty, whether iodine treatment has been used or not. We agree with M. Oswald that here too the cases cited were predisposed to goitre and of unsound nervous constitution. Only one case of Graves' disease before puberty has come to our notice. This was a young girl of 13 in whom the disease had fatal results scarcely two months after the appearance of the first symptoms. With regard to iodine hyperthyroidism the following observations are of interest: A girl, aged 9, took a tablet of iodostarine (5 mg.) once a week for several months. This had no noticeable effect on the goitre, but also caused no other trouble. After this she increased the dose to 1·75 grm. of iodostarine, equivalent to 0·83 of iodine in fifteen days. The goitre diminished rapidly—but symptoms of marked hyperthyroidism made their appearance: tachycardia, loss of weight, nervousness, &c. When the

iodine treatment was stopped these symptoms gradually disappeared —but the goitre began to grow again slowly. The smallest doses of iodine had caused symptoms of hyperthyroidism in this girl's grandmother who also suffered from goitre.

This case is interesting because it shows that the usual dose given in schools is harmless to girls distinctly predisposed to the disease, although unfortunately it is quite inefficient in curing the goitre.

There remains for consideration *the effect of iodine prophylaxis on the other glands of the body—principally the genital glands and the mammary gland.* The influence of this treatment has been stated many times during the last century; the information given has been taken from observations made in isolated clinics, so that we do not know the accuracy with which they have been made. Rilliet, quoting the observations of Coindet and Jahn, mentions this in his pamphlet of 1860. Trousseau in his account of this, refers to Cullérier's work on this subject. Ricord denies any influence in this direction. Experiments on rabbits, mice and dogs were made by Adler, Loeb, and Zœppritz Jastram in 1914. The result of these experiments shews that iodine may produce in animals at least temporary sterility and histological lesions of the genital glands. The doses used per kilogram of animal weight and per day were from 900 to 180,000 times as great as those given to school children. Thus the quantities are not comparable, and no clinical fact exists which would permit us to attribute any deleterious effect on the genital and mammary glands to the use of an iodine prophylactic. There is no medical evidence to show that the administration of this minimum quantity of iodine has any bad effect upon the glands of internal or external secretion.

Just another word on the subject of this general objection to prophylaxis. *Science is not yet sufficiently advanced to institute a general campaign against goitre.*

It is certain that the physiology and pathology of the thyroid and other glands of internal secretion will have much to teach us in the future. To wait for these revelations before acting would postpone the prophylactic treatment of goitre indefinitely. This is one of the problems that cannot be studied in a laboratory alone—much more widespread investigation is called for. We know sufficient about goitre to-day to justify this attempt in countries where it is endemic. The observations which would be made if such a course were to be pursued would show us the proper dose—i.e., the dose that would act as a preventive to goitre without producing hyperthyroidism. It has been necessary to repeat the prophylactic treatment used in the schools of France during the last sixty years, because frequent relapses have occurred. In this way permanent results are obtained, and the use of iodized cooking salt has the desired effect.

It is needless to say that all prophylactic measures must be under

responsible *control*. Not only should the condition of the children be investigated before treatment is begun, but while the treatment lasts they should be examined at least once a year, and the reports succinctly summarized. It is also necessary that the medical officer of the school devotes the required time to this part of his work. Besides this he should make sure of the co-operation of his colleagues and the teaching staff, so that they may tell him if the treatment is having harmful effects. Control is just as necessary in general prophylaxis by means of cooking salt. There can be no individual control of the whole population. The public should be made to understand that as soon as any signs of Graves' disease appear they should consult their doctor. Certainly there would be a large number of hysterical cases of pseudo Graves' disease; but these occur in all kinds of medical campaigns. There should be no cause for anxiety in this particular. The doctor must have his eyes open and not diagnose a case as purely "nervous" when the history and careful examination point to the presence of Graves' disease through iodism or some other cause.

We reproduce the *form* used for the control examination of the Swiss Commission on Goitre.

School

Name of pupil *Sex*

Name and occupation of parents (or guardian)

Birthplace *Home* *Date of birth*

Former residence (state duration)

Former treatment for goitre

Names of brothers and sisters

Date of examination	Age	Class	Weight	Height	Chest measurement	Arm measurement	Thyroid*	Treatment	Observations

* O = gland imperceptible. I, gland perceptible flat. II, gland clearly perceptible on palpation, but scarcely visible externally. III, "enlarged neck." IV, large goitre. Add N to the number indicating the category when nodules are present.

Mark on this figure the position and size of the nodules and date of observation.

Measurement of Thyroid.
For use in more complete examination.

Date of Measurements.	Height of lobes L.	Height of lobes R.	Size of gland	Surface	Maximum diameter antero-posterior	Maximum circumference of neck	Consistence soft hard

CHAPTER VIII.

NON-OPERATIVE TREATMENT OF GOITRE AND GENERAL THERAPEUTIC INDICATIONS.

I.—GENERAL REMARKS.

THE therapeutic treatment of goitre, in the same way as the prophylactic treatment, has so far not been based on ætiological considerations. It, too, depends on the empirical fact that iodine is of value. This drug was substituted for the ashes of burnt sponge by Drs. Straub (near Berne) and Coindet (of Geneva) in 1820. Up till now no rival has been found. The principal advances made since 1820 concern the question of doses and indications.

Iodine is administered in many forms. We will not treat of the external applications of ointments or iodized liniments—certainly a very active method and much in the public favour, but one which does not allow accurate dosing. Moreover, an active dose is so small that the precaution of external application is unnecessary, seeing that most stomachs can tolerate a few milligrams or even centigrams of potassium iodide, or an iodine compound of a fatty acid. The problem of iodine treatment was dealt with by our teacher, Kocher, in 1898. This work has since became a classic.

The chief iodine compounds in actual use are: potassium iodide (iodine 76 per cent.) and sodium iodide (iodine 84 per cent.) on the one hand, and on the other, compounds of iodine with fatty acids (iodostarine, lipoiodine, iodipine, sajodine, riodine, &c., containing about 50 per cent. iodine).

Inorganic iodides are rapidly absorbed and completely excreted at the end of thirty or forty hours. Iodine combined with fatty acids is decomposed in the small intestine, and absorbed in an inorganic form. It appears in the urine after about half an hour, and its excretion lasts several days. The retention of iodine by the body is greater after an organic compound has been taken than after an inorganic preparation.

The significance of these observations has been variously estimated. We think, until we hear further, that the form in which the absorption occurs is of little importance as long as the small dose required by the treatment is really absorbed.

2.—INDICATIONS AND CONTRA-INDICATIONS FOR CONSERVATIVE TREATMENT.

(*a*) *Goitre in School Children.*—It is here that iodine has its chief use as a medicine. The weekly dose of 1-3 mg. of iodine corresponding to 2-6 mg. of iodostarine, or one drop of 10 per cent. tincture of iodine, is enough to cure goitre after six months or a year in most school children. If a more rapid cure is required there is no harm in giving this dose two or three times a week for a shorter period. These doses do not produce iodism or Graves' disease in infants. Their efficiency is most marked in cases of diffuse goitre, although nodular goitres have been cured by this treatment. Daily experience is showing us that the result achieved is not permanent. The treatment must be repeated a few times because the influence of a small quantity of iodine is not lasting in places where goitre is endemic.

(*b*) *Diffuse goitre in adults* and certain *nodular goitres*, provided they are not too large, are cured or improved by a prolonged stay at the seaside or by repetition of iodine treatment. Here, too, the increased doses which certain investigators recommend are unnecessary (Beese). The physicians of Geneva estimated seventy years ago that a daily dose of 2 cg. was sufficient to cure most goitres which responded to iodine treatment. Some fixed it even lower. It is desirable, in accordance with an ancient rule of popular medicine, to give treatment during alternate fortnights. Generally the dose given is ·003 (3 mg.) every day for a number of fortnightly periods, or once or twice a week for a few months. Diffuse goitres, multinodular goitres and most nodular goitres are amenable to this treatment, according to the degree in which the tissue is yet able to function. This point is brought forward as a result of clinical experience, and was especially emphasized by Kocher in his classic work on the medical treatment of goitre, which we have already mentioned.

The risk of iodism is, correctly speaking, almost nil, if the doses above indicated are adhered to, unless one is dealing with a patient who has an intense constitutional peculiarity. Disappearance of a goitre is, on the other hand, sometimes accompanied by a syndrome characteristic of Graves' disease. This occurs in subjects over the age of forty, though sometimes it may happen in younger patients. Lebert accounts for it by the intoxication produced in the absorption of the goitrous tissue. The symptoms disappear spontaneously in certain cases, a few months after the cessation of iodine treatment, although sometimes they persist for years and may even cause death. We have had an opportunity of confirming Lebert's observation that this thyreo-sensibility is a hereditary condition, or runs in families.

Wherever iodine treatment of goitre has become popular the number of cases of Graves' disease due to iodism has increased. No form of iodine seems proof against this occurrence, which is not due to the drug, but to the fact that the goitre itself is absorbed, no matter in what quantity or form the iodine is given. Regarding this subject St. Lager said in 1867, "The physicians of Lausanne have had ample opportunity of studying the toxicology of iodine. Many people in this town drink a few drops of iodine solution every day, in order to guard against goitre. They carry small flasks of it hanging round their necks—like a charm." All iodine treatment of a goitrous patient should be under strict medical supervision, and the patient should be told to come to the doctor if quickening of the pulse-rate or wasting occurs.

All that has been said concerning iodine applies equally to *thyroid preparations*, which at one time seemed to supplant iodine treatment. Their administration was much simpler, but the results obtained were in no way superior.

We will pass over the trials given to arsenic, silica, quinine, &c., because the experiments that have been made so far give no indication of any specific action.

Nor will we treat of the attempts made formerly by surgeons to cure goitre by *injection* of *preparations of iodine*, from the very dangerous tincture of iodine to iodoform and other iodine preparations. That was a blind method of treatment whose very inaccuracy is repulsive to the spirit of surgery. The cases of sudden death witnessed by our predecessors seem to be forgotten by youthful practitioners—if one reads recent publications—until such fatal accidents recur.

The theory of infection and toxic infection suggested to McCarrison the treatment of goitre by *disinfection of the gut* and by *vaccine treatment with Bacillus coli*. These investigations were taken up again by Galli-Valerio and Messerli. The question is still an open one but the observations of these experimenters are worthy of our attention.

The conservative treatment has in the last few years had recourse to *radiotherapy* and administration of *radium*. When we deal with the treatment of exophthalmic goitre we shall go into this matter more fully. It is doubtful whether one can destroy thyroid tissue by sufficient application of X-rays or radium emanation. This proceeding is always ill-advised, because we do not know the extent to which not only the diseased tissue, but the normal tissue which we want to preserve, is destroyed. In addition, the ultimate effects are uncertain because the cumulative action of the rays may occur. We do not know whether a dose that at first sight appears "therapeutic" may in

the long run prove to be harmful. Although burns have not yet disappeared from radiotherapeutic treatment, and are still accepted with resignation in cases of cancer, they are not to be lightly passed over in cases of mild goitre, because operation can be performed with very slight risk and leaving a scar that is hardly visible. Radiotherapy is expressly contra-indicated in those cases of goitre which sooner or later would be liable to be treated by the knife. The operation is so apt to be complicated by perithyroid adhesions after radiotherapy that the game is really not worth the candle.

The most modern attempt in the province of conservative treatment is that of *injection of boiling water into the goitre*, recommended by Porter. This method aims at producing an aseptic necrosis of the goitrous tissue, and eventually reabsorption of the necrosed tissue. This, I think, should be regarded as one of the foolish procedures the results of which cannot be estimated beforehand. The extent and intensity of destruction is quite uncontrolled, to say nothing of the deleterious and dangerous effect that they may produce among the tissues of the body and other organs.

(*c*) *Large nodular goitres* of any kind, but especially calcified and cystic goitres, are very resistant to all conservative treatment. One should therefore waste no time with iodine, X-ray or radium treatment. Generally speaking, resistance to treatment is offered in proportion to the age of the goitre.

(*d*) All goitres which show rapid growth in patients of over the age of thirty should be excluded from conservative treatment and operated on before signs of malignancy appear.

3.—OPERATIVE INDICATIONS.

The *operative indications* for the most part follow on from what we have just said. Conservative treatment—that is to say iodine administration, or a stay at the seaside—should always be tried where there is any chance of success, and the risk of Graves' disease through iodine is not so great as to make surgical treatment preferable at the outset. The patient generally gives the doctor information on this last point, because there are very few goitrous subjects who do not try iodine before consulting a surgeon. When the patient says that all therapeutic treatment causes palpitation, nervousness or even wasting, we cannot insist on it, but we should suggest that surgical treatment is indicated, or wherever there is a definite contra-indication we must advise abstention from drug treatment. In these cases even a stay at the seaside may stir up a dormant Graves' disease.

Operative treatment is first indicated—leaving Graves' disease out of the question—when medical treatment is unsuccessful—as in

calcified cystic goitres—or when the clinical symptoms and radiography show that the trachea and jugular veins are being compressed.

The *contra-indications* are drawn from the condition of the patient: diabetes, nephritis, arteriosclerosis, cardiac insufficiency, &c. Lesser cardiac troubles should not interfere with the operation, for in many cases a properly carried out operation on a goitre is of great benefit to the action of the heart.

Nowadays the operation entails so little danger that consideration should be given to the *æsthetic* aspect of the disease raised by the patient. This indication is nearly always clinical as well, because a goitre which is unsightly very often involves the trachea and blood-vessels, or has a harmful effect on the general health of the patient—through the excessive secretion which occurs. The *fear of relapse* should never be a deciding factor. The fact that conservative treatment is in some cases followed by a relapse does not make us give it up where it seems to be definitely indicated, nor do we abstain from surgical treatment just because many patients—especially young ones—seem fated to undergo a succession of operations. Further on we shall see that the improvement in surgical technique together with preventive iodine treatment after the operation diminishes the number of fatal relapses.

There remains only the local treatment of the so-called focal infections. In America these are considered to be the causes of certain goitres—more especially the goitre of Graves' disease. It is doubtful whether there is any truth in Rosenow's theory, that infection of quite distant areas affects the thyroid gland. This idea is merely an amplification of the observations made twenty years ago by Roger and Garnier, which we completed by our own researches. It also confirms up to a certain point Bayon's view concerning the toxi-infectious origin of goitre. It seems quite possible that hyperplasia of the thyroid disappears after the suppression of an infectious focus, such as chronic tonsillitis, dental abscess, suppurating cholecystitis, &c., but it would be quite wrong to generalize and go too far in the investigation and treatment of these so-called focal infections: witness the case recently published of the girl who was slightly hyperthyroidic and died after her sixth "focal" operation, because the surgeon's curette entered the meninges during the curetting of a real or supposed ethmoidal sinusitis. We have seen a goitre in Graves' disease growing notwithstanding the suppression of a chronic dental abscess, while operation quickly cleared up the symptoms of hyperthyroidism.

CHAPTER IX.

OPERATIVE TREATMENT OF GOITRE.

A.—PREPARATION OF THE PATIENT.

OPERATION on an ordinary goitre calls for no special preparation. It is assumed that the usual hygienic precautions regarding the patient's mouth are observed. One should however always avoid stirring up the bacterial flora of the mouth by excessive antiseptic measures. If it is thought advisable to remove any decayed teeth, this should be done—not on the eve of the operation but about a fortnight beforehand. Needless to say no operation should be performed when there has been any recent infection of the tonsils or pharynx, no matter how slight it may have been. Senile bronchitis should not be a contra-indication—because there are some cases which are cured by the removal of a constricting goitre. If need be, the heart can be strengthened by a small dose of digitalis or strophanthin. A dose of veronal or some similar hypnotic on the eve of the operation will ensure sound sleep for the patient, especially if he is a nervous subject. This precaution is very advisable whether the operation is to be performed under a general or local anæsthetic. The preparation of a case of Graves' disease requires special care. The patient should not be operated on the day after his arrival at the clinic. He should have from eight to fifteen days, or even longer complete rest, according to the gravity of his symptoms. It is sometimes astonishing to see how this simple measure facilitates the surgical treatment. This rest treatment is readily combined with the administration of an average dose of sodium bromide (from 3 to 4 grm. per day), and quinine (0·3 grm. per day). Digitalis is useless for the purpose of counteracting the nervous and toxic acceleration of the pulse, but it should always be given in cases where there are circulatory troubles due to a cardiac lesion. But we prefer the intravenous administration of strophanthin because a more immediate action is obtained. The diet should be principally vegetarian. These precautionary measures are particularly important in cases of rapidly progressive exophthalmic goitre.

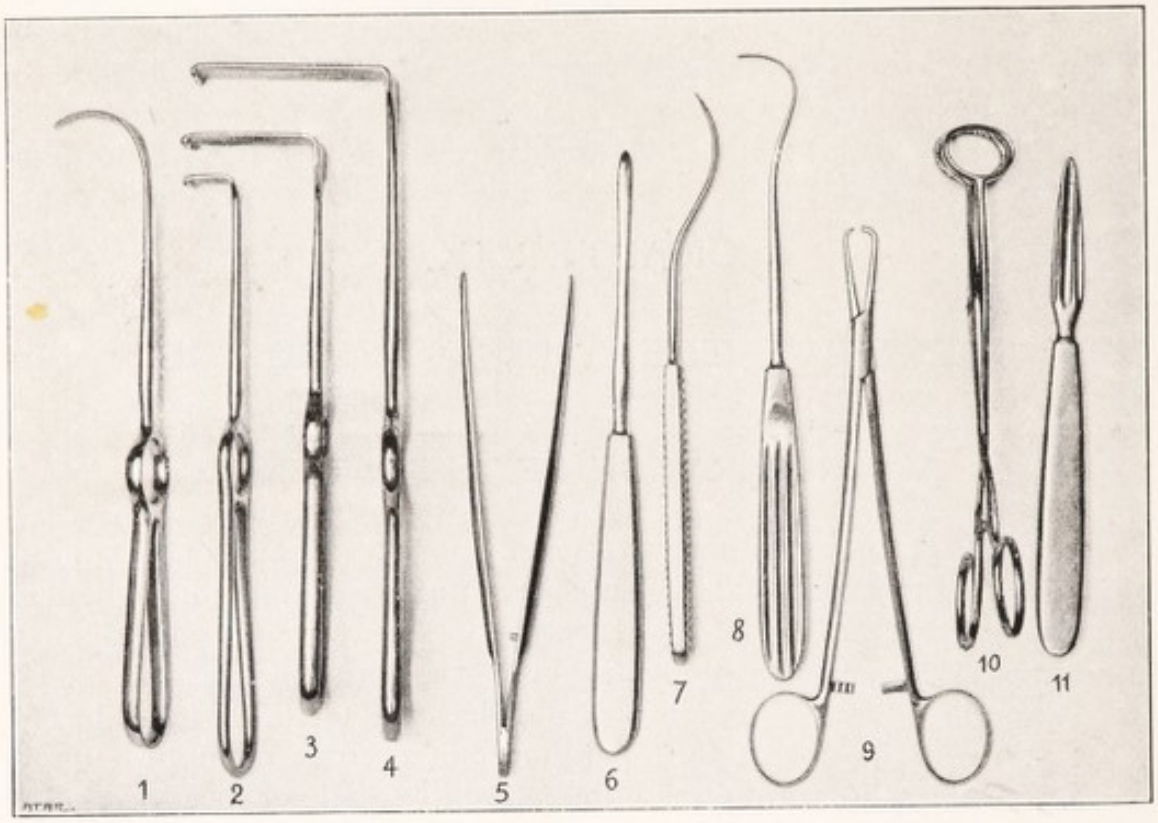


FIG. 67.—1-4. Retractors. 5. Dissecting forceps (blunt), 17 cm. 6-7. Dissectors for isolating the inferior thyroid artery, with slight and marked curves. 8. Cooper's needle. 9. Forceps à godet. 10. Ring forceps. 11. Kocher's dissector.

B.—INSTRUMENTS, LIGATURE AND SUTURE MATERIAL.

It is evident that an operation for goitre can be conducted without any special array of instruments. The more one works in the daylight and sacrifices the muscles, the less is one dependent on that important instrument—the retractor. But if one is anxious to avoid injuring the small muscles and disturbing the contour of the neck, it will be necessary to have at hand a goodly

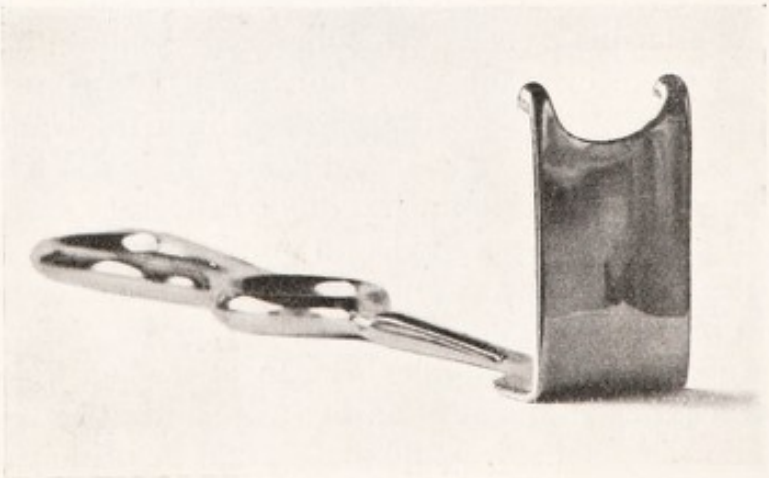


FIG. 68.—Retractor for protecting the great vessels and sympathetic nerve while ligaturing the inferior thyroid artery.

assortment of retractors. In fig. 67 (1-4) illustrations are given of the very simple and very old model (Kocher, Halsted), which we use. The bent portion of this instrument varies in length from $1\frac{1}{2}$ to 7 cm.

It is useless to attempt the primary ligature of the inferior thyroid artery, as is our constant practice, unless appropriate retractors are employed in the depths of the wound. But if the surgeon is provided with the proper instruments, the procedure is quite easy. In some cases Kocher's scoop (fig. 69) facilitates the dislodgement of deep goitres.

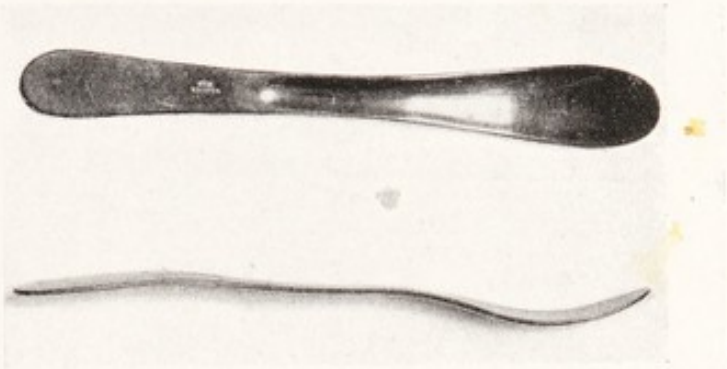


FIG. 69.—Kocher's scoop.

In regard to the other instruments mentioned subsequently, they are essentially identical with those found in the armementarium of every operating theatre. They are reproduced in fig. 67 (5-11) merely as a reminder.

But a word may be said about the forceps à godet (fig. 70). It possesses the great advantage over the classical worm-screw type of forceps, that its grip never loosens. We use it for taking hold of the skin or a muscle, or for retracting them, or for taking hold of a goitrous nodule. It is not an absolutely indispensable instrument, but we regard it as a very serviceable addition to the ordinary complement of instruments.

FIG. 70.—Forceps à godet.

It is necessary to say something about *material for ligatures and sutures*. Silk or thread is advocated by some, while others are in favour of catgut. Our own practice is eclectic in this matter, and we use very fine thread for ligatures which ought not to be absorbed, i.e., for the great vessels, and for ligatures which must not become loosened at any cost. On the other hand we decidedly prefer fine catgut (No. 00) for bringing together the various layers of the wounds and for

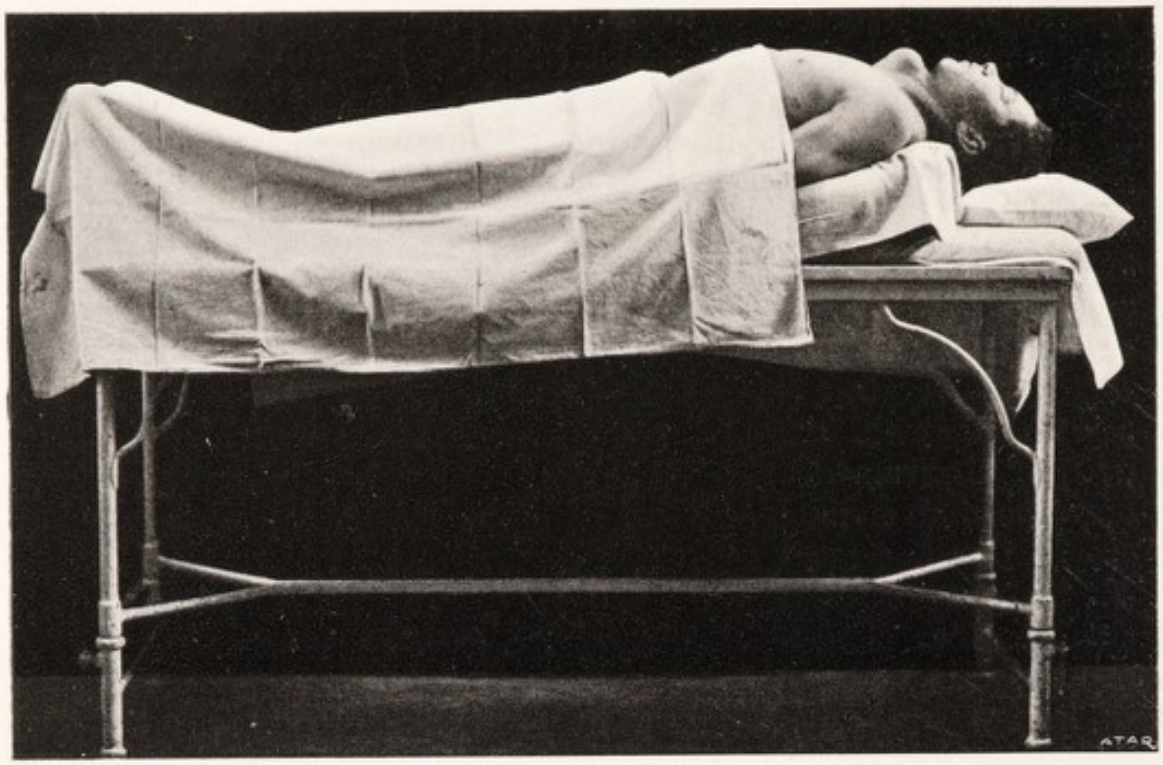


FIG. 71.—Position of the patient on any ordinary table. The shoulders are supported by a hair cushion. The head is turned in such a way as to render the throat prominent.

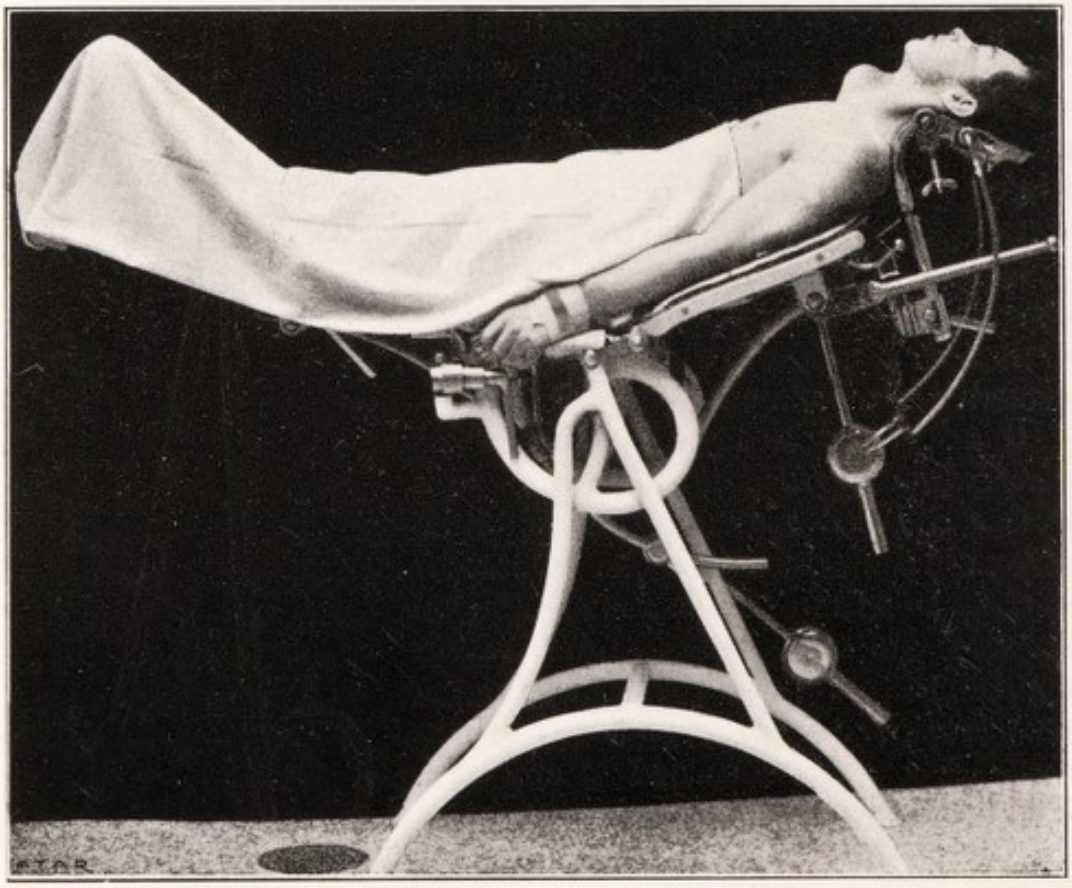


FIG. 72.—The same position secured by means of the small model of our special operation table.

suturing the external incision. The muscles which have been cut through are also united by catgut. Any material is serviceable for bringing the skin together, provided that the suture points are not allowed to remain in place more than forty-eight hours.

There is no device (intradermic suture) which is so reliable for obtaining a satisfactory scar as this simple method. We are in the habit of using Michel's clips, except at the two points which are contiguous with the drainage tube.

FIG. 73.—Isolation of the operation area by means of Kocher's "arch."

C.—THE OPERATION.

(1) The Posture of the Patient.

The position of the patient during the operation is a matter of great importance for the purpose of facilitating its performance. The head must be well extended backwards, but should not drag the

entire cervical spine with it. The extension should be limited to the articulations of the upper vertebræ but should not involve the lower ones. If only an ordinary operating table is available, without any special mechanism, a firm pillow must be placed under the patient's back in such a way as to secure good support for the shoulders and the lower portion of the cervical spine. The head should lie back (fig. 71). This position is best obtained on a specially adapted table, such as the one we designed some twenty years ago. The extended position is easily attained thereon and the table has proved of the greatest utility (figs. 72 and 73). The patient is fixed thereon with the thighs slightly flexed. The chest is raised, so that the patient is in a position of semi-recumbency. This posture is indispensable in cases of constricting goitre, because it is the only one in which the patient is able to breathe. The head rests in a head-piece which is jointed on to the table. One of the hands should be fixed against the edge of the table, while the other should remain free, to observe the pulse during the course of the operation.

FIG. 74.—Field of operation (anterior aspect).

(2) The Disinfection and the Protection of the Field of Operation.

The area of the operation must be shaved as far as the retro-mastoid region, including the chest if necessary. All ordinary methods of disinfection are satisfactory in cases of Graves' disease,

but tincture of iodine should not be used. The disinfection must extend to all the parts, near or remote, which might possibly come in contact with the operation area. This area must be isolated from the face by a double towel fixed by clasps at the level of the jaw. The towel must be made of some impermeable material so as to prevent any contamination of the field of operation by the expectoration of the patient. The towel placed at the side of the operation area must be of sterilized cloth. The manner in which the operation area is screened off is illustrated in figs. 73 and 74. The procedure is greatly facilitated by the use of the "arch" suggested by Kocher.

(3) Anæsthesia.

Operations on goitre were among the first of the surgical procedures wherein general anæsthesia was replaced by local anæsthesia. This improvement was established by Kocher, based upon the earlier work of Reclus and its perfection by Schleich. For some time a ½ per cent. solution of novocain, with the addition of adrenalin, has been substituted for cocaine. At present we perform most of our goitre operations exclusively by means of local anæsthesia. The great advantage of this method is, that we have the function of the recurrent laryngeal nerve under control, at any moment of the operation. It also reduces the risk of bronchitis, and post-operative pneumonia. It does away, almost entirely, with vomiting after the operation, which is particularly distressing in cases of goitre. We are well aware that these advantages will not

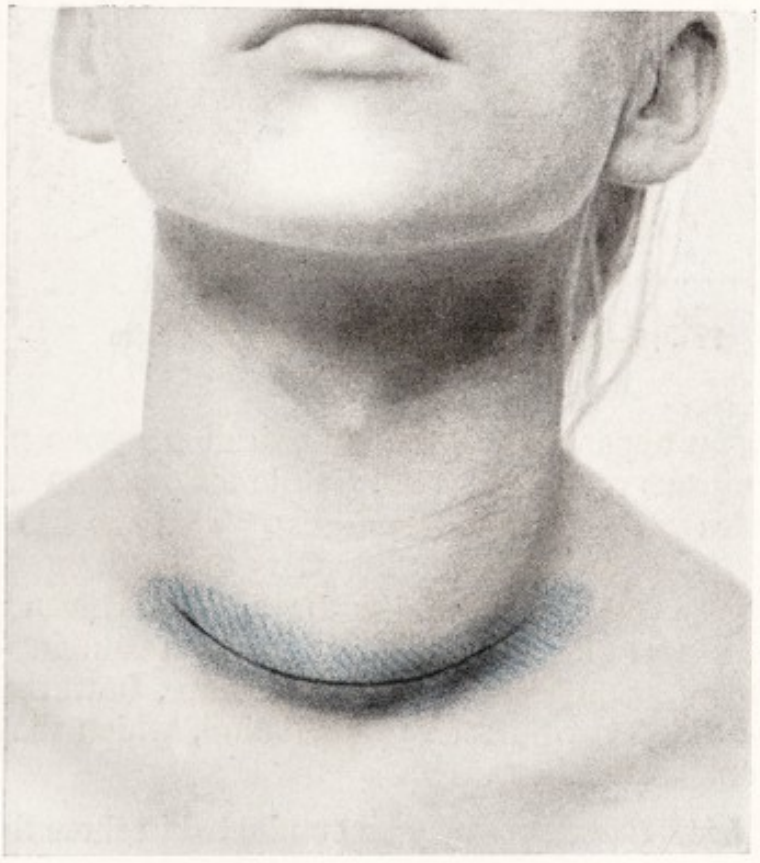


FIG. 75.—Kocher s "necktie" incision (en cravate).

suffice to convince all patients, or all surgeons, for many will continue to maintain that the method of anæsthesia must be dictated by the temperament of the patient and of the surgeon.

We are convinced that there is a special advantage in avoiding general anæsthesia in operating upon cases of exophthalmic goitre. If the patient is exceptionally nervous we still adhere to local anæsthesia, but we give a few drops of chloroform or ether during the few moments when the operative procedures are distressing. There is no actua pain, the distress consists of a feeling of dragging, pulling and pressure, which is not completely suppressed by local anæsthesia. In the rare instances when we do employ general anæsthesia (namely in children) we use a mixture of chloroform and ether administered by means of Roth - Draeger's oxygen apparatus. Some American surgeons prefer a combination of nitrous oxide and ether. Crile always uses small doses of nitrous oxide (so-called analgesic doses). This gas has the disadvantage of being very expensive and appears to cause more mishaps than ether. An injection of morphia (·01 to ·02 grm.) is given before the operation, and if the patient is very sensitive this is combined with ·0003 to .0005 grm. of scopolamine. This procedure, however, has the drawback of causing peripheral vaso-dilatation, which makes it more difficult to control bleeding.

FIG. 76.—Cystic goitre showing the slightly oblique folds in the skin.

Local anæsthesia may be conducted in three different ways:

(*a*) Simple *subcutaneous and subfascial injection* in the whole area of the skin incision and for 1 to 2 cm. beyond (fig. 75). This

procedure does not abolish the sense of dragging and pressure caused by manipulation in the deep parts of the wound. We employ this method as an addition to one of the other methods to be described.

(*b*) *Injection of the nerve trunks at the level of the point of exit of the cutaneous nerves, a point corresponding to the middle of the posterior border of the sterno-mastoid muscle.* A solution of ½ to 1 per cent. of novocain is used and 10 to 20 c.c. of this solution is injected at the posterior border of the middle of the muscle (fig. 78). If the injection is done on both sides, there results a complete anæsthesia of the skin and subcutaneous tissue. But it does not render the deeper tissues anæsthetic.

FIG. 77.—..... Old angular incision of Kocher.
——— Girard's incision "en cravate," with a somewhat ascending limb.

(*c*) *Injection of the points of junction of 2nd, 3rd and 4th cervical roots at the level of their exit from the intervertebral foramina in front of the transverse processes*, i.e., *the method of paravertebral anæsthesia* (Haertel and Geiger's procedure). The following is Braun's modification of this method: A line is drawn from the anterior border of the mastoid process to the clavicle, passing through the tubercle

of Chassaignac; the point of junction of the first and second third of this line is fixed (fig. 80). This point corresponds practically to the level of the upper border of the thyroid cartilage; and here the needle is plunged in, until it reaches the transverse process of the third cervical. The needle is then slightly withdrawn and again plunged in, about one centimetre or more in front of this process (fig. 81). A few seconds are allowed to elapse to see whether any blood flows into the syringe, and aspiration is practised in order to be absolutely sure. If no blood is obtained, 10 c.c. of a $\frac{1}{2}$ per cent. solution of novocain is injected, and the needle is withdrawn a little in order to inject the same amount of solution in front of the fourth transverse process (fig. 79). The greatest care must be taken to avoid injecting the vertebral artery or vein, for the consequences are very serious and may be fatal. If the injection has been accurately placed, there is complete anæsthesia of the superficial and deep tissues in about ten minutes.

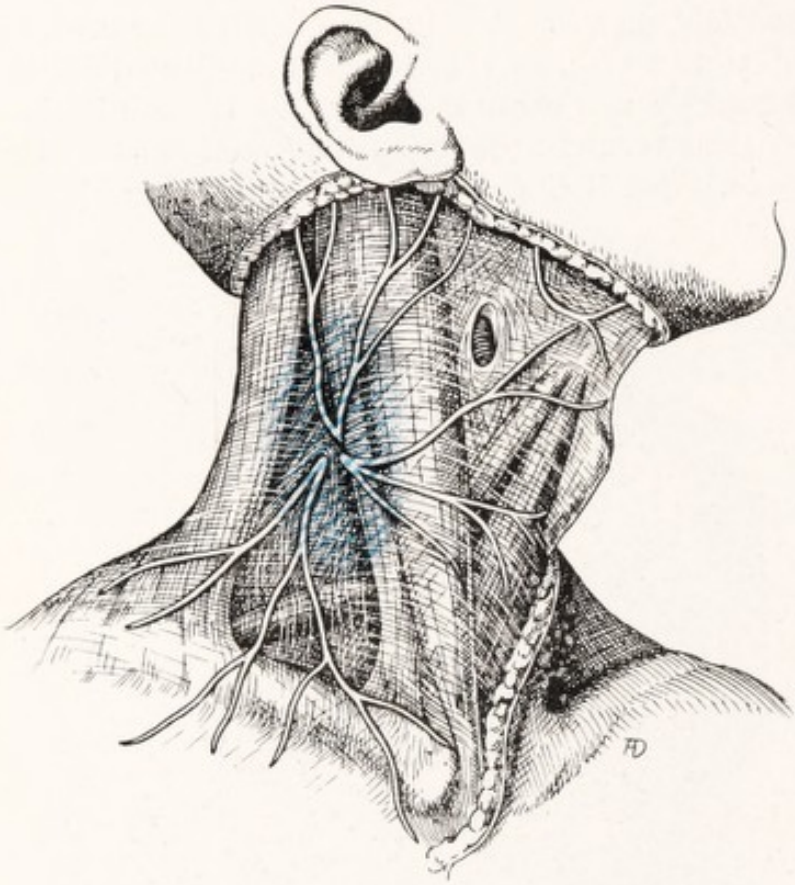


FIG. 78.—Injection of the superficial nerves (after Corning).

(*d*) *Injection of the perithyroid space* (Kulenkampff and others).

The needle is brought into immediate contact with the goitre, in the perithyroid space on the inner side of the sternomastoid and the small muscles. The requisite amount of the solution—some 50 to 100 c.c. of the $\frac{1}{2}$ per cent. strength—is thus distributed over the entire surface of the goitre. This perithyroid injection results in a very good anæsthesia of the anterior surface of the goitre. The anæsthesia of the posterior surface is sometimes not quite so good, if the amount of anæsthetic has been kept within very prudent limits.

This manipulation within the perithyroid space is a very delicate piece of work, and it is sometimes quite impossible to prevent the formation of a hæmatoma. The greatest care must be taken not to inject the novocain into a blood-vessel.

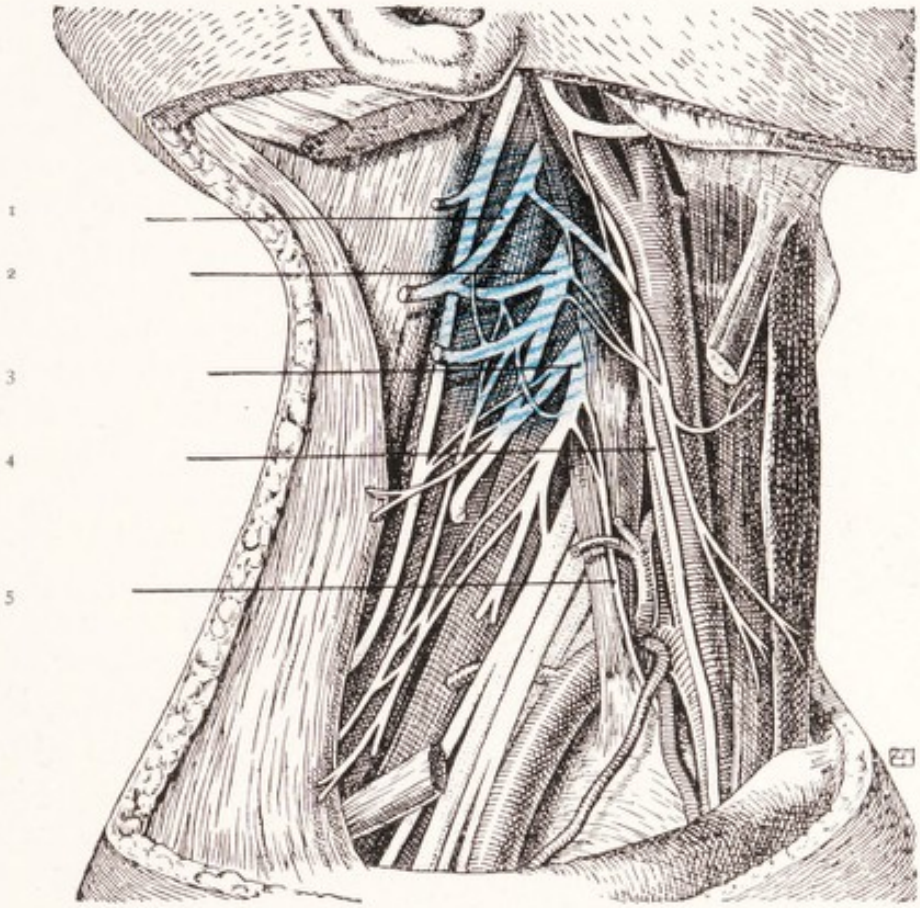


FIG. 79.—Paravertebral injection (after Schultze). 1. Second cervical root. 2. Third cervical root. 3. Fourth cervical root. 4. Pneumogastric nerve. 5. Phrenic nerve.

The perithyroid space can be approached in various ways. In our opinion one of the following routes should be chosen (fig. 82).

(*a*) Injection at the upper pole, the needle being plunged in at the level of the thyroid cartilage and directed towards the upper pole of the lobe. The needle must be kept in contact with the gland, the area of the pole and the anterior surface of the lobe must be infiltrated, taking care not to inject into the vessels. As the nerves of the gland enter mainly through the upper pole, the injection of this area blocks the sensation of the posterior surface.

(*b*) Injection in the region of the isthmus, the needle being directed to the left and right, towards the edge of each lobe. The injection easily reaches the area of distribution of the inferior artery, and the large vessels are not endangered.

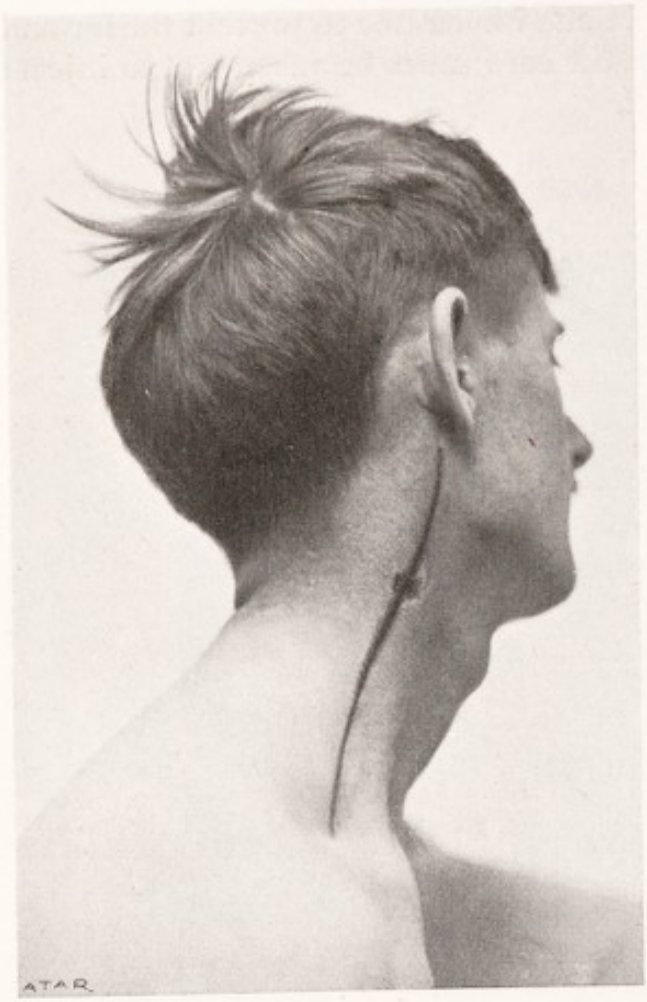


FIG. 80.—Delineation of cervical plexus preparatory to paravertebral anæsthesia (Haertel's method).

Criticism of these procedures. — The first two methods by themselves are inefficient. Bilateral injection of the plexus produces the most complete anæsthesia, but is attended by the risk of bilateral blocking of the pneumogastric, sympathetic and phrenic nerves. Fatalities have been recorded as the result of one or other of these accidents.

The injection of the perithyroid space is attended by the same danger, if it is done "too thoroughly" and if the needle is not kept strictly to the space prescribed. Bilateral retro-thyroid injection should never be practised.

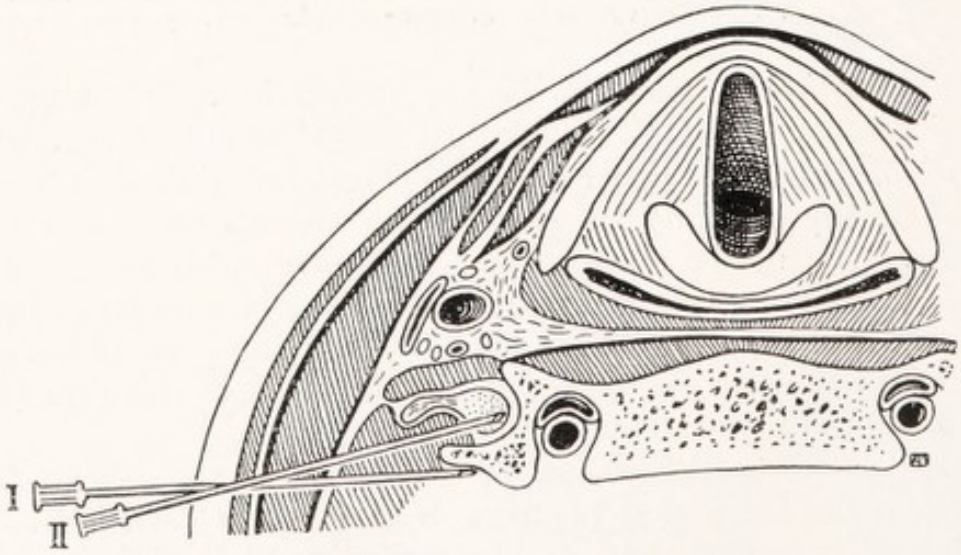


FIG. 81.—Determining site of cervical plexus.
I. Determination of transverse process. II. Determination of plexus.

Choice of method.—There are several combinations, which are quite safe if careful dosage is adhered to.

(*a*) Paravertebral injection of the side chiefly affected. A careful perithyroid injection on the opposite side. Subcutaneous and subfascial injection in the area of the skin incision.

(*b*) Bilateral injection at the border of the sternomastoid muscle, with subcutaneous and subfascial injection in the area of the skin incision.

(*c*) Careful bilateral perithyroid injection. Subcutaneous and subfascial injection of the area of the skin incision.

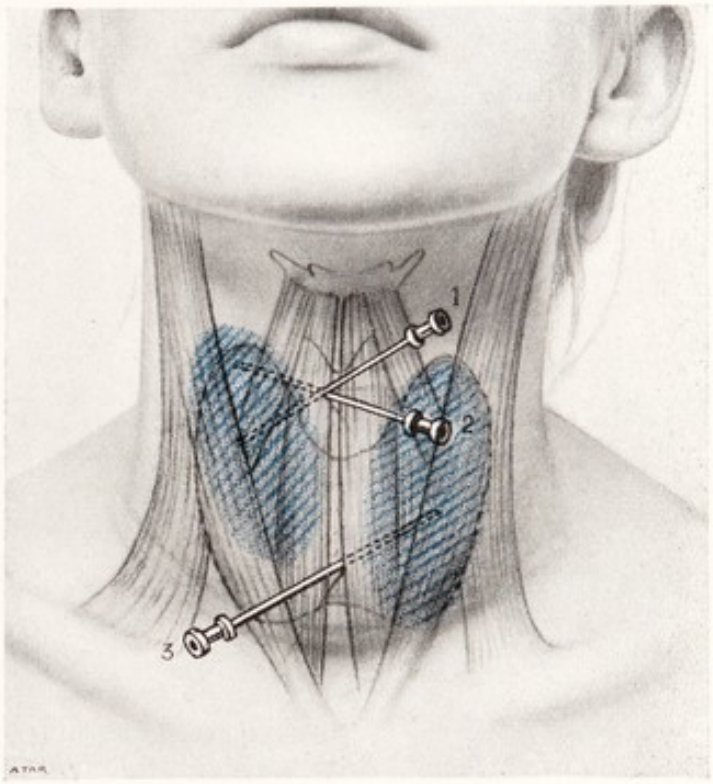


FIG. 82.—Injection of the perithyroid space in three different positions.

Dosage.—We employ exclusively a ½ per cent. solution of novocain, with the addition of four drops of 1 in 1,000 adrenalin to 100 c.c. of the solution. The amount of 1 grm. of novocain should never be exceeded, i.e., 200 c.c. of the ½ per cent. solution, and if possible, it is safer to use less than this amount. In most cases, one half of this quantity will be sufficient. The instability of patients with Graves' disease calls for extreme care, even in regard to such doses of novocain as are reputed to be harmless.

(4) The Methods of Operation.

We must reluctantly pass over the history of the operative treatment of goitre, although this is one of the most interesting chapters in the development of surgical technique. The story was well told by J. Reverdin in 1898, and subsequently by Bérard in his well-known treatise, and more recently by Kocher (Report of the Swiss Surgical Congress in 1917), and by Halstead. The work of Halstead on this subject is the most complete résumé which we possess. We shall

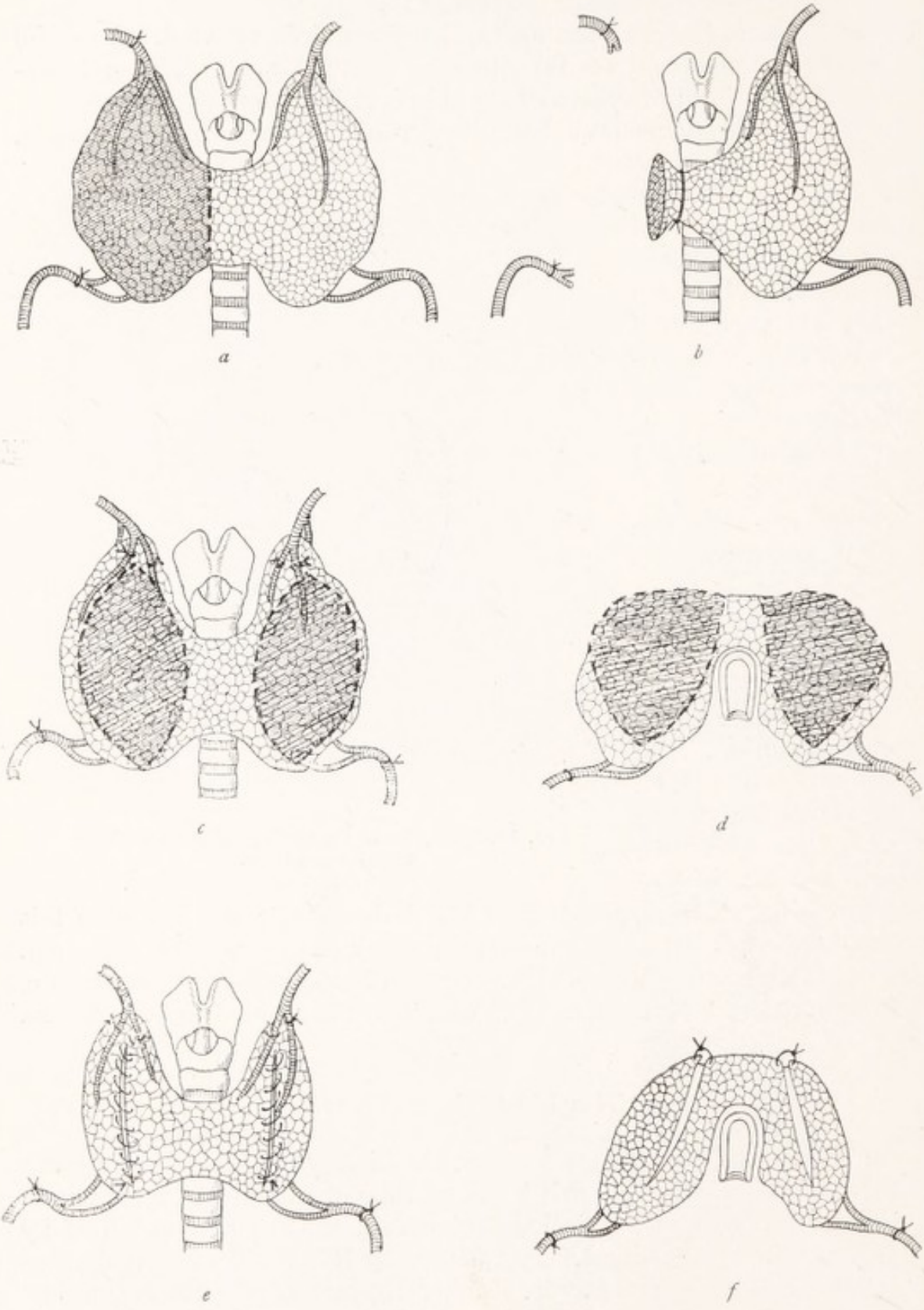


FIG. 83.—Diagram of the principal operations practised for goitre.
a-b, Unilateral excision ; *c-f*, Bilateral excision.

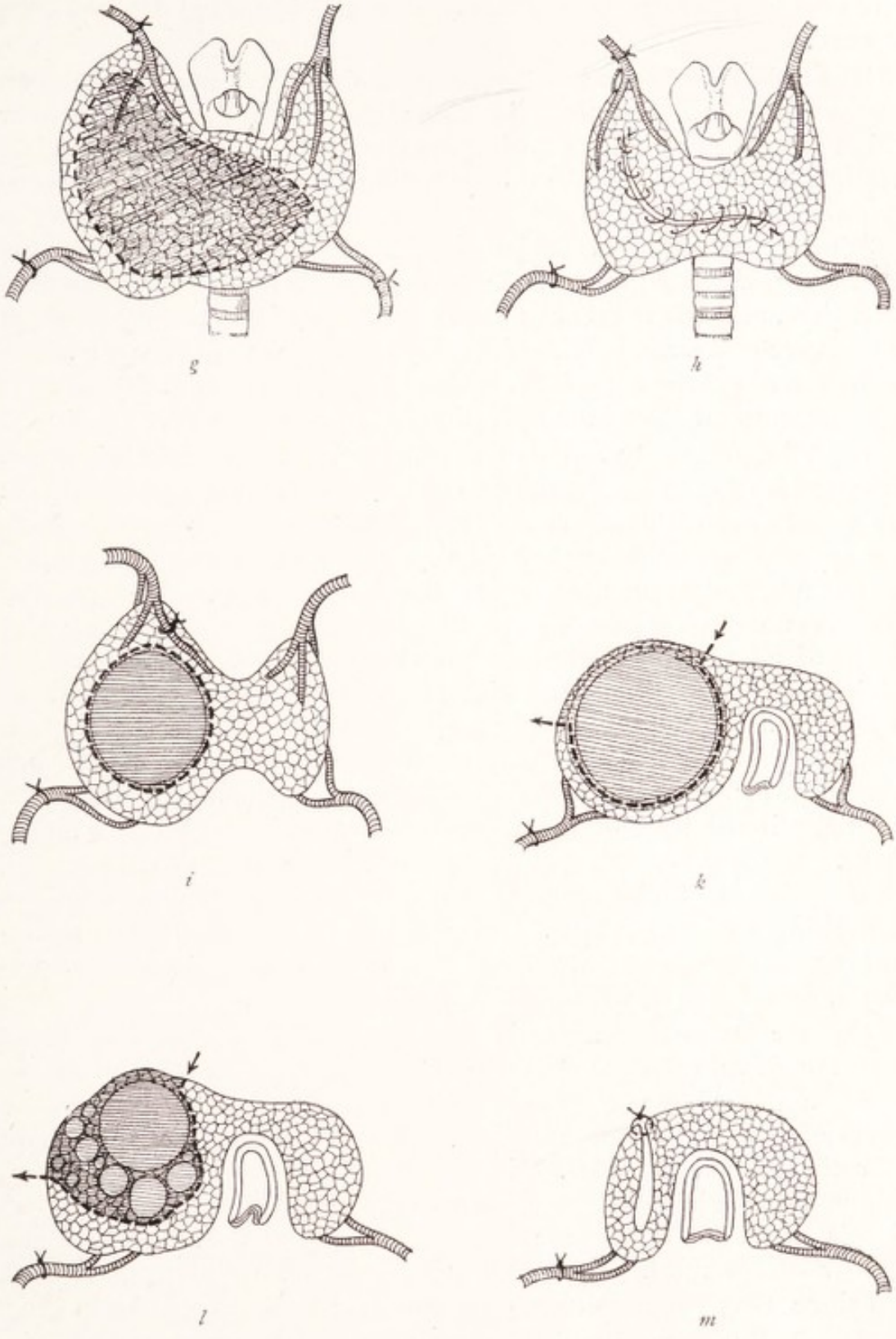


FIG. 83.—Diagram of the principal operations practised for goitre.
g-h, Resection of one lobe and a part of the isthmus ;
i-k, Enucleation ;
l-m, Unilateral resection—enucleation.

have occasion to refer to one or other of the historical details, as we proceed.

The following pages will demonstrate that there are really only a very few classical operations in comparison with the large number which have been described during the last half century. The surgical problem has been considerably simplified by discarding numerous procedures which were merely tentative and which have given way to a technique accurate in all its details. In addition, patients now present themselves for operation in a much fitter condition than heretofore, and the number of cases wherein it is necessary to resort to tentative measures, is becoming very much less than formerly.

In actual practice, the first problem which presents itself concerns the principles on which the operation is to be conducted.

(*a*) The goitre may be regarded as a *sort of tumour*, and it is therefore necessary to excise the portion of tissue which must be got rid of: the vessels are clamped as the operation proceeds, when the knife encounters them or when they bleed, without any particular attention to the anatomical conditions of the blood-supply. This method demands a complete exposure of the anterior surface of the gland by means of a transverse section of the small muscles. This method of bilateral resection, combined with resection of the isthmus without any previous steps to prevent bleeding, is still the favourite operation with many surgeons, particularly for diffuse colloid goitre. But this procedure cannot usually be carried out with anatomical accuracy, especially if the field of operation is obscured by persistent hæmorrhage. It may succeed very well in the hands of a skilful surgeon, whose assistant is able to avoid the recurrent nerve while engaged in controlling the hæmorrhage. It is not an advisable method of operation for very vascular goitres, and the inexperienced can only undertake it, as Roux says, with considerable trepidation.

(*b*) The second principle is that of *methodical operation*, based upon the anatomy of the planes of cleavage, the arrangement of the vessels and the precise knowledge of the structure of the different forms of goitre. This methodical technique is due to the work of Billroth, Kocher, Woelfler, Mikulicz, Socin, Reverdin and Halstead, although due acknowledgments must be made to the efforts of others in this direction, during the last century. J. and A. Reverdin and Kocher discovered the dangers of total removal of the thyroid gland, and since 1883 surgeons have only practised total extirpation in cases of malignant goitre. In all operations for simple goitre, only *partial* removal of the gland is practised.

Hemithyroidectomy is the most simple of the procedures for the partial removal of the gland. It consists of the removal of the thyroid

lobe which contains the most obtrusive part of the goitre. The operation has the advantage of comparative ease and rapidity of performance, but it has the disadvantage of causing great disturbance in the internal architecture of the neck. It disarranges the equilibrium of the contents of the neck, because the remaining lobe of the thyroid will push the trachea towards the side operated on. This displacement becomes much more prominent, and may indeed threaten obstruction if the other lobe eventually becomes goitrous. In bilateral goitre, this displacement of the trachea begins at the very time of the operation, and the patient leaves the table with the certainty of a relapse.

A second disadvantage of this type of operation is the destruction of the two parathyroids, situated on the side of the operation, which is almost certain to occur.

A third disadvantage is the risk of injury to the recurrent nerve on the posterior surface of the lobe, which is involved by this method of operation. Indeed, this has been the cause of the numerous cases of paralysis of the recurrent nerve, which figure in the older statistics. It was this calamity which led to Kocher to deal with the posterior capsule of the lobe in such a way as to protect the recurrent nerve, even before the functions of the parathyroids were known. If ever occasion arose at the present time to resort to the operation of hemithyroidectomy, we would employ this last method in order to safeguard not only the recurrent nerve, but also the parathyroids (Kocher's resection-excision).

There are two other operations which for the last forty years have contested the position with hemithyroidectomy, viz., resection and enucleation.

Resection consists of reducing the size of the lobe by a more or less cuneiform excision (like a slice out of a melon) of a part of it. The knife works through the actual substance of the gland. This operation is indicated, and is indeed indispensable, in *diffuse parenchymatous or colloid goitres* (brawny goitres). It is also indicated in *diffuse multinodular goitres*, i.e., in those large goitres which consist of an aggregation of small nodules, in which it is impossible to undertake enucleation. If statistics show that a certain surgeon employs a certain form of operation, it does not necessarily prove that he specially favours that method, it may very well be that the type of goitre in his district demands that method of procedure. We refer the reader to the remarks in Chapter III on this subject. It is, therefore, not at all surprising that the classical operation of resection has been eulogized by surgeons practising in lowland countries, by Mikulicz, Hahn, Zöge, von Manteuffel, and by American surgeons.

C. *Enucleation.*—This, the oldest of the operations, consists of removing the goitrous nodules from their shell or the intrathyroid capsule one by one. The operation is conducted in one of the planes of cleavage of the gland, and can only be performed in cases of *nodular goitre with large nodules.* It is quite erroneous to think that there is an intraglandular plane of cleavage in every goitre. One would no more attempt to perform an enucleation in a diffuse goitre than to perform a classical resection in a goitre with large nodules. The operative technique of enucleation has been developed particularly by Porta, Socin and J. Reverdin.

The frequent occurrence of mixed goitres, which are partly diffuse and partly nodular, led Kocher to invent a type of combined operation, half enucleation and half resection. He termed the operation *resection-enucleation*, and it has become the most widely adopted procedure in all districts of Switzerland. It is not the universal operation, because there is no universal type of goitre.

(5) The Ligatures.

Before dealing with the methods in which the goitrous tissue is cut away, a brief section should be devoted to the treatment of goitre by simple arterial ligature, for the purpose of producing atrophy. This method was suggested by Ph. Walter over a century ago, and it has gained the commendation of Woelfler and Kocher, and more recently of Rogers. It still remains the classical treatment for vascular goitres of moderate size, and especially for certain cases of exophthalmic goitre. There are two preliminary questions to be considered.

(1) *How many arteries may be tied?*—The answer is very simple. The three main arteries may be tied without any disadvantage, or even three and a half arteries, i.e., the two inferior thyroids, one of the superior thyroids and one of the main branches of the other superior thyroid. We have never encountered any trouble after this procedure. Indeed, one may go further. In cases of very vascular diffuse goitre, the four main arteries may be tied without compromising the vitality of the gland, as long as the connections between the gland and the surrounding tissues are not disturbed. The collateral anastamosis of the thyroid arteries is so widespread that the blood supply of the gland is at once provided for. We have never seen any evidence of thyroid inadequacy or of tetany after tying the four arteries; but, of course, we do not recommend this procedure as an operation of choice —far from it. As a rule we would limit the procedure to the ligature of three or of three and a half arteries. Formerly, when we decided to tie the four arteries we did so in two stages, in accordance with Kocher's advice; but observations made by numerous operators and our own experience show that this latter precaution is unnecessary.

We do not now hesitate to ligature the four arteries simultaneously under appropriate conditions, viz., a very vascular goitre and precautions not to disturb the connections of the gland with the surrounding tissues.

These remarks apply equally to arterial ligatures as independent procedures, as well as when undertaken in the course of an operation for ablation of goitrous tissue.

(2) *What is the Effect of Ligatures on Thyroid and Goitrous Tissue?*—If a ligature is employed in order to produce atrophy, the results must be differentiated in accordance with the condition of the gland which may be normal or contain a diffuse, parenchymatous colloid or nodular goitre, or may be the subject of exophthalmic or vascular goitre.

For many years we have, in conjunction with our colleague Dr. Wydler, been experimenting on dogs to study the atrophic effect of complete blockage of the arteries of the gland, taking care that the gland itself maintains its normal connections with the surrounding tissues and receives the benefit of the collateral circulation. These experiments have proved that the ligatures do cause atrophy, as shown by the decrease of colloid substance, the increase of connective and interacinous tissue and decrease in the size of the gland. The atrophy decreases however in the course of time. A progressive return to the normal condition occurs, owing to the collateral circulation, but it takes some two years to effect a complete restoration. These results confirm those obtained by M. Varebely, working under Kocher in 1910.

In cases of non-vascular diffuse parenchymatous goitre, which do not present the character of Graves' disease, the atrophic effect of ligature is very little, and we have long abandoned this procedure, as the sole method of treatment, in cases of this type.

The experiments of Roux and Fritsche, and our own, show that ligature is no safeguard against recurrence. Roux, indeed, is of opinion that it tends to encourage the ultimate change of a diffuse into a nodular goitre. In our experience, this transformation occurs, as it were, automatically after the third decade, and a diffuse goitre in an adolescent, which has been operated on, is quite likely to recur as a nodular goitre. The only forms of goitre which we now treat by ligature in order to produce atrophy are certain forms of exophthalmic goitre. The effect of the operation is more manifest on the symptoms of hyperthyroidism than on the size of the goitre. It is quite certain that three or four ligatures often cause a more or less definite disappearance of the symptoms of Graves' disease, whereas the goitre itself decreases but slightly. In many cases when we have applied four ligatures, we have removed small fragments of thyroid tissue in order to compare their histological appearances with tissue from a

thyroid which has been subjected to ligatures for some months. We have, however, never been able to detect any essential differences. Later on, we shall see the practical deductions from these observations. The numerous investigations made by Plummer, Boothby and Crile have established the effect which the operation of ligature has on the respiratory exchange.

The operation for multiple ligatures may be carried out according to two different principles.

A. *Ligature of the superior and inferior arteries by two separate incisions.*

(1) *Ligature of the Superior Thyroid Artery.*—This artery is easily detected on palpation, either at the level of the thyroid cartilage or higher up, but always in relation with the upper pole of the goitre.

The *skin incision* should follow accurately the direction of the folds of skin, which are generally well marked in this region (fig. 76). It should correspond to the middle of the thyroid cartilage, unless the excessive development of the lobe necessitate an incision higher up. Its length should be 4—6 cm. The exact course of the artery can often be detected by palpation. It should, however, not be forgotten that the portion of the artery which can be felt does not always correspond to the trunk itself, but may be the antero-internal branch. The incision which was formerly practised, parallel to the anterior edge of the sterno-mastoid, has no advantage whatsoever and results in an ugly scar.

The platysma and superficial cervical aponeurosis are cut through, and then the anterior edge of the sterno-mastoid is drawn to the side (fig. 84). This being done, the finger works its way towards the upper lobe of the thyroid in order to ascertain the precise situation of the artery, which is covered at this level by the omohyoid muscle. This muscle is drawn inwards. The facial vein will be protected by the lateral retractor. The external laryngeal nerve lies under the median retractor. If the trunk of the artery is not found easily, the upper pole of the thyroid lobe should be deliberately exposed in order to follow up the antero-external branch of the branch. This branch is always easy to recognize on the thyroid substance. The ligature must be applied just above the point where the posterior branch of the thyroid artery is given off. At the same time the veins and nerves of the upper pole of the thyroid are all ligatured together in one bundle (polar ligature of American authors). It is very important to keep at a sufficient distance from the thyroid cartilage in order to avoid any injury to the recurrent laryngeal which penetrates under the crico-pharyngeal muscle at this level. The operation is completed by the insertion of a few sutures and a dressing of collodion or masistal.

(2) *Ligature of Inferior Thyroid Artery.*—The inferior thyroid artery is one of the easiest of the deep arteries to ligature, if one follows exactly the route we have studied on the cadaver and which we have applied on the living subject over a thousand times. The anatomical details are of the greatest importance because this ligature constitutes, in most cases, the first step in the removal of the goitre, according to the method which will be described later on.

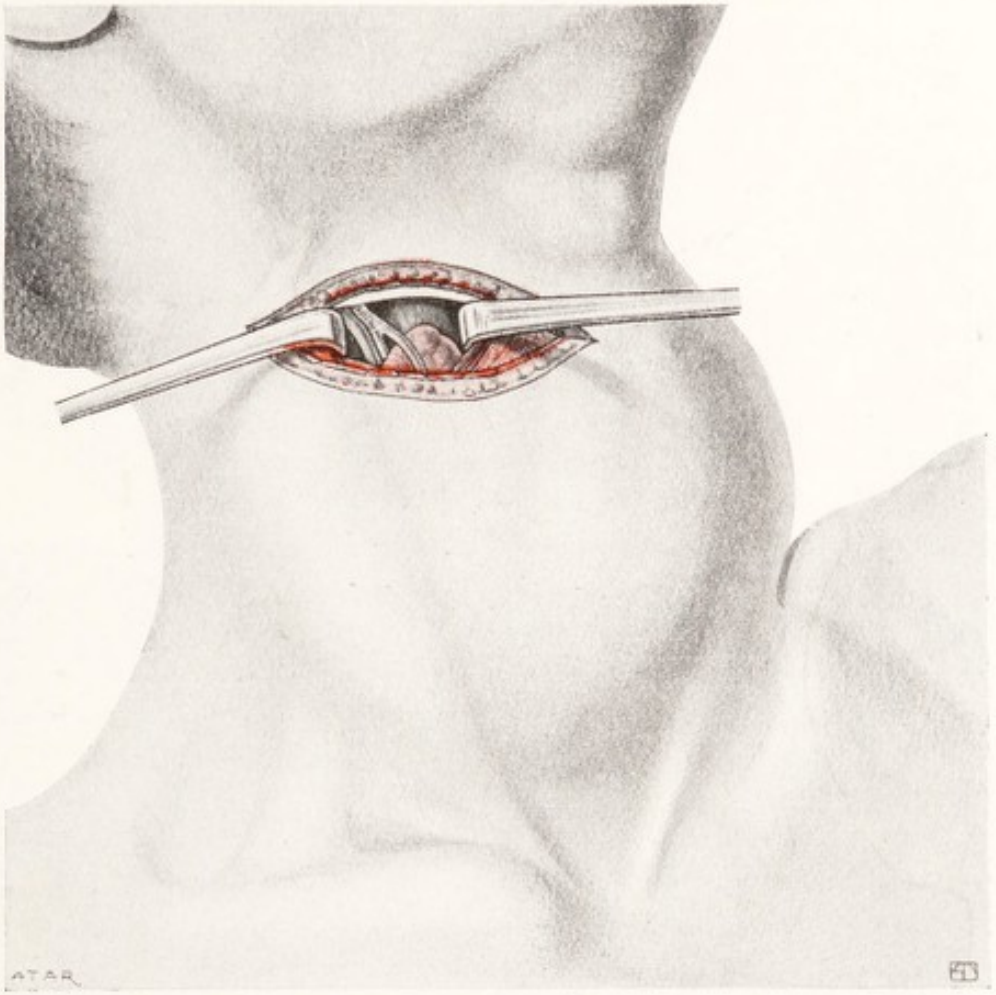


FIG. 84.—Ligature of the superior thyroid artery according to the classical method. Under the retractors: Sternomastoid muscle *externally*. Omohyoid muscle *internally*.

The skin incision must follow the folds of the skin with scrupulous exactness (the incision en cravate of Kocher). It should be on one side only for a unilateral ligature and complete (symmetrical) for a bilateral ligature of the artery.

The subcutaneous tissue and platysma are cut through and the anterior jugular veins are cut and tied. The anterior edge of the sternomastoid is then gently freed, care being taken not to proceed

too far forwards and penetrate between the sheath of this muscle and that of the small thyroid muscles (sternohyoid and sternothyroid). This space, which is made use of in the classical method of Porta, Velpeau and Kocher, leads directly to the internal jugular vein, and we greatly prefer to leave this structure outside our field of action. We then make an incision 3 cm. in length in the aponeurotic sheath of the small muscles, parallel to the edge of the sternomastoid. The

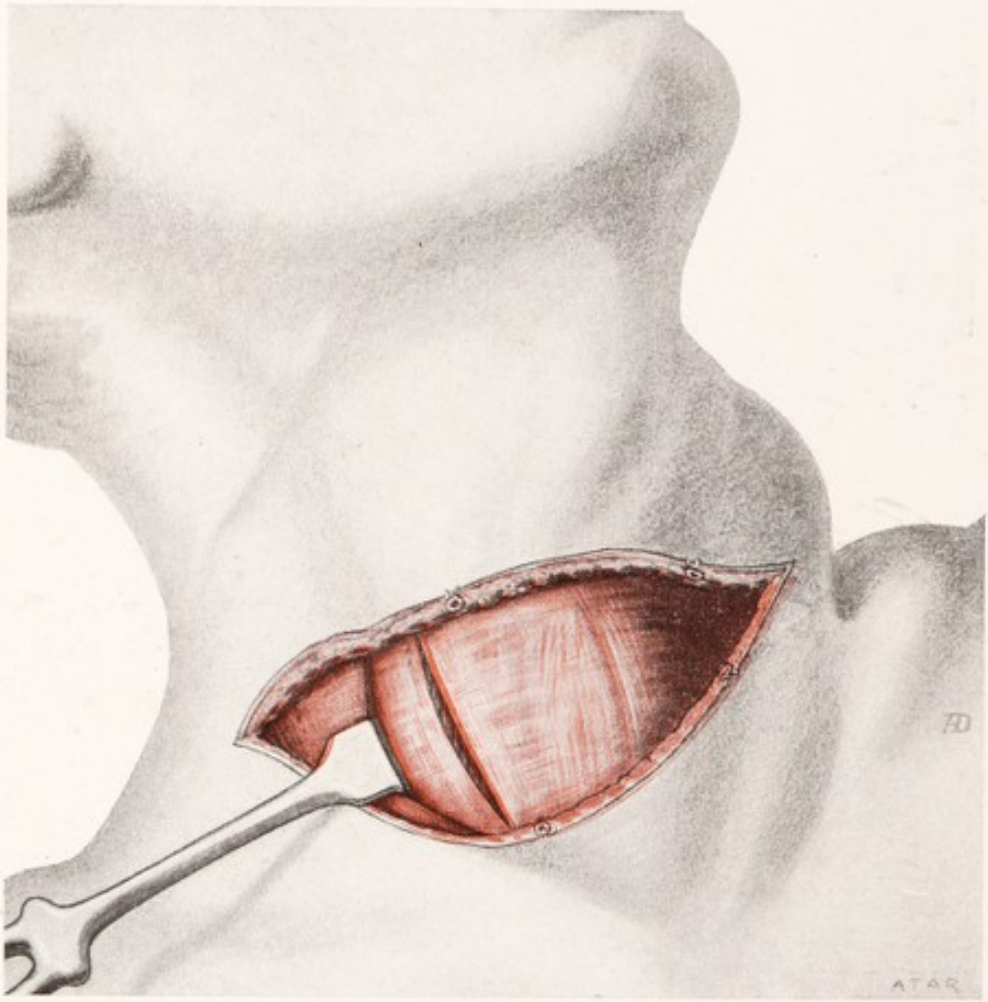


FIG. 85.—Neck incision. Anterior jugular veins tied, and the aponeurotic sheath of the small muscles incised. The sternomastoid muscle is under the retractor.

external layer of this sheath is retracted under the same instrument which retracts the sternomastoid muscle (figs. 85 and 86). If the finger is inserted between this aponeurotic layer and the exposed substance of the small muscles it will soon encounter the internal edge of the carotid. This edge is freed after having overcome a slight resistance—a thin layer of deep cervical aponeurosis—and the finger is deliberately inserted between the posterior surface of the thyroid

lobe and the vertebral column. The finger then travels upwards and downwards in order to define the trunk of the inferior thyroid artery, which runs in a transverse direction. The exact position of the artery depends upon the amount of growth of the goitre; it may be at the typical position (tubercle of Chassaignac), but it is sometimes higher up and sometimes lower down. The artery is absent in 2 to 3 per cent. of the cases and is replaced by an abnormally developed superior

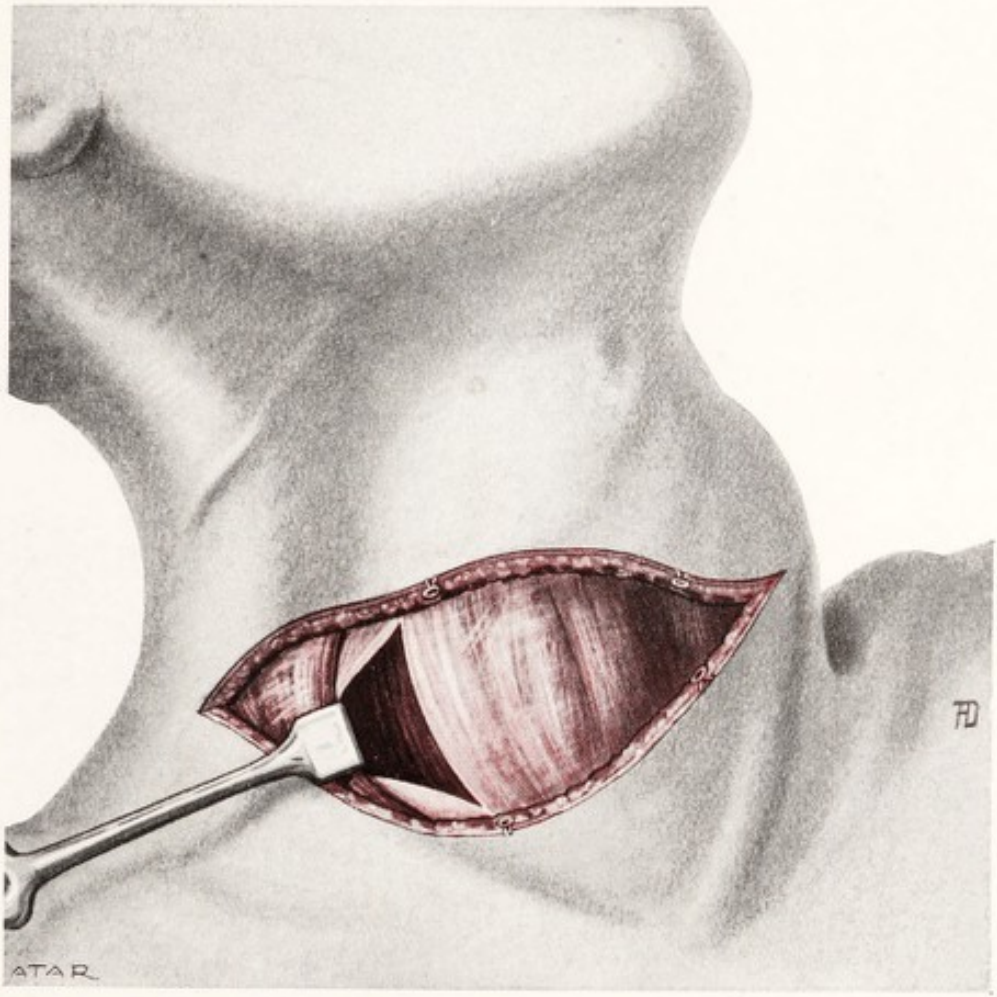


FIG. 86.—The aponeurotic sheath of the small muscles and the sternomastoid are beneath the retractor: The sternohyoid and sternothyroid muscles are exposed. The finger penetrates through the space thus made in order to find the inferior thyroid artery.

thyroid, or more frequently by a greatly enlarged arteria ima (artery of Neubauer). When the inferior thyroid artery is found it is gently disengaged from the surrounding connective tissue by the pulp of the finger. An appropriate retractor is introduced to the inner side of the finger before the latter is removed. At this stage it is of advantage to replace the lateral retractor by a deeper one. When this part of the operation is completed the artery is seen covered by a thin layer

of connective tissue and the lateral retractor is keeping the arterial and nerve trunks out of the way (fig. 87). The great sympathetic encircles the trunk of the artery behind the carotid by its two branches which unite the middle cervical ganglion with the inferior cervical ganglion. As the sympathetic nerve is so sensitive to pressure we prefer to use a retractor which has only two points of pressure, so as to obviate as far as possible any injury to the nerve.

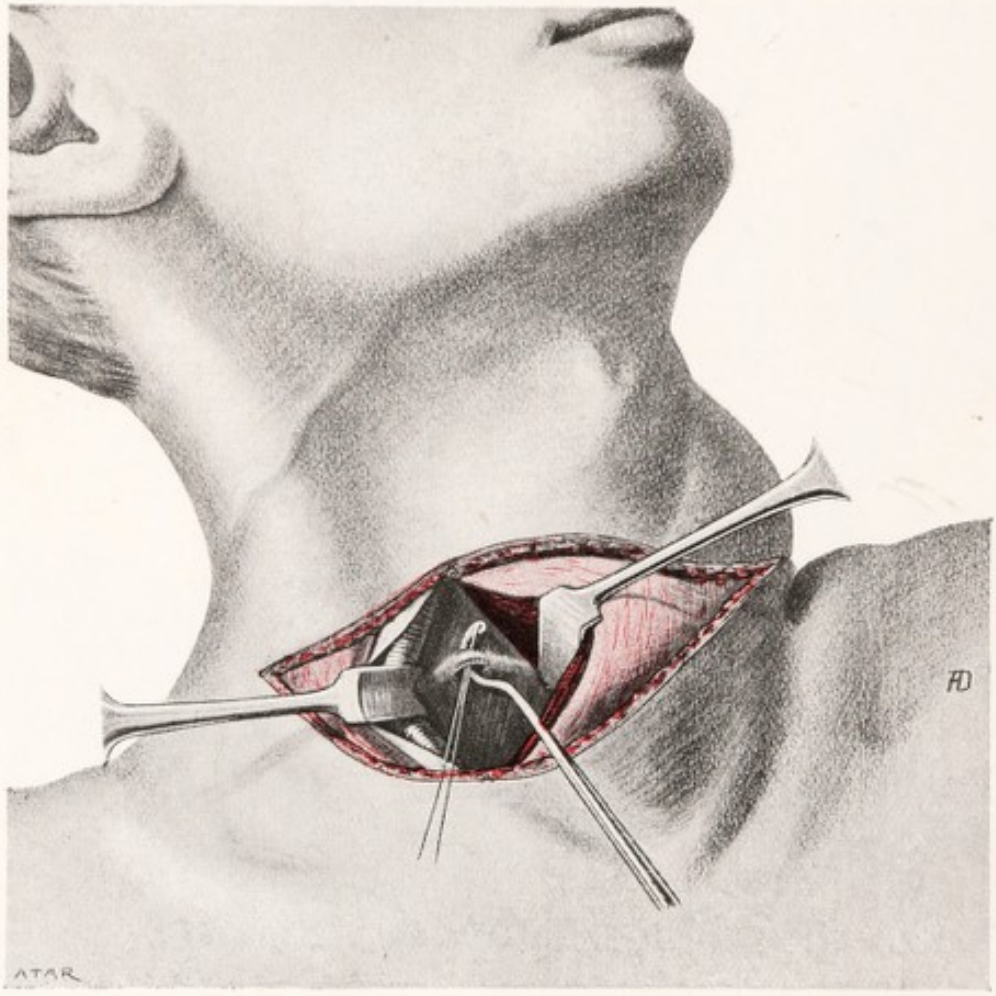


FIG. 87.—Exposure and ligature of the inferior thyroid artery. The carotid artery, superficial aponeurotic sheath of the small muscles, and the sternomastoid muscle are under the *external retractor*. The goitre covered by the sternohyoid and sternothyroid muscles are under the *internal retractor*. The carotid is really covered more than the illustration indicates, by the prolongation of the sheath of the small muscles.

If the thyroid lobe projects above the retractor and thus interferes with the manipulations required for ligaturing the artery, a third retractor must be placed in the upper angle of the wound. The thyroid artery which is thus exposed in the middle of the field of operation, is freed from the surrounding connective tissue, by means

of blunt forceps of sufficient length and of the dissector illustrated in fig. 67 (6-7). As the artery is often very friable we avoid close dissection and do not peel off all the adjacent tissue. On the contrary, we prefer to include a thin layer of connective tissue in the ligature, for we have seen more than once that a ligature of fine silk tied too tightly can cut right through the artery. The surrounding connective tissue thus acts as a useful protective. The ligature of the artery can be effected in a very few minutes without any preliminary ligature, unless it be that of the anterior jugular veins. We have already stated in the chapter dealing with the anatomy, that the recurrent nerve is not in the same plane as the artery at the level where the ligature is performed; the nerve is separated from the artery by the thyroid fascia. If the ligature is properly carried out, the nerve is not encountered. The same applies to the parathyroids which are right away from the surgeon's sphere of action. At times, however, some difficulty may be caused by the middle thyroid vein. As a rule, it runs in a plane superficial to that of the inferior thyroid artery, but occasionally it is on the same level. It should be drawn carefully upwards or downwards, or cut between two ligatures. If the vein be torn, owing to the digital manipulations being somewhat too boisterous, it may be enough to compress it under the retractor until the artery is tied, or the bleeding can be arrested by plugging for a few minutes, after which it will be easy to find the vein and tie it. This slight accident has never prevented us from ligaturing the inferior thyroid artery in the proper manner.

The chief difficulty in carrying out this ligature is caused by excessive lateral growth of the goitre. The dragging of the latter towards the trachea by means of the median retractor may embarrass the respiration so much as to necessitate the abandonment of the procedure. In these circumstances, we endeavour to liberate the goitre by transverse section of the small muscles, which is sometimes very successful, or we attempt to displace the goitre in the perithyroid plane of cleavage, as will be described later on. But we must repeat that it is very exceptional for topographical conditions to interfere with our method of tying the inferior thyroid artery, even including a large number of cases of massive goitres.

We must allude to the posterior carotid route of access—a method devised by Drobnik and advocated by Reverdin, Delore and Alamartine who studied the method on the cadaver. This method is more complicated than ours when the inferior thyroid artery is easily accessible, and it is not easier to carry out when the cervical vessels are considerably overlapped by the goitre. The method is fraught with more danger to the sympathetic than ours. It should be said that the reason it is so important to tie the inferior thyroid artery in

its first portion, is in order to carry out this procedure away from the region of the recurrent nerve and parathyroids. This also prompted Reverdin's investigations on the cadaver, to determine the possibility of tying the artery at the edge of the scalene muscle, after employing Kocher's transverse incision.

Much discussion has arisen in regard to the question of the relative value of ligature of the superior or inferior artery. From the standpoint of comparative anatomy there is no doubt that the superior artery is the more important. In normal conditions the calibre of the artery is at least equal to that of the inferior artery; but this is not the case in goitre. The changes in goitre mainly concern the middle and lower parts of the gland, and therefore the inferior artery increases in size and for practical purpose is the important artery in goitre. This therefore is the artery which must be tied, if an artempt is be to made to diminish the vascularity of a goitrous thyroid.

B. *Ligature of the Four Thyroid Arteries by One Incision.*—We adopt the practice of Tavel and ligature three or four of the thyroid arteries through one incision, whenever the size of the thyroid gland does not exceed the medium dimensions. This operation is performed more quickly than ligature through three or four separate incisions, and obviously a single scar is less unsightly than three or four separate scars. It is advisable not to make the transverse incision in one of the lower folds of skin. We tie the two inferior thyroids to begin with, but take care to make sure of the integrity of the recurrent nerve after the first ligature. We then separate the fibres of the small muscles over the middle of one of the lobes, in order to expose the corresponding upper cornu. We follow one of the anterior branches of the superior thyroid artery to the upper pole of the gland and free the vessels at this point. We then put a single ligature round the trunk of the superior thyroid, or tie a ligature completely around the pole. We repeat the procedure on the opposite side, but limit ourselves to the ligature of one of the anterior branches.

It is hardly necessary to say that no drainage is required after this operation, even when multiple ligatures are employed.

We will now proceed to describe the various forms of removal of goitrous tissue, showing how the primary ligature may be combined with one or other method of operation.

(6) Forms of Removal of Goitrous Tissue.

A. *Hemithyroidectomy* (complete excision of one lobe).—We have already referred to the advantages and disadvantages of hemithyroidectomy. This operation is indicated when the goitre is distinctly unilateral, and when it replaces all the normal thyroid tissue. These conditions, however, only occur in the case of the large single colloid or

cystic nodules in patients of middle or old age. Unilateral removal is also indicated in cases of bilateral goitre when the size of the tumour or the general condition of the patient renders it inadvisable to perform the bilateral operation, and when there is no more normal thyroid tissue, capable of being saved, on the side to be operated on. We have already stated that we do not usually perform the classical operation of hemi-thyroidectomy in this type of case, but that we preserve the upper pole and the entire posterior capsule in order to save the parathyroids (resection-excision or enucleation-excision after Kocher).

Skin Incision.—The only incision which will ensure a scarcely visible scar is the "incision en cravate" (fig. 75). We can confidently assert, on a basis of 2,000 cases, that this incision is adequate for all forms of innocent goitre and for all types of operation. In certain exceptional cases, it may be necessary to perform a preliminary ligature of the vessels of one of the upper poles, through an independent incision, if this pole is displaced abnormally upwards. We only employ this expedient in cases of Graves' disease where the goitre is very large. This double scar, hidden in the folds of the skin, is less unsightly than a single scar running in an awkward direction. A female patient may justifiably be vexed with the surgeon who signs his handiwork with an ugly scar.

A few words are now required in regard to the exact direction and level of the incision.

The incision should not be absolutely transverse, but must follow the folds of the skin precisely. On each side, therefore, its direction will be slightly upwards, like a short necklace encircling the base of the neck. The skin of even the youngest patients affords definite indications of these folds. When required, the line of the incision may first be marked out faintly on the skin with the point of the knife.

The level of the incision depends upon the precise situation of the goitre and upon the folds formed by the skin. There is often one fold about 2 or 3 cm. from the base of the neck, and another exactly at the base of the neck. The upper fold is chosen if the goitre mainly concerns the upper portions of the gland, and the lower fold is selected if the goitre is mainly developed in the inferior cornu.

Steps of the Operation.—The following are the steps of the operation: incision of the platysma, ligature of the anterior jugular veins, transverse incision of the small thyroid muscles or separation of their fibres (figs. 88-94), and dissecting down to the actual capsule of the lobe. The lobe is then liberated throughout its entire extent by means of the finger, in the plane of cleavage situated between the thyroid fascia and the actual capsule of the gland, i.e., in the

perithyroid space. The lobe is then grasped and its upper pole is ligatured (artery and vein) (fig. 88) ; the middle thyroid vein is tied in two places and cut through—if it is present—ligature of the inferior thyroid artery external to the recurrent nerve, which crosses it at this level or passes between its two chief branches (fig. 92), ligature of the lower pole (veins and artery of Neubauer) (fig. 89), crushing and ligature of the bridge which unites the lobe to the isthmus and separation with the isthmus (fig. 83 *a-b*).

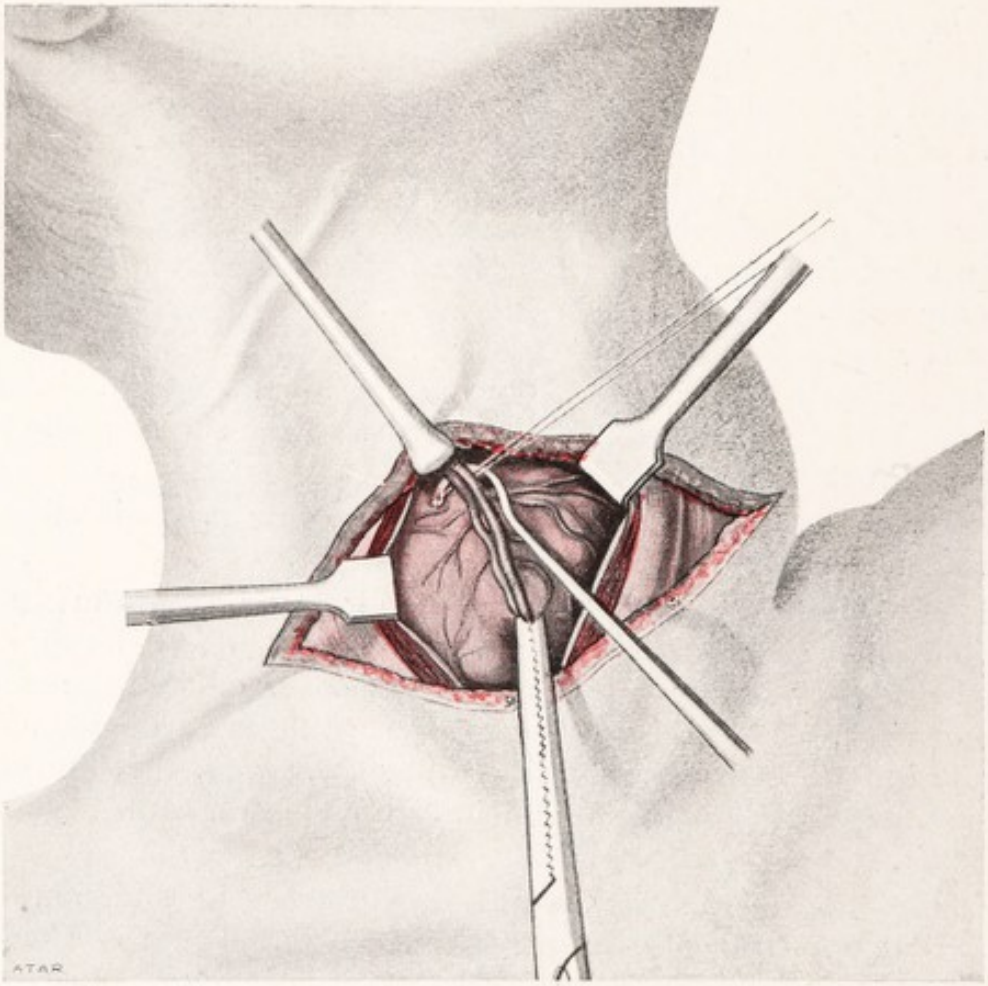


FIG. 88.—The compartment of the small muscles is left behind, and the visceral compartment is opened by the separation of the fibres of these muscles, and the deep layer of their aponeurotic sheath has been incised (thyroid fascia). Under the retractors, *both outwards and inwards*, there are the small muscles with their superficial and deep aponeurotic sheath. The artery forceps is pulling gently on the lobe. The ligature is holding the anterior branches of the vessels of the upper pole. In order to tie the trunks themselves, the edge of the wound should be drawn more towards the skin.

By this method, the two parathyroids are sacrificed. Kocher advises that the posterior part of the capsule should be saved, for this covers the recurrent nerve and also contains the parathyroids (fig. 93). This, however, is not a true hemithyroidectomy, but is rather a

procedure which partakes of the nature of a resection or an enucleation, according to the variety of the goitre which is present. We have abandoned in most cases the ligature of the isthmus and we unite the posterior segment of the capsule, which is retained, to the anterior border of the glistening substance of the isthmus (fig. 98).

We have just described hemithyroidectomy as the operation is usually carried out, the dislodgment of the goitre being a primary step

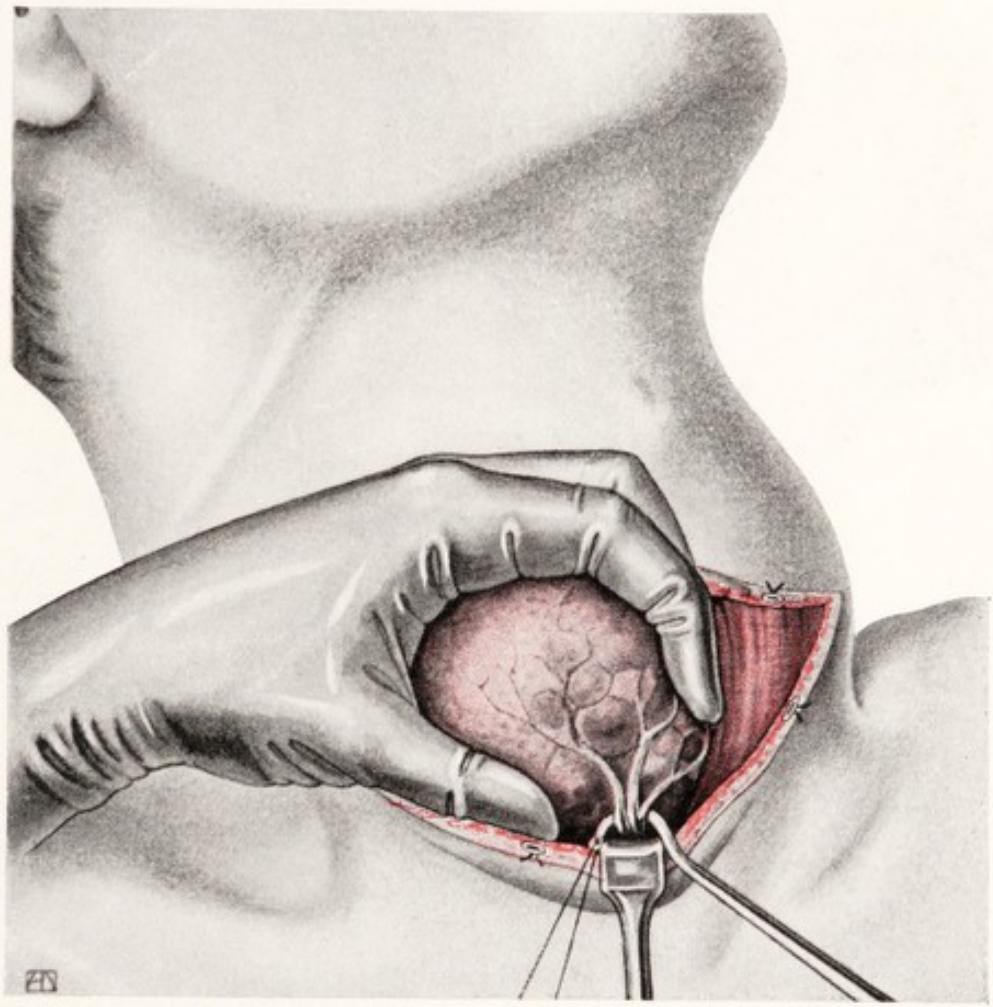


FIG. 89.—The lobe is delivered. Ligature of the inferior thyroid veins, and the artery of Neubauer, if it is present.

in the procedure. But it is obvious that a lobe can be removed *in situ*, without this previous dislodgment, but this method demands the complete cutting through of the small muscles, which is quite unnecessary in the majority of cases, though it may be required in certain conditions, viz., adhesions, recent inflammation, severe compression of the trachea, an intrathoracic or retrovisceral situation, over growth of the isthmus and malignancy.

Hemithyroidectomy can also be performed by the method

of primary hæmostasis which we will describe in dealing with resection and enucleation. We employ this method when we undertake a single and complete removal of one of the lobes in those rare instances when such a procedure seems to be indicated. The dislodgment of the goitre is then preceded by extra-fascial and extra-muscular ligature of the inferior thyroid artery.

B. *Resection, Enucleation, Combined Operation.*

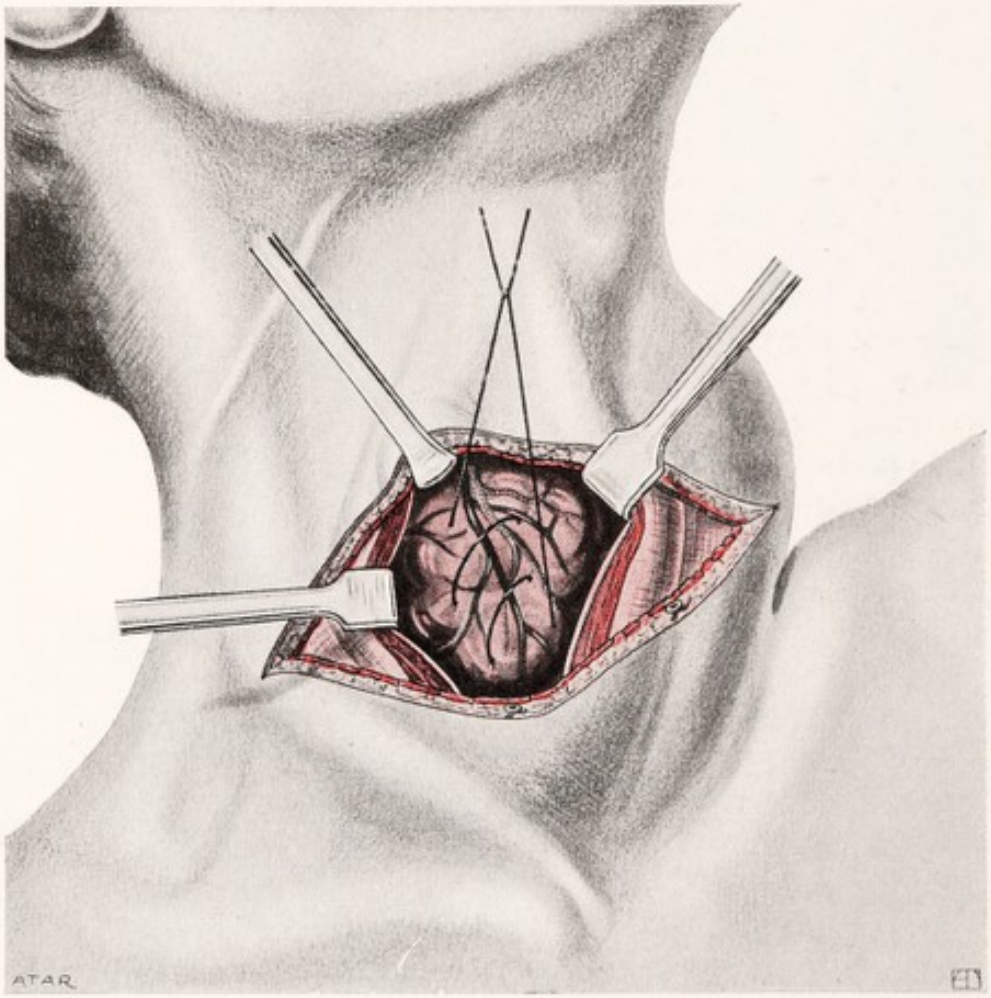


FIG. 90.—The device of Perthes and Clasen to facilitate the fixation of the lobe.

We will now proceed to describe the operation for goitre which we usually perform. In our view the first steps of the operation are identical whatever be the form of the goitre, and we decide as we go along upon the exact method to employ for removing the pathological tissue, resection, enucleation or combined operation. The skin incision is always an incision "en cravate."

Most surgeons perform resection, enucleation or the combined procedures along the lines we have just laid down for hemi-thyroidectomy, i.e., immediate exposure of the gland, dislodgment of

the lobe, partial or complete ligature of the upper pole, ligature of the inferior thyroid artery in the thyroid space, according to the necessities of the case, and then resection, enucleation or the combined operation, varying with the form of the goitre. We adopt this method whenever the excessive lateral growth of the lobe prevents us from commencing by tying the inferior thyroid artery. These cases represent about 5 per cent. of the whole, which includes an abundance

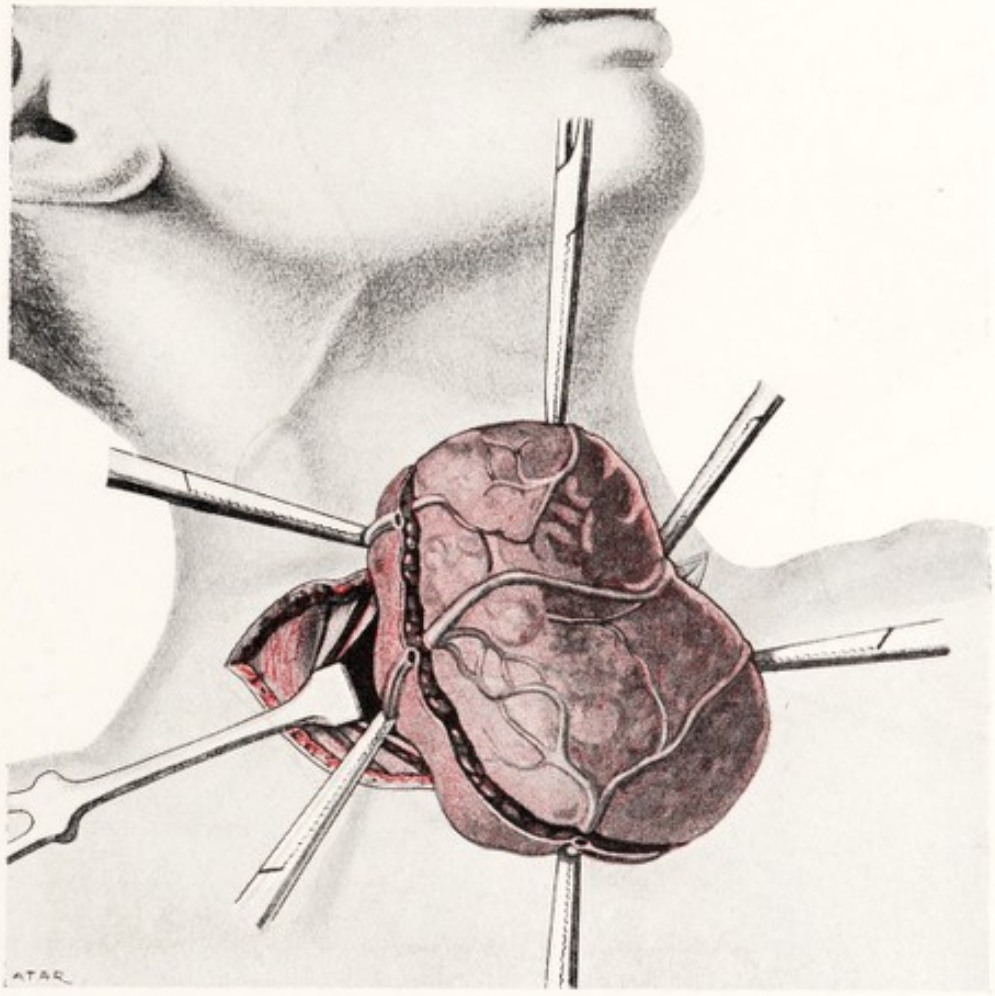


FIG. 91.—The lobe delivered. The true capsule of the gland is incised over the extent necessary for the resection or enucleation, the posterior surface of the lobe being preserved. (Dangerous zone.)

of massive goitres. For the last twelve years we have abandoned this operation in most cases for one whose description will follow.

Many surgeons, especially those who have developed a method of their own, consider that we are a little biased in seeing the advantages of this method of operating. But these advantages have been confirmed by so many colleagues that a description of the method ought to find some place here. The method is as follows.

The skin and the platysma are cut through, and the anterior jugular veins are tied as in all the other methods. These vessels must be tied and not merely seized by pressure forceps. There is no necessity to overcrowd the neck with a collar of pressure forceps which some people consider to be an indispensable embellishment for an operation for goitre. We prefer to ligature as we go along. The operation is

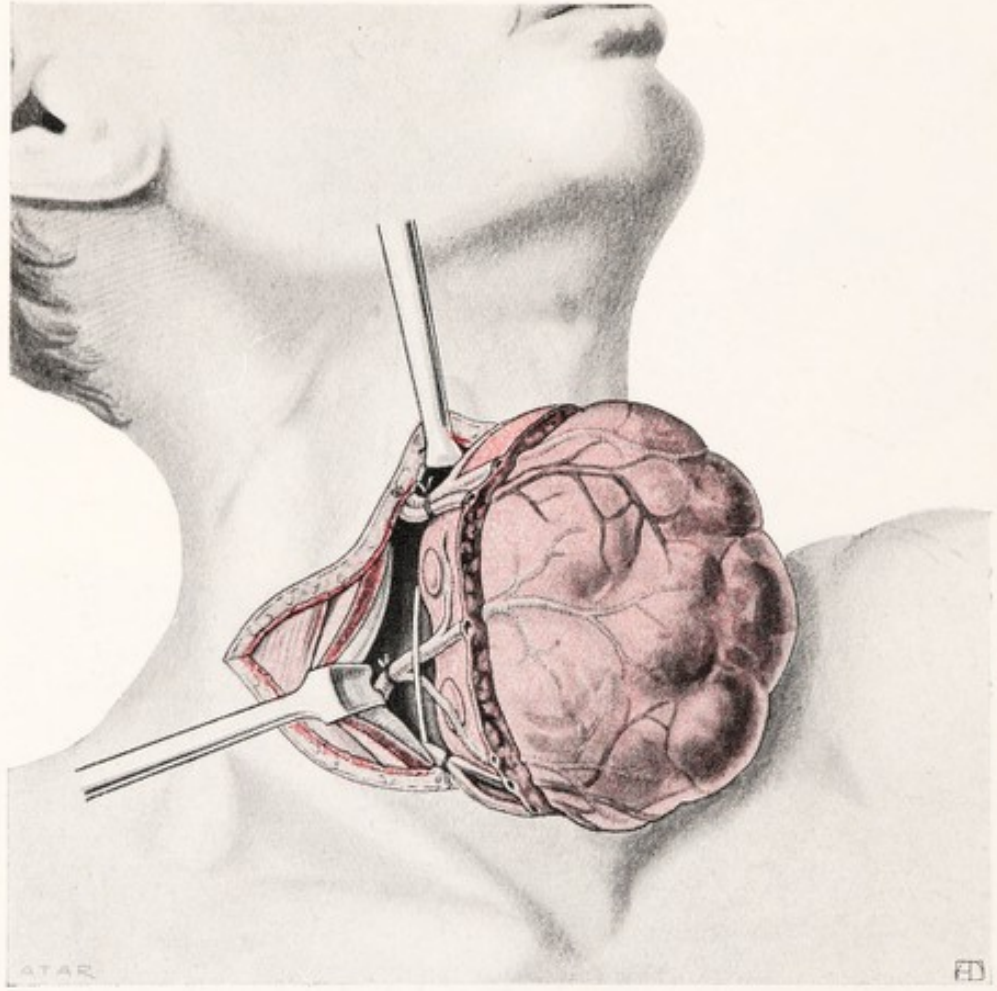


FIG. 92.—Illustration of the anatomical relations of the posterior surface of the lobe in a case of intra-fascial ligature of the inferior thyroid artery. The vessels of the upper pole are tied. The recurrent nerve and the parathyroids are seen.

facilitated when encumberance is absent and the patient is saved a useless nightmare.

When the edges of the sternomastoid and the fascia of the small muscles have been freed, we can decide which side to attack first. The considerations which should guide us will be explained later on. Instead of advancing on the gland immediately, according to the time-honoured procedure, all the preparations for ligature of the inferior thyroid artery are first made. This ligature is uni- or bi-lateral, varying

according to the indications mentioned above (fig. 85-7). Anyone who has seen this method in practice can testify to the ease with which the artery is exposed. This ligature guarantees a much easier operation from the start than that of immediate dislodgment, and affords a secure protection for the parathyroids and recurrent nerve. After this ligature is tied, we enter the thyroid space. In order to do this the small muscles on the convex surface of the goitrous lobe must be

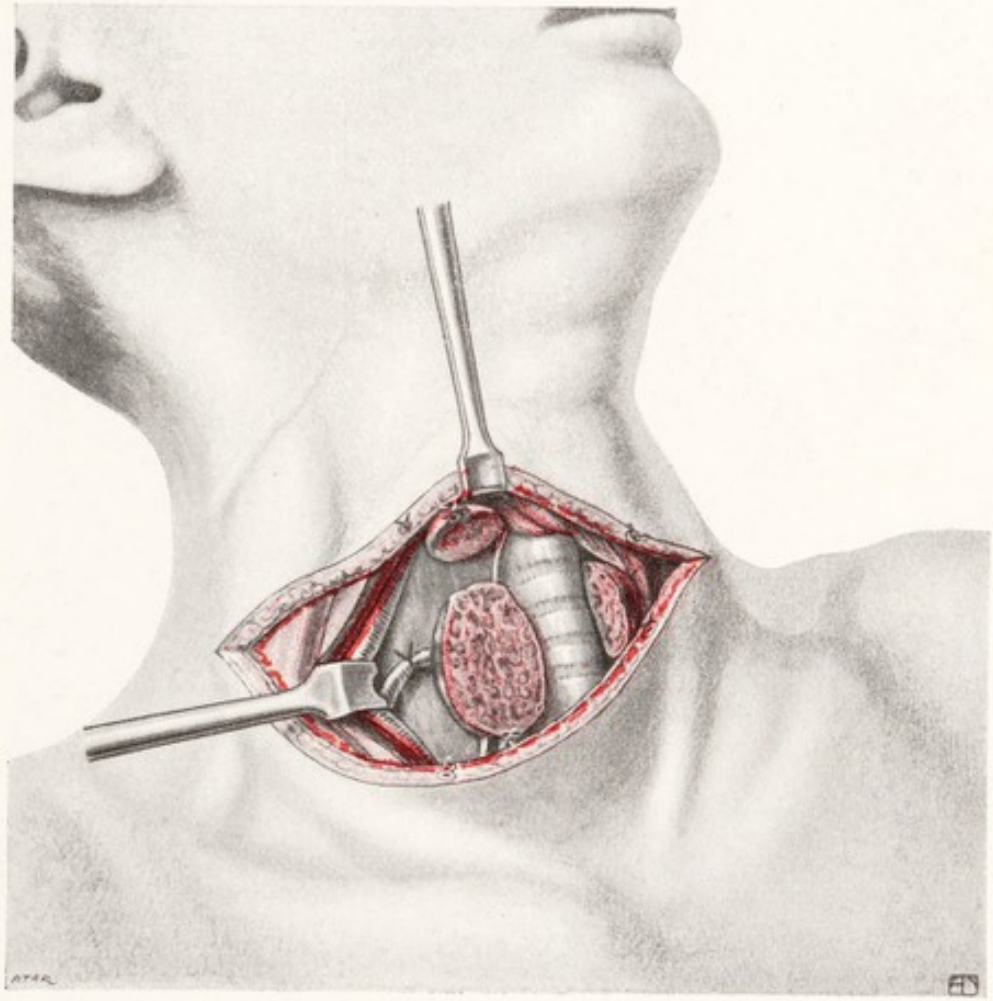


FIG. 93.—Excision of lobe with ligature of the isthmus; a small portion of the tissue at the upper pole and of the posterior surface is retained. (This procedure is better than a complete hemithyroidectomy.) We ligature the isthmus in one piece instead of in several separate sections.

cleared away. Then we make an incision in the internal layer of the aponeurotic sheath, a layer corresponding to the fascia of the thyroid and sometimes called "the external capsule." This layer is extremely thin; in some cases it may be thicker, but in others it is scarcely visible. We may be sure that we have gone through it if there is no other connective tissue thickened into a layer, which can be lifted off

the thyroid. We then follow the antero-external branch of the superior thyroid artery and tie it near the upper pole, unless we ligature the whole of the upper pole forthwith. When this is done, the next step is to dislodge the goitre, a measure which has been facilitated by the cutting off of a considerable portion of the blood supply. To effect this, we free the entire lobe from its connections with the thyroid fascia (external capsule), with the exception of its posterior surface.

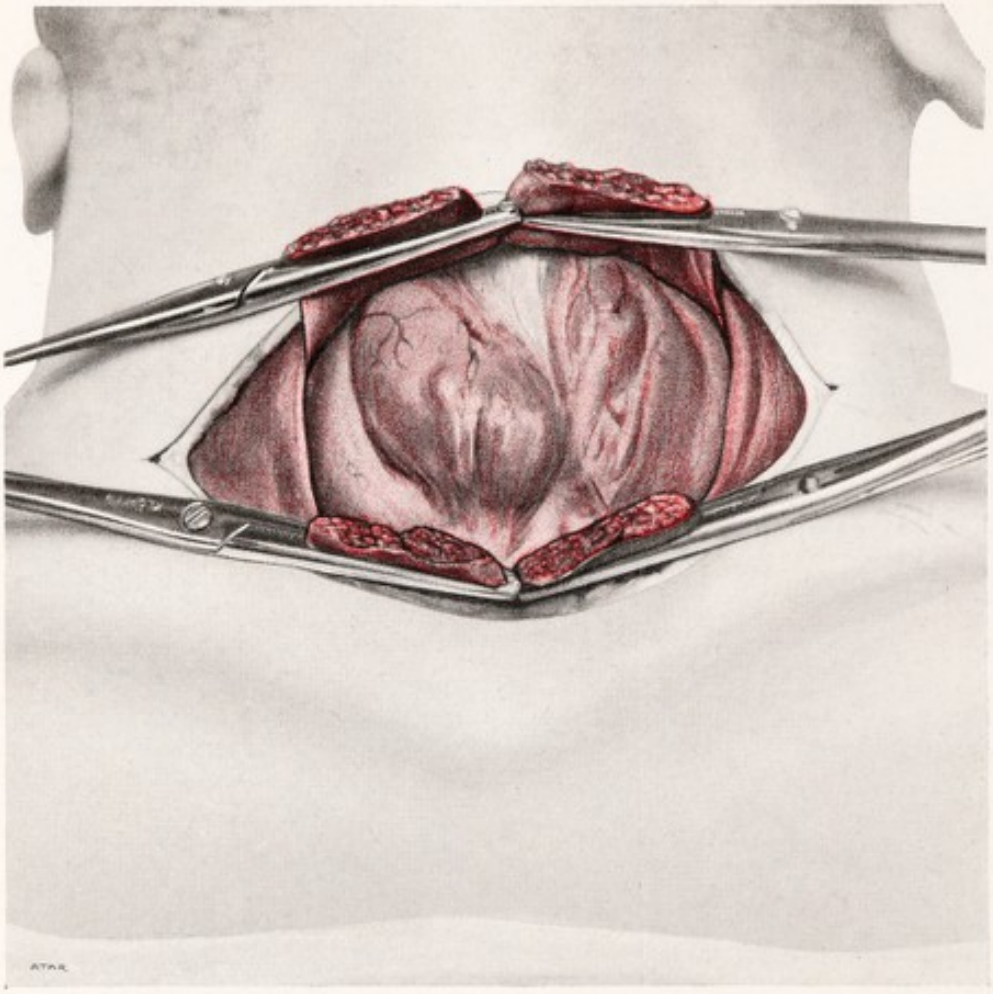


FIG. 94.—Complete exposure of the goitre. The small muscles, held by the forceps, are cut transversely. The thyroid is covered by thyroid fascia (external capsule).

These posterior connections are treated with respect, so as to avoid the risk of injury to the recurrent nerve or the parathyroids. There is no difficulty in dislodging the lobe; in most cases it is a matter of the greatest simplicity. It is not quite so easy, if the lobe is fixed behind the cervical viscera (retrovisceral goitre, retrotracheal), or if its lower pole extends into the throracic cavity (deep goitre, retrosternal).

The dislodgment is facilitated considerably by the following manipulation, suggested by Perthes. A loop of stout thread is passed

through the tissue of the lobe, in order to serve as a tractor. It acts better if, instead of merely being passed through once, it is made to traverse the tissue of the lobe two or three times, as shown in fig. 90. The first point is fixed at the level of the middle of the lobe, and the threading is continued towards the lower pole in such a way as to gradually draw it towards the surface. Afterwards the two ends of the thread are tied together. If traction on the thread is not enough

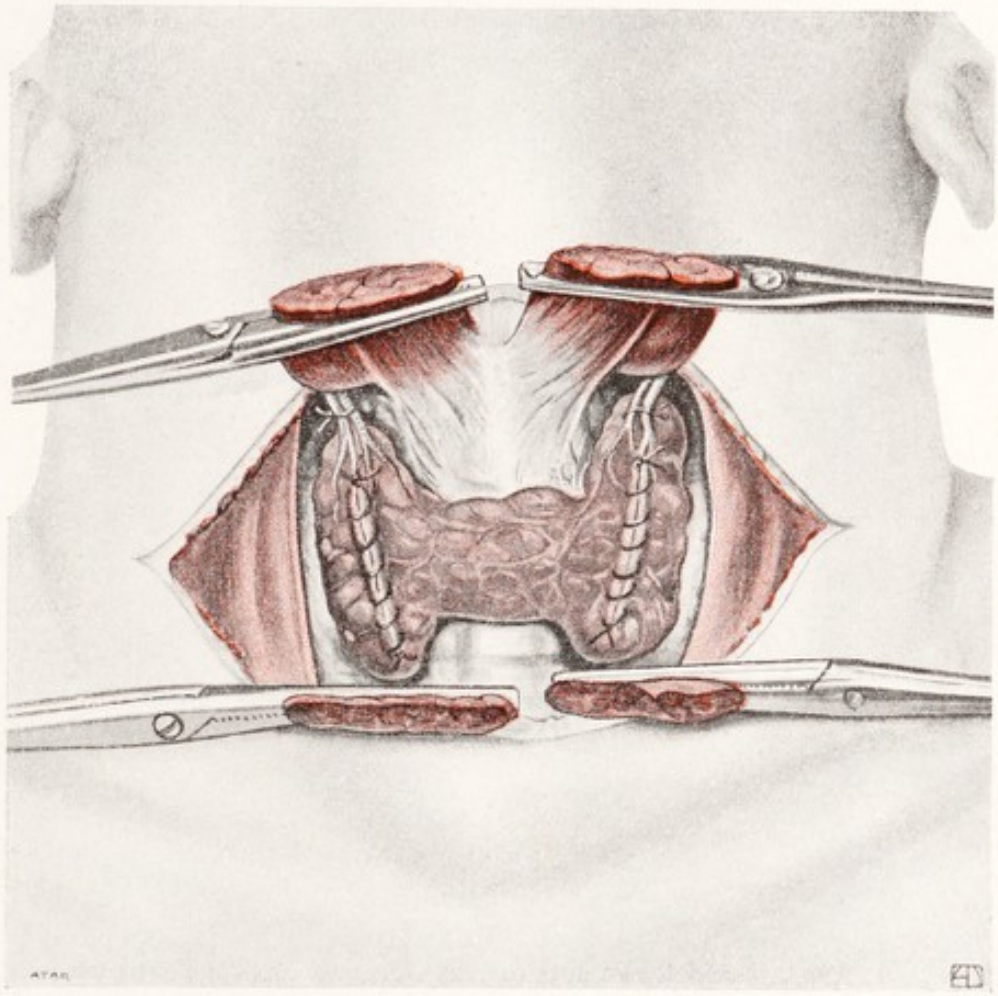


FIG. 95.—Appearance of the gland after the lobes have been reduced in size by the "melon slice" method. The isthmus is preserved either entirely or partially, according to its size.

to dislodge the lobe, the index finger should be carefully insinuated under the lower pole, or Kocher's scoop (fig. 73) may be used, and success is certain. The process of delivery demands much patience and care in cases of true retrosternal goitre, where most of the goitrous tissue is in the thoracic cavity and may even lie on the auricles of the heart. The venous hæmorrhage which may set in at this stage is of no importance as long as the two arteries have been carefully ligatured

beforehand. It can easily be stopped by a temporary plugging. The dislodgment of the goitre is complicated in some cases by its extreme lobular character. Here the root of the vessels and also the recurrent nerve running between two nodules can be seen. Unless the greatest care is taken, there is a risk of injuring the latter. The actual dislodgment is greatly facilitated by cutting the small muscles transversely. However, the more these are cut, the

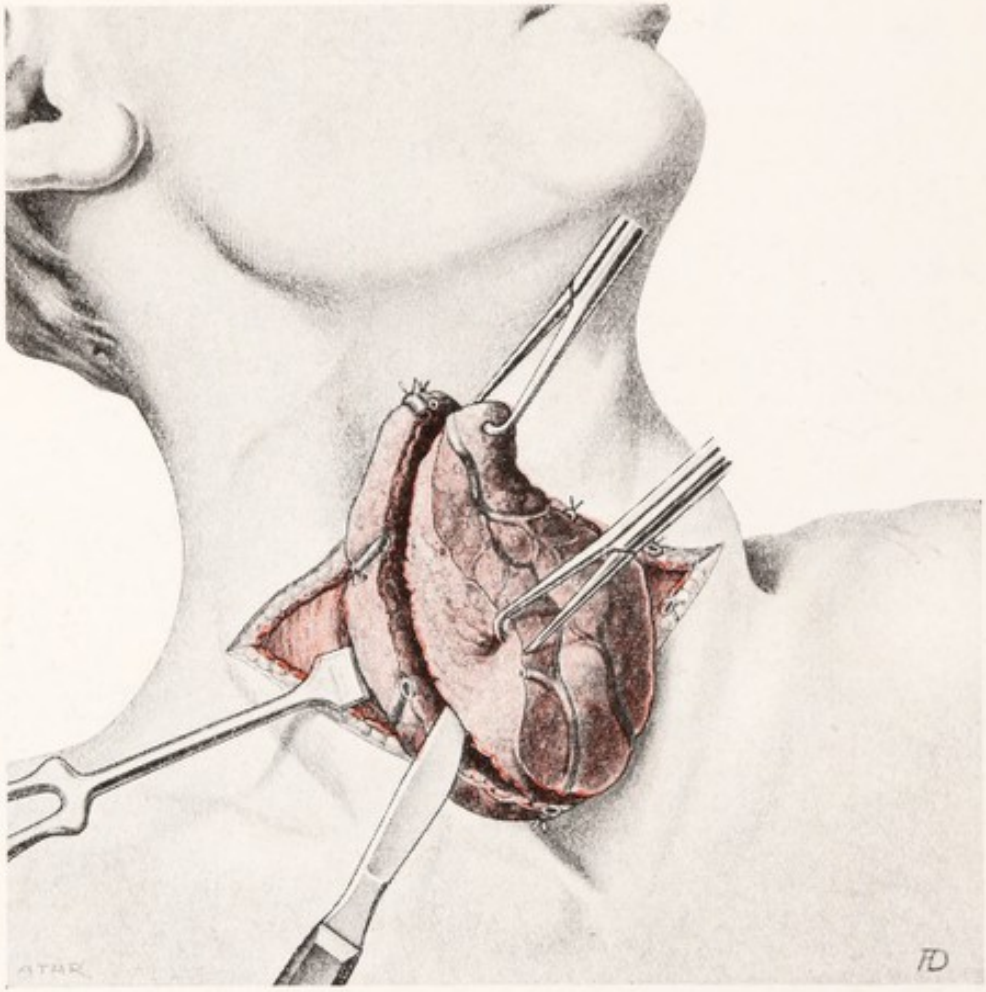


FIG. 96.—The left lobe brought outside the wound and resected by the "melon slice" method.

greater the injury to the contour of the neck. Even the suture of the divided muscles does not entirely overcome the difficulty. The inexperienced surgeon will find more occasion to cut the muscle than the surgeon who is used to the operation. The partial cutting of the sternomastoid, which is a totally unnecessary and injurious proceeding, in cases of extrathoracic goitre, is often a great help in the dislodgment of a large intrathoracic goitre.

We have supposed hitherto that the ligature of the superior thyroid

artery or its principal branch has been successfully tied before the dislodgment of the goitre (fig. 88). However there are always some cases where the upper-pole is very high and the retractor placed in the direction of this pole does not afford a sufficient space. In such cases it is better to dislodge the lobe before proceeding to ligature the upper pole; then no damage is done to the veins or recurrent by attempting to tie ligatures where it is impossible to see them.

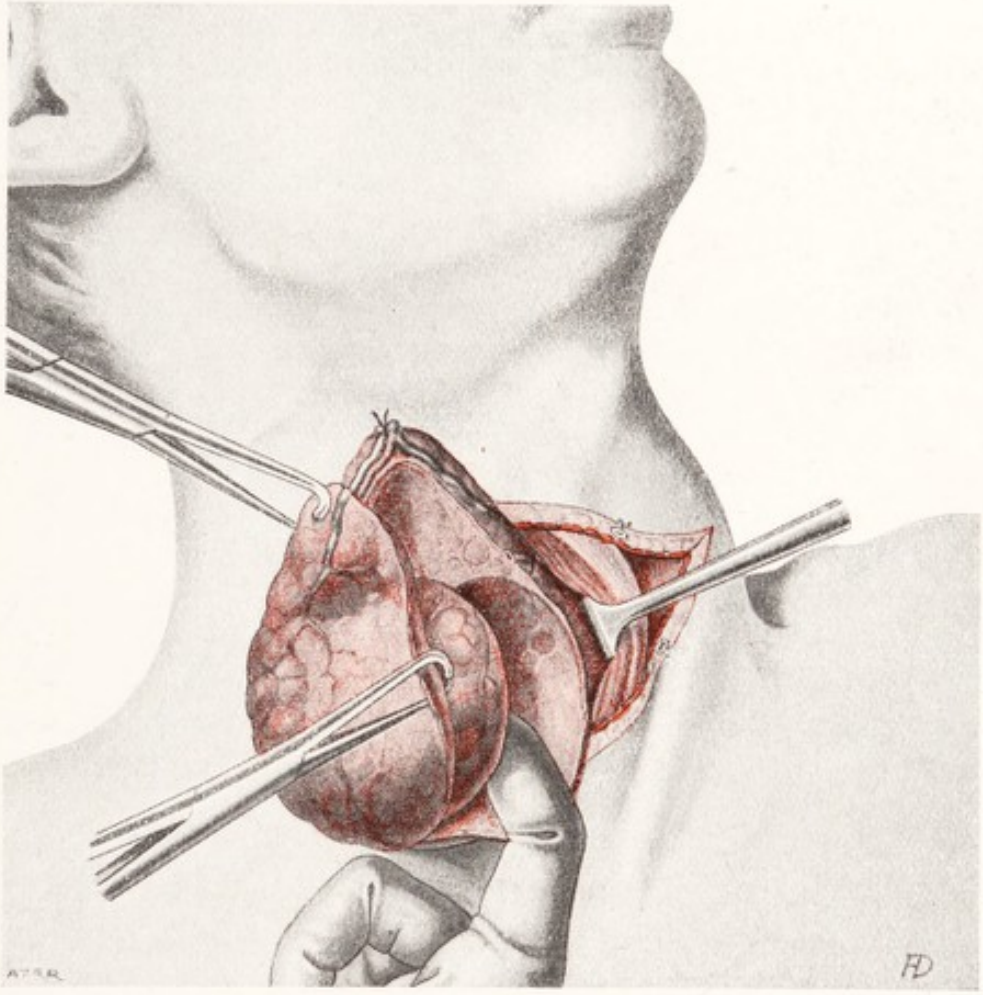


FIG. 97.—Ditto, resection enucleation.

An examination and palpation of the lobe upon exposure will indicate at once whether resection enucleation or a combined operation should be performed.

(a) *Resection.*—In a case of very enlarged, diffuse, parenchymatous or colloid goitre (fig. 96), or in a case of a collection of small nodules, *resection* is the only possible method of operation. It should be done by the "melon slice" method, otherwise a very irregular shape will be imparted to the gland whether the operation is confined to the lateral lobe, or whether a part of the isthmus is included in the

resection (83 *e-f* and 83 *g-h*). Thanks to the preventive hemostasis, hæmorrhage is of very little importance. Some of the vessels of the posterior surface of the gland may bleed, as well as those of the superior edge of the isthmus, in the angle formed by the lateral lobe and the isthmus, if they have not been ligatured beforehand. The necessary ligatures must be made, and care taken not to come too near to the posterior capsule and the recurrent nerve. We will deal

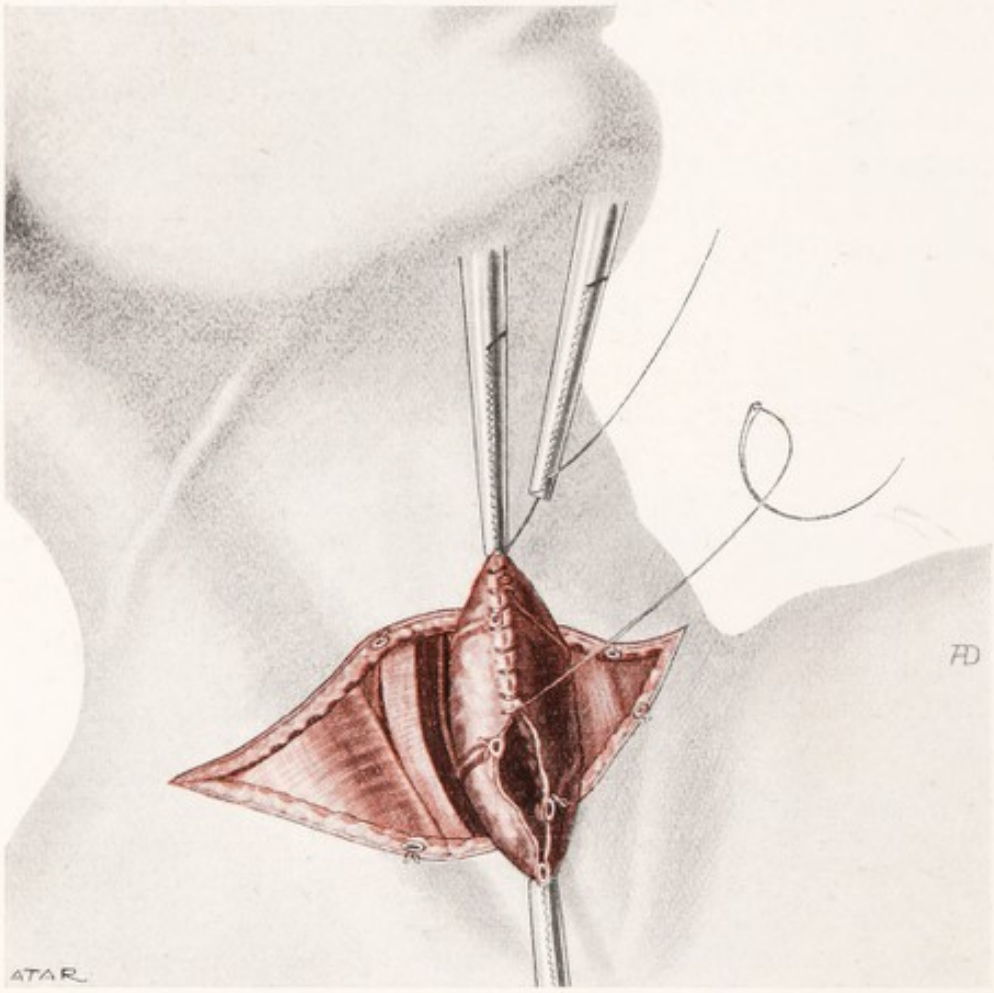


FIG. 98.—Reconstruction of the stump after resection or enucleation by a continuous suture (or separate stitches) of fine catgut.

in a later chapter with the extent to which the thyroid tissue may be reduced. In performing this resection care should be taken to preserve the extremity of the upper pole, in order to prevent any slipping, after the ligature placed on its vessels has been cut.

All bleeding having been arrested, the thyroid wound is closed by a suture of fine catgut, either in separate stitches or continuous suture (figs. 95 and 98). The first intrathyroid sutures are introduced to act as a kind of padding, and then the edges are united if a large

amount of tissue has been removed. After the lobe has thus been reconstructed, the same operation is performed upon the other side. When the condition of the goitre is such that from the first a bilateral resection is indicated, the hæmostatic precautions in regard to the upper pole are usually confined to its anterior branches, so that the two other branches, or at least the posterior branch, may be preserved on each side. Goitres which are particularly vascular in character,

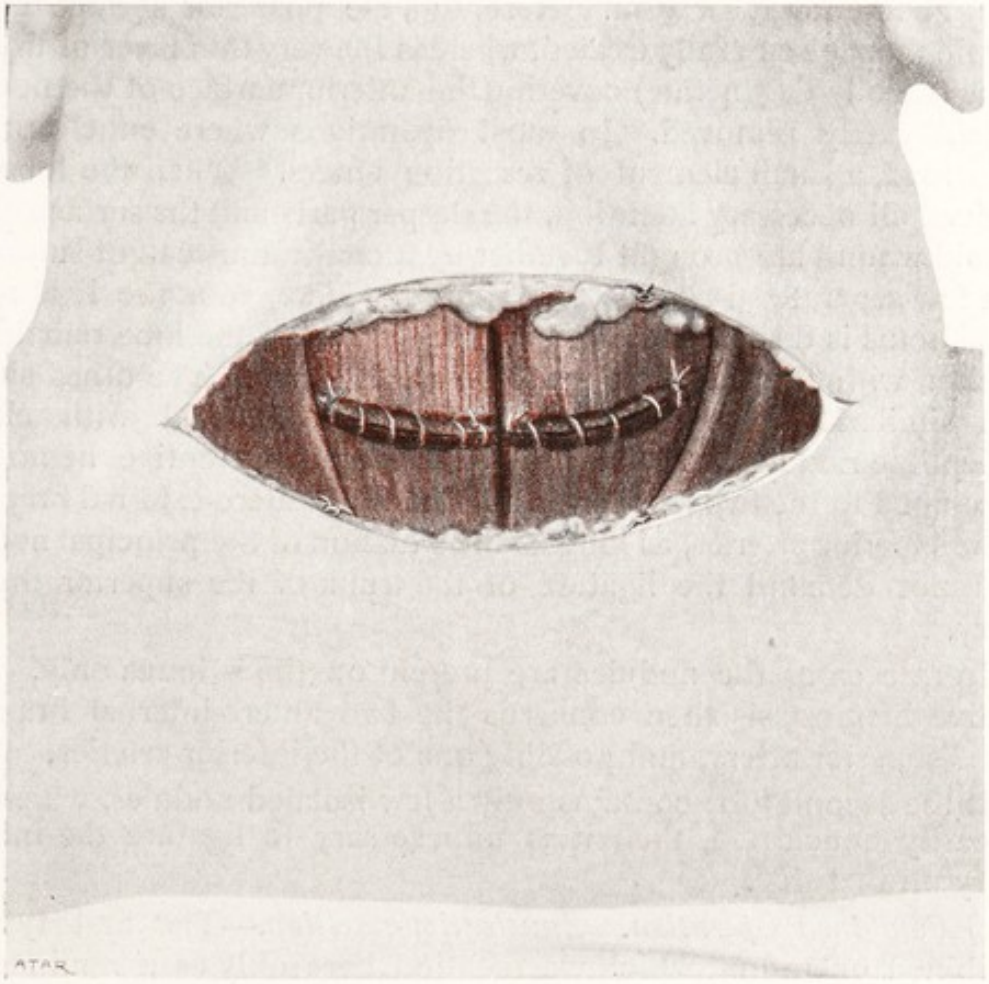


FIG. 99.—Restoration of the muscular plane after the muscles have been cut through.

especially exophthalmic goitres, form exceptions to this rule, because in such cases there is no risk in ligaturing the four principal trunks. The drainage is performed in a manner which we will consider later on.

(b) *Enucleation.*—The method of procedure is quire different if, instead of diffuse or nodular hyperplasia, one has to deal with a nodular goitre where large nodules are present. Enucleation pure and simple is performed wherever there is a limited number of nodules, or a single large nodule. As each nodule is surrounded by a fibrous

shell, derived from the adjacent thyroid tissue, the intrathyroidean plane of cleavage must be found by making an incision to the depth of the nodular substance, whether this be solid or a cyst. In most cases the enucleation is easily performed with the finger (fig. 97) or a pad of gauze. Sometimes, if the preliminary ligatures have not been made, there may be a fairly copious venous hæmorrhage, but if these are secure, or the inferior thyroid artery has been tied, the operation is practically bloodless. Where several nodules are present they should be removed seriatim. Here, too, the posterior surface of the thyroid must be carefully treated, whereas the very thin layer of thyroid tissue (usually degenerate) covering the anterior surface of the nodules is deliberately removed. In most operations where enucleation is performed, a small element of resection enters. When the lobe has received all necessary attention, the deeper parts and the surface of the thyroid wound are brought together by a continuous catgut suture, or by a few separate stitches as in resection. Here, too, the ligature of the isthmus is dispensed with, because the rest of the lobe remains in relation with the adjacent parts of the isthmus. The other side is then similarly treated, if that lobe is also affected with clearly perceptible nodules. In bilateral enucleation, preventive hemostasis is confined to the two inferior arteries and the antero-external branches of the superior arteries, as long as the situation of the principal nodules does not demand the ligature of the trunk of the superior thyroid artery.

In rare cases the nodules are present on the isthmus only. Preventive hæmostasis then concerns the two antero-internal branches of the superior artery, and possibly one of the inferior arteries.

If the second lobe contains only a few isolated nodules, which can be easily enucleated, then it is unnecessary to ligature the inferior artery on that side.

(c) *Combined Operation. Enucleation-resection.*—The first type of combined operation, which we mention here only as a reminder, is the enucleation of one lobe with the resection of the other.

Kocher's *enucleation-resection* is a combination of the two types in the operation on the same lobe. This procedure is indicated when it is necessary to remove goitrous nodules and hyperplastic tissue at the same time, and also where a number of small nodules may be associated with one large one. The exact method of procedure varies according to the individual circumstances of the case. Enucleation is performed wherever it can be done easily, and where the plane of cleavage is clearly indicated, and resection where the degeneration of the goitre is such that the knife or scissors are needed (fig. 97). Hæmostasis is the same as for simple enucleation. In addition it

should be said that it is nearly always the posterior surface of the lobe and the upper pole that contain the most healthy tissue, and so have to be treated with care. The operation may involve one lobe only, one lobe and the isthmus, or both lobes, according to the requirements of the case. The wound is closed in the same way as in resection and simple enucleation.

So far we have supposed that the ligature of the inferior thyroid

FIG. 100.—Suture of the skin. The drainage tube is inserted between two of the superficial stitches.

artery was tied at the commencement of the operation. But, as already stated, there are certain cases in which this vessel may not be accessible, because of the excessive lateral growth of the goitrous lobe, or it may be altogether absent. This being so, in order to expose the goitre immediately, and dislodge it, as indicated above, it is necessary to go beyond the space of the small muscles. The ligatures are then placed according to the necessities of the case in the manner

described in connection with hemithyroidectomy. Here Kocher's advice should be followed, and the ligature of the inferior thyroid artery placed as much to the side as possible. Even then there is nothing to prevent the ligature being made by the extra-fascial or extra-muscular route—though this would be a roundabout route in most cases.

(7) The Treatment of the Isthmus.

This isthmus is sacrificed, or, at any rate, cut through in hemithyroidectomy, resection, and resection-enucleation, by most surgeons, and it is only in the operation of enucleation that it is untouched as long as it does not harbour the nodule which is to be enucleated. Personally, we always endeavour to spare it if it does not actually participate in the actual goitre. Even in those cases wherein we diminish the size of the goitre by resection or enucleation, we try to preserve some part of the isthmus for the following reasons:—

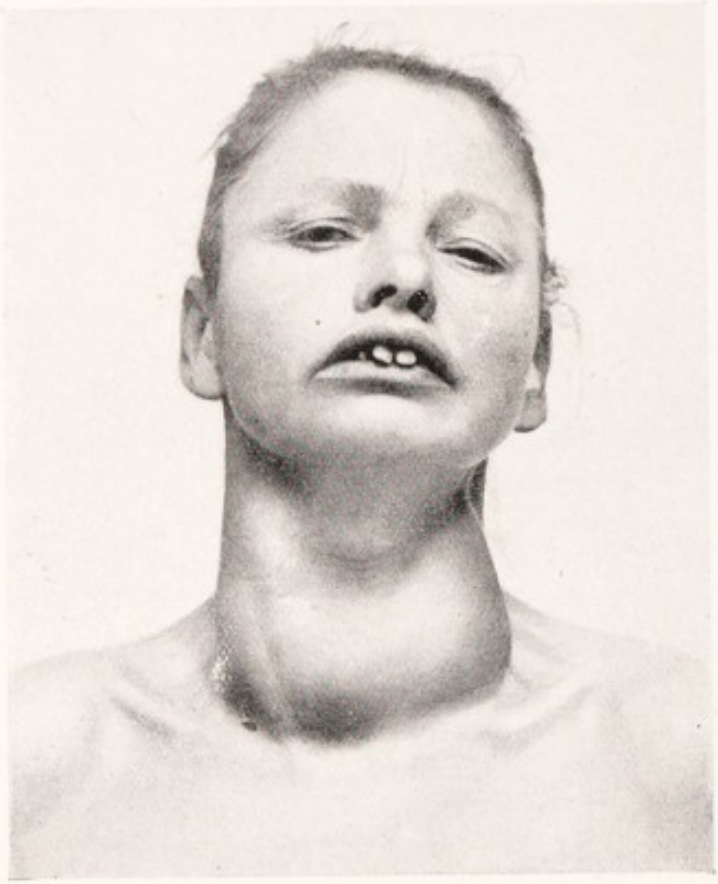


FIG. 100*a*.—Nodular diffuse goitre with small nodules. Case treated by resection of both lobes in one piece, and of the isthmus (see figs. 100*b* and 100*c*).

The isthmus acts as a protector to the trachea, and by taking away this support the trachea is liable to collapse into the shape of the sheath of a sword. We have not seen this happen very often, and we attribute this circumstance to the fact of the preservation of at least a portion of the isthmus.

The preservation of the portion of the isthmus attached to the trachea guarantees its normal circulation. If we strip the isthmus off the trachea, there is a risk of setting up circulatory disturbances in its mucous membrane, which are better avoided.

There is also an æsthetic reason for this proceeding, for the isthmus, in addition to the small perithyroid muscles, fills up the space above the sternum and gives shape to the throat. Removal of the isthmus causes an unsightly depression which patients do not appreciate. We therefore exert every endeavour to retain for the isthmus its triple rôle, and if we are compelled to diminish its size we do so within the imperative limits, scarcely ever removing it entirely. We also safeguard the connection between the isthmus and the posterior capsule of the resected or enucleated lobe, and we secure this contact by means of the suture which is used for reconstructing the lobe.

The operations of *isthmotomy* and *isthmectomy* have been recommended by Sydney Jones, Diel and Allan. We, however, look upon these procedures merely as methods for liberating a trachea which is compressed by a goitre of the isthmus, and isthmectomy should be reserved exclusively for goitres which spring from the isthmus.

We have followed the functional results of preserving the isthmus in 250 cases. In twenty-nine of these it had been diminished in size by enucleation or resection, but was never removed completely. There was not one instance in which this conservative treatment of the isthmus was responsible for the persistence of the pre-operative respiratory troubles, among the few cases which were not relieved by the operation (cardiovascular disease, recurrence of goitre).

(8) Selection of Lobe to be operated on first.

The clinical examination comprises palpation, laryngoscopy, radiography, an accurate determination of the condition of the trachea, in regard to the lobe or nodule which is compressing it. In doubtful cases decisive information will be yielded by skiagrams taken anteriorly and in profile, as already mentioned. These two plates should always be consulted before the operation, even in those cases wherein inspection and palpation appear to lead to unequivocal conclusions. This precaution is never superfluous, because it is never possible to exclude error absolutely. A skiagram may show that the trachea is being compressed at a spot which was not suspected clinically, possibly even in the thorax. We have encountered unexpected surprises in some cases where we have dispensed with a radiographic examination, from motives of economy.

The following are the actual conditions which may occur:—

(*a*) The width of the trachea is normal, or nearly so, in both directions.

The course to be adopted depends upon the results of palpation.

(*b*) The trachea is compressed or is deviated, or is both compressed and deviated at the same time in one direction.

The compressing lobe should be operated on first, whatever be the results of the palpation.

(*c*) The compression is double and alternating, and imparts to the trachea the shape of the letter S.

The lower lobe is operated on first.

(*d*) The compression is in an anteroposterior direction.

The side from which the compressing nodule appears to arise is operated on first, unless it originates in the isthmus. In such rare cases the two antero-internal branches of the superior thyroid are tied, and the isthmus is dealt with directly.

FIG. 100*b*.—Anatomical specimen obtained by resection of the two lobes and isthmus in one piece. Anterior surface. The posterior surface of the two lobes and of the isthmus was retained.

(*e*) The seat of the compression is retrotracheal.

The side which is clinically the larger is operated on first, unless a slight lateral deviation of the trachea affords a more precise indication.

(*f*) Radiography and palpation show that the trachea is bound down in a mass of diffuse goitrous tissue, and that the compression is equal on both sides.

It is in this type of case that it is always necessary to tie one or even both inferior thyroid arteries. It is a matter of indifference on which side the operation is begun.

It follows from what has just been said that the information given

by clinical examination and by radiography is so definite that there can never be any doubt as to which side to submit to operation first. The preliminary ligature of one of the inferior thyroid arteries before the goitre has been exposed is not such a blind procedure as it would seem at first sight, and nevertheless there are some experienced surgeons who expose both lobes completely before applying any ligature, and indeed before deciding upon their plan of operation. This method would be justified and even preferable to our own if the actual inspection of the gland revealed anything about the

FIG. 100.—Same specimen, posterior surface.

anatomical condition of the trachea which could not be ascertained by palpation or skiagraphy. But this is not the case. An absolutely precise knowledge of the condition of the trachea could only be obtained by a kind of anatomical preparation of the goitre *in situ*, which would involve very much more operative injury, and even then the inflammation would be falsified by the cutting of the small muscles and thus removing an important element in the compression of the trachea. We do not wish to minimize the importance of inspection during the operation, but this is no substitute for a skiagram which,

if taken under proper conditions, is alone able to estimate all the factors of the case including the effect of the muscles. The skiagram which is taken as the basis of the operation meets all the necessary precautions and gives more reliable information of the state of the trachea than inspection during the operation, when that structure is no longer subject to the compressing action of the muscles and is altered in its position by the manipulation for dislodging the goitre. The truth of this point of view is confirmed by every operation on a goitre which is compressing the trachea.

The first inspection of the goitrous gland will give immediate information concerning the anatomical characters of the tissue ; diffuse parenchymatous, colloid, nodular, &c. It may seem that we are judging a case before knowing all the facts, in adopting the method of ligaturing the inferior thyroid before exposing the goitre, but this is not really so. The diagnosis of diffuse goitre, and especially of vascular goitre in which the preliminary ligatures of the arterial trunks are particularly useful, can be made definitely before exposing the diseased organ. The preliminary ligature is attended with the same advantages in goitres which are partly diffuse and partly nodular as in those which are composed of a congeries of small nodules. In no case can the ligature of the inferior thyroid be considered as superfluous, and the fact that this artery is occasionally very large in simple nodular goitres (we have seen it 1 cm. in width) is ample justification for this measure of precaution. A certain amount of doubt may arise in cystic goitres, the diagnosis of which is almost always made before the operation. In these cases the gland may be exposed first, and then if it is decided to ligature, the extrafascial or the intrafascial route may be chosen according to circumstances.

Although we advise that the operation should begin with a preliminary extrafascial ligature of the inferior thyroid we do not wish to exalt this into a rigid rule. We merely desire to indicate a method which in our opinion greatly facilitates the performance of the operation and pays due regard to the anatomy and physiology of the thyroid and parathyroids ; but it is a method which may be discarded whenever there is any good reason to adopt another. Experience in all methods of the operation, including extensive exposure of the gland, has impressed us with the fact that a better view of the tout ensemble of the gland can be obtained when the two inferior thyroids have been tied as a preliminary measure. No possible harm can be done by this because the two superior thyroids by themselves are more than enough to guarantee the vitality and the functions of the entire gland.

How is the exploration of the goitre to be carried out during the operation ?

This may be done in one of two ways. We have already men-

tioned one; the extensive exposure of the whole goitre after the transverse section of the small muscles, with or without dislodgment of the entire goitrous mass outside the wound. The disadvantages of this method have already been pointed out. The operative injury is increased, and the anatomical and physiological relations of the trachea are disturbed. We prefer the following method. We cut through the small muscles over each of the lobes and incise the thyroid fascia. We then introduce the finger into the thyroid space and endeavour to feel round each lobe, particularly at the level of the lower pole. This procedure which in no way interferes with the anatomy of the part often adds some useful information to that which has already been derived from clinical examination and from the skiagram. This method does not prejudice the procedure of preliminary ligature and does not come into conflict with the important vessels in an ordinary goitre if it is carried out carefully. But we should not employ this manipulation in cases of large goitre with Graves' disease, nor in the very vascular fleshy goitres met with in adolescents. There is a risk of hæmorrhage in these cases, and the exploration of the thyroid space may start very profuse bleeding, especially from the veins. In these circumstances digital exploration should not be practised until after the inferior thyroids are tied.

(9) The Question of Uni- or Bi-lateral Operation.

After the disastrous results of complete removal of the thyroid became evident, surgeons became attracted to the operation of hemithyroidectomy, i.e., the unilateral operation. Kocher always adhered firmly to this principle, even after he had abandoned the practice of excising the entire lobe, and had adopted in most cases the more rational operation of enucleation-resection. But the frequent recurrences of the goitre, both anatomically and clinically, on the side which had not been operated on turned the thoughts of surgeons once more to the bilateral operation in a modified sense. This operation did not comprehend the complete removal of the whole gland, but enucleation, resection or bilateral enucleation - resection. Brunner was one of the first to emphasize the importance of this method, and his work appeared in 1900. Since 1911 we have ourselves adopted this view, and more than half of our cases of goitre now undergo the bilateral operation. In other words, we endeavour to remove all tissue which threatens to cause a recurrence in the immediate or remote future. There is no doubt that this treatment of the gland diminishes the number of recurrences, but its success is not uniform at all age periods. The younger the patient, the more likely is it that the gland contains foci of recurrence which are unrecognizable at the operation. Recurrence is therefore comparatively frequent among the young however thoroughly the operation may have been performed. In older patients the power of the gland to

develop recurrences seems to have become exhausted and the result of operation is definitely better. In our last series of sixty cases of operation for recurrence, the primary operation had been done in fifty-nine of these before the patients had reached the age of 41.

We perform the complete bilateral operation on young subjects, but are not very enthusiastic about the future, we are much more hopeful when the patient is of middle age; but we do not perform this operation on the aged. The latter only require to be relieved of a nodule which is annoying them at the moment, and this must be done with as little risk as possible. There need be no anxiety about small nodules in the other lobe, and they may safely be left alone. Although we are strongly in favour of the bilateral operation, we readily recognize that there are cases wherein the unilateral operation is indicated. Sometimes the choice of operation may be open to doubt and the decision will depend upon the temperament and personal experience of the surgeon. The difficulty of the problem is increased in the case of young subjects by the fact that the operation for the recurrence of a goitre is a much more troublesome procedure when the primary operation has been bilateral, than when it has been unilateral. Roux has emphasized this circumstance justifiably, but the weight of this objection must not be exaggerated. We have operated in a large number of instances of recurrence, upon the lobes previously operated on, and despite the difficulties which may arise, we still adhere to our view that the bilateral operation is preferable. This question is however closely associated with the following.

(10) How much Thyroid Tissue may be Removed?

Experimental investigation has shown that at least three-quarters of the gland may be removed without causing hypothyroidism, as long as the gland tissue is healthy. In most goitres, however, the functional value of the thyroid tissue is diminished, whether they be diffuse or nodular. It is therefore necessary to be the more sparing with the gland, the more diseased the organ appears to be.

The functional value of goitrous tissue ought to be estimated by the data of the pathological physiology of goitre; but our knowledge of the subject is still incomplete, and we are still awaiting the accurate results of biological experiment and of the study of respiratory exchange. The following are the conclusions which are derived from the experiments of Graham, Wegelin, Abelin, Plummer, Boothby and Wilson, and from our own investigations conducted in association with Messrs. Doubler, Hara and Branovacki :—

(1) *Diffuse Colloid Goitre and the Diffuse Parenchymatous Goitre of Adults.*—In these cases an extensive removal of thyroid tissue is

permissible, especially where there are symptoms of hyperthyroidism, including an increase of tissue exchange.

(2) *Large Diffuse Goitre of Puberty, usually Parenchymatous.*—If these cases do not improve under iodine, a considerable amount of the gland may be removed, even in the presence of certain symptoms of hypothyroidism and when examination shows there is no increase of respiratory metabolism. Our own experience on this matter coincides with that of M. Hotz. One should, however, be very cautious in operating on those cases wherein the rate of this exchange has been lowered from the onset of the disorder.

(3) *Nodular Colloid Goitre.*—The functional value of the gland in these cases appears to be greater than in adenomatous goitres. If the respiratory exchange exceeds the normal limits, the amount of thyroid tissue removed may be more extensive.

There are still two other points to mention, the one being compensatory to the other. The one is the fibrotic degeneration which may occur in a part of the tissue included in the goitre, and the other is regeneration of thyroid tissue upon which we may rely, especially in young patients.

We endeavour to take these two factors into account when leaving in each lobe an amount of tissue equal to that of a normal lobe, if the tissue appears to us to be healthy. As the normal gland weighs 25 to 35 grammes, the volume of a lobe is roughly equivalent to that of the thumb of an average individual, and in our opinion this is the minimum amount which should be left. We generally leave more than this in nodular goitres, especially in those of an adenomatous type.

One might be able to discount the chances of a recurrence if one could be sure that the administration of very small doses of iodine continued for many years, with suitable intervals, would succeed in preventing the formation of new goitrous tissue—assuming that the patient submitted to this precaution. Perhaps these conditions will be realized one of these days in countries where goitre is endemic, by the establishment of a general anti-goitrous prophylaxis (see Chapter XX). Unfortunately, there is a risk of Graves' disease in adopting this post-operative iodine treatment in patients over 40 years of age.

(11) Preliminary Hæmostasis.

Perhaps we may refer very briefly to the reasons for our advice to ligature the inferior thyroid artery at the beginning of the operation. Ever since operations on goitre have been undertaken, it has been realized that this preliminary hæmostasis is of the greatest importance, and the hæmostasis should be carried out as far away from the goitre

as possible. For this reason, Billroth and his school (Drobnik, Woelffer, Rydgier, &c.), endeavoured to reach the inferior thyroid artery outside the vasculo-nervous bundle, and Kocher, in 1883, adopted the method of ligature outside the thyroid fascia. The experiments made on the cadaver by Reverdin in 1898, and subsequently by Delore and Alamartine, had the same object in view, the ligature of the inferior thyroid to the outer side of the great vessels of the neck being a useless complication in the majority of cases. It is so easy to dislodge the goitre in most cases of nodular goitre—even if they are very large, and especially when the patient is over 40, that it is quite unnecessary to encumber the operation with any preliminary complicated step. The great justification for the preliminary ligature which we practise is its simplicity; it usually takes less time to perform it than to describe it. Moreover it facilitates the removal of the goitre, especially in difficult cases. In order to realize the advantages of blocking the principal arterial supply outside the whole venous network of the thyroid, one has only to think of the diffuse, fleshy, highly vascular goitre in adolescents, of the goitre which is partially intrathoracic and is pressing on the jugular veins and which causes the venous blood to pass through an extensive collateral network just above the thorax, and especially of certain very vascular exophthalmic goitres where the bleeding is persistent. These are the cases which many surgeons hesitate to operate on, and some even assert that operation is contra-indicated. But if the inferior thyroid is ligatured before the veins are interfered with, the rest of the operation will proceed without difficulty. If, in addition to the ligature of the inferior thyroid, the upper lobe of the gland is tied *in situ*, it will facilitate the disengagement and dislodgment of all highly vascular parenchymatous goitres, situated more or less behind the sternum. The goitre gives way easily and yields to the pressure of a finger passed beneath the sternum. The fear of being unable to reach the inferior thyroid in retrosternal goitres is very often unjustified. The retrosternal portion developed at the expense of the inferior cornu, often presses the inferior thyroid upwards, in such a way that its position is often much higher than normal.

The *unilateral* operation usually requires ligature of the inferior thyroid and one of the branches of the superior thyroid, if the vascularity is only moderate in amount, but if the goitre is very vascular the trunk of the artery itself must be tied.

The *bilateral* operation on a *diffuse* goitre requires the ligature of both inferior thyroids and the two anterior or antero-external branches of the superior thyroids, unless one prefers to ligature one of the superior thyroids completely, as is our practice when operating on very vascular goitres. We do not scruple to tie the four arteries, especially in the very vascular goitres of Graves' disease.

In performing the *bilateral* operation on a *nodular* goitre, we always tie the two inferior thyroids, but spare one or two branches of each superior thyroid in order to ensure sufficient blood-supply for each lobe.

When the character and shape of the goitre demand the ligature of the two inferior thyroid arteries, we strongly urge that the one should be tied immediately after the other. The more complete depletion of the gland which results from this double ligature facilitates all the subsequent manipulations.

It will be of interest to place before the reader a table showing the number of ligatures—most frequently preventive—of the large arterial trunks, in our last 1,000 operations.

Number of ligatures ...	0	½	1	1½	2	2½	3	3½	4
Number of cases ...	14	25	66	345	143	92	209	95	12

This shows an average of 2·15 arteries ligatured in each operation. The figures also show that we do not recklessly resort to the ligature of all the arteries at once, as we have only employed this method in 1·20 per cent. of the cases. The tying of three and a half arteries is also exceptional, as it was only practised in 9·5 per cent. of the cases. We tied the inferior thyroid *after* the dislodgment of the goitre in fifty-four cases, i.e., internal to the small muscles, and not in accordance with the method we usually adopt.

These figures also acquit us from the charge that we risk the ultimate function of the gland in order to secure a bloodless operation.

The preliminary ligatures of the principal arteries are most essential in cases of highly developed vascular goitre, whether this is due to hyperthyroidism (toxic) or not. This type occurs largely in countries where goitre is endemic. It differs entirely from the diffuse colloidal goitre of the countries where the endemic type is rare. This colloidal goitre, though it may often be due to hyperthyroidism, is associated with a much less developed vascular supply than is usually present in adenomatous goitres—even in cretins. The condition of the arteries and veins does not nearly keep pace with the clinical evidences of the function of the gland. This comparatively limited size of the diameter of the vessels of a colloidal goitre necessitates some modification of the operative technique. The chief vessels are on the surface of the gland, and the interior bleeds but slightly. These facts have been known for a long time, and Mikulicz made use of them when he improved and elaborated his method of resection. They are also responsible for the method of resection, which with a few individual modifications is used by almost all American surgeons.

The goitre which is nearly always diffuse and bilateral, is exposed in its entirety by an incision in the neck, followed by the transverse section of the small thyroid muscles. These muscles are held up on either side at the top and bottom by a pair of forceps placed transversely, and then turned under at each end.

In order to preserve the innervation of the small muscles it is as well to cut them as near as possible to their points of insertion at each end, because the motor nerves approach them laterally and branch in the two directions parallel with the muscular fibres. The cutting of the upper part (Kocher) is preferable in most cases.

Upon complete exposure of the gland the surgeon ligatures the right superior pole, and then puts forceps on the superficial vessels of the right lobe in a circular formation. When this is done the lobe is excised with the exception of its posterior surface. Hæmostasis is secured by the application of forceps to any bleeding vessels. It does not take as long to perform the actual resection as it does to replace the forceps by ligatures. The edges of the remainder of the two lobes are united by a few stitches, so that a small stump is left on either side of the trachea. In cases where the isthmus is completely removed, the edges of the two lobes are brought together by a suture in front of the trachea (Halsted). The strands of muscle are united by transverse sutures on each side, and the cutaneous incision sewn up in the same way. Some surgeons employ this preliminary partial hæmostasis merely as a measure for the temporary checking of hæmorrhage.

We have already suggested that the less method one brings to these operations the greater the skill required by the surgeon. The temporary hæmostasis, involving no ligature of the trunks, should not be practised by the inexperienced, even in cases where the goitre is apparently a simple one, because they are sure to be disappointed in their results. The history of the operation includes some mishaps which are better left undescribed. This method is still less advisable for large goitres in countries where the disease is endemic, for these goitres often contain very large arteries.

(12) The Control of the Recurrent Nerve.

One of the chief objections raised against operations for goitre is that damage is done to the recurrent nerve. This objection is justified by statistics which show from 4 to 14 per cent. of actual injury to the recurrent nerve. The frequency of this accident has diminished since the operation has become more widespread, and hemithyroidectomy avoided. The technique of the operation and skill of the surgeon also have something to do with this improvement.

The nerve may be injured at any part of its course; but the most vulnerable points are where it crosses the trunk or the branches of the inferior thyroid artery, and where it penetrates under the cricopharyngeal muscle. In this part of its course it is in the thyroid space, that is to say, it is ensheathed by the thyroid fascia, a little beyond the middle line and more towards the right than the left. The nerve incurs the greatest danger in the classical operation of hemithyroidec-

tomy, where it can be unwittingly included in the ligature of the lower pole. A hasty or unskilful manipulation of the forceps may crush it on the posterior capsule, either in the operation of resection or enucleation. This accident is most likely to happen in those cases where the precaution of preliminary hæmostasis has not been taken. The nerve is also endangered when the upper pole or the antero-internal branch of the artery is being tied, if this is not done sufficiently free of the thyroid cartilage. It is liable to be dragged upon when the goitre is being dislodged, if it is very large or retro-visceral or intrathoracic. It may also be included in the ligature of the veins of the lower pole, or of the arteria ima, more especially if perithyroid adhesions attach the nerve to the vessels of the pole. The nerve is particularly sensitive to these injuries, however slight they may be, in the female, more especially if stout, and after the menopause (Roux).

No surgeon has succeeded in avoiding these perils completely, and a certain number of cases of paralysis of the recurrent nerve have occurred in our operations. These paralyses may be *partial*, i.e., paralysis of the posterior arytenoid muscle, with the median position of the vocal cord, or *complete*, i.e., paralysis of all the muscles with the intermediate or cadaveric position of the cord. The clinical observations are in general accord with Semon's law, viz., median position of the cord in cases of slight lesion and lateral position of the cord when the lesion is severe or the nerve has been cut right through. These two types are differentiated from the first by their clinical symptoms. In complete paralysis the voice is suddenly lost and becomes exceedingly hoarse. In partial paralysis there is very little alteration in the voice. Often it is so very slight that there is no indication of the mishap if tested by phonation. We always complete this test by making the patient cough. If there is paralysis or paresis of the posterior crico-arytenoid, it is impossible for the patient to produce a clear, dry resounding cough. This test should be made in every case during the operation and subsequently controlled by the laryngoscope. It is of the greatest importance to make sure of the condition of the recurrent nerve after having operated on one side and before proceeding to the other. A complete bilateral lesion will set up aspiration pneumonia, and an incomplete bilateral lesion diminishes the glottis to a narrow slit. Tracheotomy may become urgent, and the patient may be condemned to wear a tube for the rest of his life.

If one of the recurrent nerves has been injured during the removal of one lobe, the other side should not be operated on unless the bilateral operation is absolutely necessary, and the utmost care must be exercised to avoid any retrothyroid manipulation. Great difficulty arises when one of the recurrent nerves has suffered injury in a

previous operation, and the necessity arises to deal with a recurrence on the other side owing to compression of the trachea.

The proposals made for safeguarding the nerve are diametrically opposed to one another. Payr, Hildebrand, Stierlin, Enderlen, and others deliberately expose the nerve. This anatomical dissection presupposes the previous dislodgment of the goitre—a manipulation which the most expert cannot perform without the risk of injuring the nerve by dragging on it. This anatomical preparation is, therefore, no absolute guarantee of immunity—although it saves the nerves from injury by forceps, or from being included in a ligature, or from an inadvertent cut with scissors. Personally we think that the remedy is worse than the disease, because the nerve is so exceedingly sensitive, and practical experience supports this view. It is hardly necessary to mention the risk to the parathyroids involved in such a dissection of the retrothyroid region.

The other method is the one which we adopt. It leaves the nerve in the background by proceeding with great care in the area between the posterior surface of the gland and the region of the inferior thyroid artery. This artery is tied in a different anatomical plane to that in which the nerve runs, and the superior thyroid is also ligatured in a position well away from the nerve. In this way it is impossible to injure the nerve when a ligature is being applied to an arterial trunk. This method also reduces to a minimum the risk of crushing the nerve by forceps on the posterior surface of the gland along the thin layer of thyroid tissue which separates it from the intrathyroid field of operation.

We only expose the nerve if the phonation test during the operation shows us that it has met with an injury. We then have to determine whether the nerve has merely been dragged upon, or has been included in a ligature, or has been cut through. This investigation is facilitated by the slight rhythmic movement imparted to the nerve by the pulsation of the great vessels which surround it before it reaches the thyroid region (Stierlin). This phenomenon is accentuated by slight traction applied to the corresponding lobe.

If it is found that the nerve has been caught in a ligature, it is liberated ; if it has been cut through, it is sutured. Stierlin reports a case wherein suture was followed by a result which was almost completely successful.

The protection which our method of ligature secures for the recurrent nerve can never justify carelessness in this respect. The operator may in certain rare cases encounter a recurrent nerve whose course is abnormal—especially on the right side—and he may meet with it close to the carotid artery, very near the situation where the ligature is to be made. There is no danger from this abnormality, as long as it is borne in mind. The nerve is easily seen in front of or

behind the artery, and the field of operation is sufficiently extensive to avoid any injury to it.

Our method of procedure in regard to the recurrent nerve appears to us to be confirmed by the systematic laryngoscopic examination of our cases.

There is no validity in any statistics if the patients have not been examined with the laryngoscope before and after operation. In a series of 1,000 operations there were partial or complete lesions of the recurrent in thirty-one cases before the operation, and in twenty-nine cases the lesion was caused by the operation, the operative damage thus being 2·9 per cent. These figures include slight and transient lesions due to the dragging of the nerve. Information concerning *definitive* lesions can only be obtained by examination long after the operation. This was done in a series of 250 cases. In 197 cases operated on according to our methods, and examined later on, in only one instance was there a definite paralysis of the recurrent nerve, and this paralysis came on while dislodging a very adherent goitre. The examination in 1915 of 250 cases operated on by different methods yielded the following results : three cases of definitive paralysis of the recurrent, and eight cases of paresis in course of improvement. We should add that this series includes the early cases operated on by the method just described. If the proportion between the immediate lesions and the definitive lesion remained the same, i.e., 3 : 11, it would follow that our latest statistics would show less than 1 per cent of definitive lesions.

(13) The Sympathetic Nerve.

We have already referred to the possible injury of the great sympathetic nerve, and a word or two more on this subject is necessary. We have previously described the relations of this nerve to the inferior thyroid artery. A lesion of this nerve is characterized by the narrowing of the pupil and of the corresponding palpebral fissure. In order to be sure of this sign, the pupil must be sheltered from exposure to broad daylight. It must never be assumed that this syndrome (Horner's) is due to the operation, unless the pupil and palpebral fissure have been examined beforehand. Slight differences in the size of the pupils (from 0·5—1 mm.) are not at all uncommon, as we have shown from the examination of 100 cases attending our clinic, who were not suffering from ophthalmic disease, or any manifest disorder of the nervous system. We noted this phenomenon in eighteen of the series. Slight differences in the palpebral fissures are equally frequent. This was observed in twenty-three cases of the series. Needless to say that the pressure of the goitre itself may cause paresis of the sympathetic.

We are of opinion that the lesion of the sympathetic was due to the operation in 1·8 per cent. of the cases, in a series of 250 examined from this point of view. The frequency of this lesion was 1·4 per cent. in our last 1,000 operations, and was 1 per cent. in our last 400

operations. These figures refer to immediate functional disturbances, but definitive lesions are less frequent.

The great sympathetic nerve is most sensitive to any kind of mechanical interference, and therefore the retraction of the carotid artery must be done very carefully. We have already said that we employ a special retractor which appears to us to be a great security against any damage. Care should be taken not to press the retractor in the direction of the vertebral column, and the endeavour must be made not to tie the artery above, that is to say external to its upper convexity. The position of the interlacing of the cervical sympathetic and the inferior thyroid artery is above the convexity of the horizontal portion of the artery.

(14) The Parathyroids.

Since the importance of these little glands has been recognized, surgeons operating upon goitre have taken great pains to preserve them; but perhaps there is a little too much apprehension on this subject.

Geis has suggested, as a result of his anatomical studies, that the parathyroids should be deliberately dissected out, in order to be sure that they are not injured in the course of the operation. But this very dissection is fraught with great risk to these delicate structures, even if they could be detected in every case and distinguished from little lobules of fatty tissue, or small lymphatic glands, or accessory thyroids which often exist in the retrothyroid region. Histological examination has frequently shown that errors are made by mere naked-eye inspection.

In Halsted's opinion the parathyroids can be avoided by ligaturing the inferior thyroid artery at the level where its branches cross the true capsule of the thyroid (ultra-ligature) and not at the level of the trunk of the artery. This, however, is the very spot where the lower parathyroids and their small nutrient arteries are to be found, and the remedy is therefore worse than the disease. Halsted himself recognized subsequently that it was better to tie the arterial trunks at some distance from the thyroid, and that, in these circumstances, the nutrition of the gland was not threatened even if the four arteries were tied at one time. Our own view of this matter, which was originally based upon theoretical considerations, has been confirmed by practical experience. We have performed simultaneous ligature of both inferior thyroids in 815 cases out of 2,203 operations, and not one of these has been followed by tetany, although this procedure was condemned, as recently as 1912, by Iversen, Kocher, Schloffer, Krecke and Kausch as being dangerous for the parathyroids. Among these 2,203 operations, close observation suggested the possibility of some abortive symptoms of tetany in three cases. One of these operations was performed for a recurrence, and the parathyroids had been partially destroyed in the previous operation. We simply performed an enucleation in this case and did not ligature any artery. The symptoms disappeared in the course of a week. In the second case, only one of the inferior thyroid arteries had been tied and the

operation was unilateral. The symptoms cleared up completely in a few days. The third case was that of a pregnant woman, and the operation consisted of bilateral resection-enucleation, ligature of the right inferior thyroid and of the branch of the right superior and left superior thyroid. There was no left inferior thyroid in this patient. The tetany was so slight that it would have been missed if a close watch had not been kept. After the confinement the symptoms increased temporarily. At the present time—four years after the operation—Trousseau's sign is positive and the patient sometimes complains of abnormal sensations while occupied with her domestic duties. This, therefore, is a case of slight chronic tetany.

It has been suggested that the ligature of both inferior thyroid arteries, or the simultaneous ligature of all the arteries—complete or nearly complete—may be one of the causes of tetany. We have tied three and more arteries in 611 cases and have only had one case of mild tetany, referred to above. The four arteries were tied in 22 cases and no tetany followed.

The removal of thyroid tissue from both lobes has been quoted as a possible cause of tetany. We have performed 757 bilateral operations with only one case of tetany, the same as just mentioned.

It is not the operation which constitutes the danger, but rather the manner in which it is performed. The more arterial trunks are ligatured the more necessary is it to safeguard the collateral circulation of the parathyroids by preserving the connection of these glands with the surrounding tissues and not exposing them. The bilateral operation is only justified on the condition that the dangerous area is not encroached upon. The extent of this area is indicated on the diagram drawn up by McCallum on the basis of 67 autopsies (fig. 1). It is better to be less radical in the operation than to injure the posterior thyroid capsule and the contiguous layer of thyroid tissue in this dangerous area. The following is the brief summary of the rules which are calculated to prevent tetany with almost complete certainty :—

(1) Tie the inferior thyroid arteries external to the thyroid fascia.

(2) Do not interfere with the posterior capsules and the contiguous thyroid tissue over the extent of the dangerous area.

(3) Maintain the connection of this portion of the posterior capsule with the subjacent tissues.

The operation on the first lobe should always be conducted in such a way as if one could not reckon upon the parathyroids of the other side.

Although one can practically guarantee against the danger of tetany in a first operation, there is some risk of its occurrence after an operation for a recurrence, especially if the original operation was a hemithyroidectomy. Later on we shall discuss the precautions which should be taken in such cases.

The remarkable frequency of tetany in certain clinics (especially in Austria, 1 to 2 per cent. of all cases operated on) suggests that there is a local predisposition to tetany, such as exists, according to McCarrison, in some districts of the Himalayas. Cold and malnutrition may act as predisposing factors. McCarrison does not think that there is any racial predisposition; but Wagner and Klinger assert that certain breeds of rats are predisposed to experimental tetany. According to Hammett post-operative tetany occurs more frequently in the wild Norwegian rat than in the white untamed laboratory rat, and more frequently in the latter than in the tame rat. He thinks that this has some association with an increased production of toxins and that for this reason the predisposition to tetany is proportionate to the liveliness of the animal. The fact that there is a local predisposition demands the exercise of specially great care during the operation. Burk, von Eiselsberg and Kraus suggest that the specimen should be examined after each operation for goitre, and to reimplant the parathyroids if they have been removed. This advice should be followed although it will be quite superfluous if one has succeeded in avoiding the dangerous area on both sides.

(15) The Muscles.

The *platysma* is cut through at the same level as the skin and the subcutaneous tissue, and it remains in contact with the latter. For this reason we have long abandoned suturing the platysma at the end of the operation. The less the skin layer is detached from the underlying tissues, the less displacement occurs in the platysma and suturing will therefore be unnecessary.

We have tested this point by examining 250 cases wherein there had been no separate suturing of the platysma, and we can confidently assert that the æsthetic result has not suffered in any way from this deliberate simplification of closing the wound.

The *sternomastoid* must be preserved intact in all goitres, and this can be done except in retrosternal and malignant goitres. In the former cases it will be necessary to detach the muscle from its insertion, either partially or completely, in order to obtain a proper view. The shape of the neck can be restored by accurate muscle suture.

The *small muscles*, especially the *sternohyoid* and the *sternothyroid*, can be easily retracted in most cases. If a vertical gap is made on the right and on the left, it is often possible to carry out the bilateral operation without cutting through any muscular fibres. In other cases it will be necessary to cut through these muscles more or less completely in a transverse direction, and they will require suturing with catgut at the end of the operation. It is most important to restore the muscle planes accurately, in order to prevent ugly adhesions of the thyroid stump and of the trachea to the skin, with an upward movement of the scar with each act of deglutition.

(16) The Difficulties and Unforeseen Contingencies of the Operation.

(*a*) Dyspnœa.

What is the treatment if severe dyspnœa threatening suffocation attacks a patient who has a goitre? Firstly one must make quite sure that the respiratory trouble is really due to the goitre. We have seen patients sent into hospital with the diagnosis of "obstructive goitre" when the real condition has been renal or cardiac asthma, mediastinal tumour, Pott's disease in patients who happened also to have a goitre, but the latter had no connection with their distress. As an instance we may refer to the case illustrated in fig. 65. This patient had been under observation for a long time and was thought to have an obstructive goitre, whereas the true diagnosis was a cold abscess due to a latent spinal caries. A skiagram taken in profile showing the trachea close up against the sternum, immediately suggested to us the probability of cold abscess. Clinical experience and instinct, combined with a rapid examination, will usually put the observer on the right track, providing dyspnœa is not too severe to permit of any examination. If the patient is really suffocating and relief is a matter of immediate urgency, one may be quite sure that goitre is the cause, and not any of the other conditions just mentioned.

The operation must be performed in the position which gives most relief to the dyspnœa. This will generally be the sitting position, or slightly leaning forward, or towards one side or the other. Obviously the operation will be difficult, and the difficulty will be increased by the congestion of the subcutaneous veins which is usually present in these cases. The more deliberately the operation is conducted the more likely is it to succeed. A full dose of morphia should be given, for this often alleviates the dyspnœa and is a valuable aid to the operation. If, however, the condition remains alarming the goitre must be freed rapidly after cutting through the small muscles transversely. This procedure alone suffices to give free play to the trachea; but if this fails the goitre must be exposed after rapidly penetrating the thyroid fascia, and the offending lobe must be dislodged. The vessels which are cut through must be seized with forceps and are to be tied after the goitre is outside the wound. Circumstances permitting, the surgeon should complete the operation according to established methods. But if this is impracticable the operation may be completed with a few ligatures and by fixing the goitre outside the wound with a few sutures. This operation is actually *exothyroprexy* —the hazardous procedure which was suggested by Poncet and described by Bérard—and it thus possesses some application even at the present day. If there is reason to suspect that the obstructing lobule is cystic—and its size is frequently suggestive of this—the

suspicion should be confirmed by a rapid puncture and the trachea should be freed while the cyst is being emptied before dislodging the goitre.

In some cases the dyspnœa continues despite the dislodgment of the goitre, and in others the dyspnœa comes on just at the moment when the goitre is being lifted up. In these cases the trachea is very narrow and shaped like the sheath of a sword; its support is lost and it collapses when the goitre is removed. It is then necessary to pass sutures through the cartilages on the left and right, and thus to separate the collapsed walls and to maintain them in this condition by means of two catgut loops attached to the two sternomastoids. This is however a very uncertain expedient, and it will not often be required if the isthmus is not interfered with during the operation.

It may be that the dyspnœa is too intense to permit of this procedure, and tracheotomy may become urgent during the operation. This contingency is however very rare. Our statistics show one tracheotomy in 400 cases of goitre; but we never undertake the removal of a goitre without having the tracheotomy instruments to hand. If tracheotomy has been done the wound cannot be kept aseptic, and partial plugging will be required. Healing takes place by second intention and complications are not infrequent.

The difficulties caused by dyspnœa can be avoided in certain cases by the use of a high-pressure mask connected with a cylinder of oxygen. This device was suggested by Sauerbach and we have found it very useful. A pressure of 5-8 cm. of water is enough to secure satisfactory breathing. If this device does not overcome the obstruction, the introduction of Meltzer's tube into the trachea should be tried. We have, in this way, successfully removed a malignant goitre from a woman, aged 78, who had an apparently fatal asphyxial attack before the operation. It may be very difficult to introduce the tube into the larynx, and it will always be necessary to cocainize the pharynx and larynx. If the dyspnœa is very threatening, it is preferable to do this before the operation. M. von Eiken advises the preliminary introduction of the rigid bronchoscopy tube in these cases.

(*b*) Difficulties in delivering the Goitre.

The difficulties only occur with intrathoracic goitres. We have already said that this type of operation is facilitated greatly by detaching the insertion of the sternomastoid and by a loop of thread passed two or three times through the thyroid substance, to enable continuous traction to be made. We have, in this way, succeeded in scooping out enormous intrathoracic goitres without having to cut through the sternum, as recommended by Sauerbach. It scarcely needs saying that the puncture of a cystic goitre is the best method of facilitating its removal.

(*c*) Hæmorrhage.

We will first discuss *arterial* hæmorrhage. In a well planned operation there need never be any fear of hæmorrhage from the superior thyroid. The ligature *en masse* of the upper pole never cuts through, and if this accident should occur when the artery has been tied by itself, the gaping mouth of the vessel can be seized rapidly. This artery really gives no trouble, except when the ligature slips, and this should never occur if the precaution is taken of preserving a small tip of the upper pole. We always apply a ligature to the continuity of the artery, for safety, if we have for some exceptional reason applied a terminal ligature at first. But if the *inferior thyroid artery* has been cut through by a ligature, the *arterial hæmorrhage* is apt to be troublesome. In fat women, and in patients with Graves's disease, the arteries are liable to be arteriosclerotic or very friable. But this accident is rare and it can be prevented, with almost absolute certainty, if one is careful to leave a little connective tissue around the artery which is to be tied. Errors excepted, we have witnessed this accident on four occasions before the precaution just mentioned had been adopted. To deal with hæmorrhage from the inferior thyroid artery demands all the sang-froid of the surgeon. If it is impossible to seize the artery with forceps at the moment of accident, it must be compressed with the finger just where the peripheral portion of the trunk is given off. The carotid artery must be drawn outwards forcibly. If ligature presents any difficulties a small tight plug should be applied by digital pressure for five to ten minutes, and this will give the opportunity of discovering and seizing the injured vessel. Hæmorrhage from one of the extrathyroid branches of the inferior thyroid should always be treated by ligature of the entire trunk, in order to avoid the risk of injuring the recurrent nerve. There need never be any real anxiety concerning hæmorrhage from the intrathyroid branches of the inferior thyroid. One should always be mindful of the proximity of the recurrent nerve if one is tempted to put on artery forceps hurriedly anywhere in the direction of the posterior capsule. It is much better, here also, to apply pressure locally and then ligature the trunk deliberately.

Very occasionally, there may be trouble from hæmorrhage for the arteria ima (Neubauer's). This is also best treated by tight plugging, kept up for a few minutes, after which the difficulty can be dealt with.

The hæmorrhage is very often *venous*, coming from the vessels of the capsule or from the large trunks. Capsular hæmorrhage occurs mainly in exophthalmic goitres and in cases which are associated with great venous congestion, owing to pressure on the jugular veins.

Hæmorrhage may also result from the accidental tearing of the middle thyroid vein, when the inferior thyroid artery is being exposed, or the bleeding may also arise from one of the large veins of the upper or lower pole of the goitre.

The treatment varies with the circumstances. If the bleeding is from the capsular veins or from the upper or lower pole, the rapid dislodgment of the goitre in the most convenient plane of cleavage, serves to arrest the flow of blood through the large venous trunks, and at the same time removes the congestion which is the primary cause of the hæmorrhage. Dislodging the goitre affords the opportunity of ascertaining the exact site of the hæmorrhage, it exposes the upper and lower pedicles and they can be seized with clamps. If the bleeding is due to a simple tear in the middle thyroid vein, or to any venous hæmorrhage which renders it difficult to dislodge the goitre forthwith, there is only one course to pursue, viz., to plug the bleeding spot patiently for five minutes, after which the hæmorrhage will usually have subsided sufficiently to permit of the ligature of the injured vein. It is obvious that the torn vein must be looked for and tied, even if the pressure has completely arrested the hæmorrhage.

The danger of hæmorrhage varies considerably with the kind of goitre. Even a small goitre may provide unpleasant surprises for the novice, and there have been cases where the operator has lost his head and the patient his life. The arrest of hæmorrhage demands the ability to cope with sudden emergencies, and it may mean a very tedious ordeal in exophthalmic goitre where everything bleeds, and in any large goitre (not Graves' disease), especially in young athletic patients, such as soldiers, in whom the gland is congested owing to long route marches. One cannot trust to luck in arresting hæmorrhage in goitres; hæmostasis must be secured by a carefully worked-out method, as recommended by Kocher as long ago as 1883.

We have devoted considerable space to this subject of hæmorrhage, although it is a rare contingency in the operations of methodical surgeons who adhere to the principle of preliminary hæmostasis by *tying the large arterial trunks before approaching the veins.*

(*d*) Air Embolism.

We have never encountered the complication of air embolism during an operation for goitre, but it is necessary to refer to this possibility, because the veins of the neck are liable to this accident. Ordinarily, when a vein is cut the walls fall together in such a way as to prevent any entrance of air. Nevertheless we are careful not to allow either the anterior jugular or thyroid veins to gape without clamping them immediately. Indeed, we clamp them and tie them before cutting them. All ligatures must be tied in such a way that they cannot get undone. The difficulty really arises from veins which are held open by cicatricial or inflammatory adhesions, and thus it occurs in operations for goitre after an inflammatory attack, and in operations for a recurrence. To prevent an air embolism during an operation for goitre is quite a simple matter, for it cannot occur if a careful technique is adopted.

(*e*) Accidental Injury to the Œsophagus.

The œsophagus is so well protected that an accidental injury to it is practically unknown, and nevertheless it is a possibility in certain exceptional cases. The accident has actually occurred to expert surgeons. If it is not recognized at once, the patient is confronted with the danger of fatal mediastinitis.

The following case occurred in our practice:—

A patient, aged 60, required an emergency operation owing to pressure on the trachea by a deep goitre. He was already in a precarious state. We were struck by the fibrous and almost lardaceous condition of the posterior capsule which was revealed at the operation. The patient died a few days after the operation from a gas-phlegmon. This arose from a traction diverticulum of the œsophagus 2 cm. long and of a narrow filiform calibre hardly visible to the naked eye. There probably had been some thyroiditis with an unsuspected perforation of the œsophagus. The track was so small that it was difficult to detect it in the lardaceous tissue, even at the post-mortem. The possibility of this complication should occur to the surgeon if the case presents any traces of old retrothyroid inflammation.

(*f*) Adhesions.

All kinds of adhesion may complicate the operation for goitre.

Mention may be made first of *the results of thyroiditis*. Later on we shall see that an operation on an acute or subacute thyroiditis does not give rise to any great difficulty. On the other hand, however, the results of an inflammatory affection of the thyroid may introduce grave complications in any operation that is to be performed subsequently. The adhesions between the thyroid and the perithyroid tissue may be such that the cleavage planes are completely obliterated. If any advantage is to be derived from preliminary ligatures, they should be tied as far away from the goitre as possible. The inferior thyroid artery can generally be ligatured in the extrafascial plane. There is a corresponding point on the superior artery where the ligature may be safely placed.

In exceptional cases extensive adhesions are found in goitres which have had *prolonged iodine treatment*. The softening of the thyroid tissue caused by the iodine preparations produces round the gland a zone of irritation which is finally transformed into steadily thickening adhesions. This may also occur—though in a more severe form—after *X-ray* or *radium* treatment. The gland may become a fibrous mass, adhering closely to the perithyroid tissue, the trachea and the larynx. One of the most difficult operations that a surgeon may be called upon to perform is the removal of a goitre, or more especially an exophthalmic goitre, which has previously been subjected to radiotherapy.

Some very remarkable differences, some partially physiological, have been observed between the thickness of the adhesions in the two sexes. The cleavage planes are, generally speaking, easier to find in female patients, and those who are no longer young. The tissues are denser, and the adhesions between the different layers are firmer in males and adolescent female patients than they are in middle-aged or elderly women.

Special difficulties arise where the operation of *tracheotomy has previously been performed*, for diphtheritic laryngitis for instance. Here, too, abnormal adhesions occur. In these cases the trachea becomes much flatter under the very slightest pressure, and its collapse during the operation is much more likely than when the trachea is intact.

(17) Drainage.

Should the wound be drained after an operation for goitre? This question has often been discussed, and so far no unanimous conclusion has been reached. Where hæmostasis had been efficient drainage appears to be unnecessary; it also involves the risk of secondary infection of the wound. This argument also holds good for the simple wounds which are left after such operations as hemithyroidectomy, for example. In this case hæmostasis is so easily achieved, and the wound in the thyroid tissue generally so small, that drainage can be dispensed with quite safely. It is not so easy to decide what should be done after resection or enucleation. Here, in spite of an efficient hæmostasis, the compresses of the first dressing are often soaked by the evening after the operation. When the wound is not drained small hæmatomata and serous cysts are formed which may rupture spontaneously, and so give rise to secondary infection. On the other hand, it is quite clear that by keeping the drainage tube in the wound even for twenty-four hours (because it should always be removed the day after the operation) an infection may be produced which is quite sufficient to cause the ligatures to give way. The safest procedure seems to be the elimination of drainage in cases where hæmostasis has been efficient, and to make use of it *until the evening of the day on which the operation has been performed* or *at most till the following morning* in cases where there has been any extensive laceration of the gland, so that in spite of hæmostatic measures some leaking may be expected. Drainage is also advisable in operations for exophthalmic goitre where it is necessary to prevent as far as possible any reabsorption of the thyroid products.

We use Kocher's glass drainage tube, which is fitted at the end with three small knobs to prevent it slipping into the cavity of the wound. It is inserted between two stitches of the superficial suture (fig. 100). Some make a practice of replacing the tube by a skein of Florentine horsehair, but there does not seem to be any advantage

in this. We have given up Kocher's former method of inserting the drainage tube in a special orifice outside the line of suture. Although this may be advisable in other circumstances, it seems to be totally unnecessary where the tube is removed after twelve to twenty-four hours.

CHAPTER X.

POST-OPERATIVE COURSE.

I.—IMMEDIATE TREATMENT AND NORMAL POST-OPERATIVE PROGRESS.

AFTER the operation the patient is put back to bed in a semi-recumbent position, with the head sufficiently supported to prevent any dragging at the edges of the wound. For the first two or three days only liquid food is given, because of the slight dysphagia, a temporary but usual consequence of the operation. The soiling of the dressing by liquids is prevented by a small bib of waterproof cloth, which is fixed to the chin by a band of cerecloth. One or two injections of morphia, on the first day, and, if necessary, on the second, prevent coughing and facilitate sleep. The drainage tube is removed on the same evening as the operation or the next day, but never later. Care should be taken that the clot which this usually encloses be removed at the same time.

FIG. 101.—Waterproof bib fixed to the chin by a band of cerecloth, for protection of the dressing.

The sutures are removed on the third day, the drainage tube is taken out, dressing is renewed with the help of sterile compresses, and

is replaced by a plain band of adhesive gauze with a little collodion or better mastisol (solution of cement in benzol) over the scar. The stitches or Michel's hooks are always removed forty-eight hours after the operation to prevent scarring of any kind. In this way the scar is reduced to a very thin line, pink during the first year, but becoming white later on. It is practically invisible if it has been made in the direction of the fold of the skin (fig. 102). The patient may be allowed to get up on the fourth or fifth day. Cases of Graves' disease should be kept in bed longer, because rest is an essential part of the treatment. Bromide administration is continued in these circumstances for the whole of the post-operative period, and the state of the heart is carefully kept under observation. Here, too, digitalis is indicated only where there is some organic cardiac lesion. We will return to this subject in Chapter XIV.

FIG. 102.—Normal appearance of scar, after incision in the neck.

For the first three or four weeks after resection and more especially after bilateral enucleation, the thyroid region presents a certain amount of swelling and infiltration. This will reassure those surgeons whose patients reproach them after the operation for being too cautious and not removing enough of the goitre.

In cases of retrosternal goitre the face quickly loses its puffed up congested appearance, and the "Medusa head" also disappears. Figures 104 to 107 afford the evidence of this.

At least two or three weeks' convalescence should intervene between recovery from the operation and the return to work.

In most cases there is a rise of temperature after the operation. It is temporary and may be as high as 102° F. without any infection to cause it. This fever is characterized by the almost total absence of general symptoms: the pulse is regular, the breathing calm, and the features never look pinched. It is more severe after operations entailing any laceration of the thyroid tissue, and slight hæmorrhage, than after the usual occurrences. It is most severe in cases of exophthalmic goitre. We cannot dwell here upon the theories put forward to explain this hyperthermia, and the researches which have

FIG. 103.—S-shaped hook for picking out suture knots from the tissues.

been made with this end in view. From the result of all the experiments and investigations its principal cause seems to be the absorption of the contused or necrosed tissue, and the blood discharged into the cavity of the wound. We do not deny that in certain cases a slight infection, which does not proceed to suppuration, may be a reason for the rise in temperature, but this is exceptional because the usual post-operative fever of goitre is aseptic in character.

FIG. 104.—Diffuse multinodular colloid goitre, showing the compressed veins and congested appearance of the face.

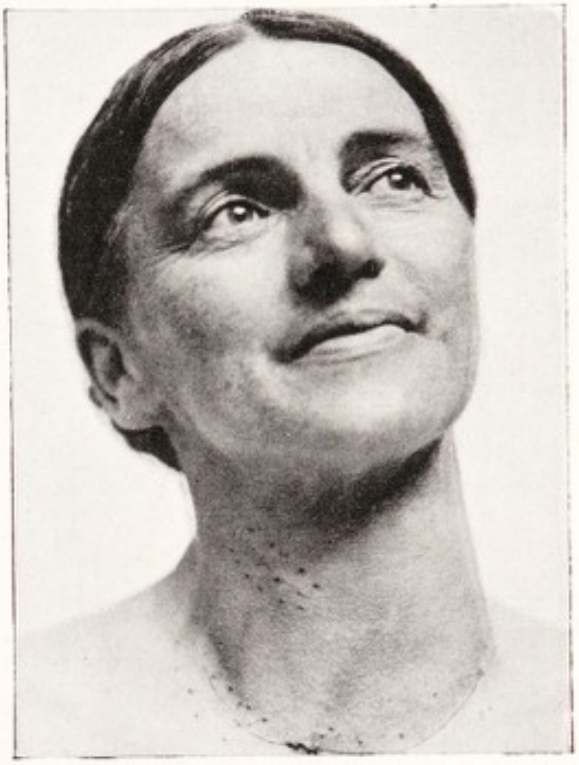


FIG. 105.—Same case, fifteen days after the removal of the goitre. (Before the operation the vessels of the right superior pole were ligatured separately.) Rapid relief of congestion of the veins and face.

II.—POST-OPERATIVE HÆMORRHAGE.

There are not many operations where the post-operative hæmorrhage assumes the alarming character that it does in goitre.

Arterial hæmorrhage is always caused by the insecure ligature of an artery; it may arise from a small arteriole on one of the main trunks. Anæmia is not the most striking symptom, because the amount of blood enclosed in the cavity of the wound is not sufficient to cause alarming anæmia. It is the compression of the trachea and possibility of suffocation that make the hæmorrhage so dangerous. After the operation the patient can be seized quite suddenly with a fit of choking which may be fatal if immediate help is not forthcoming.

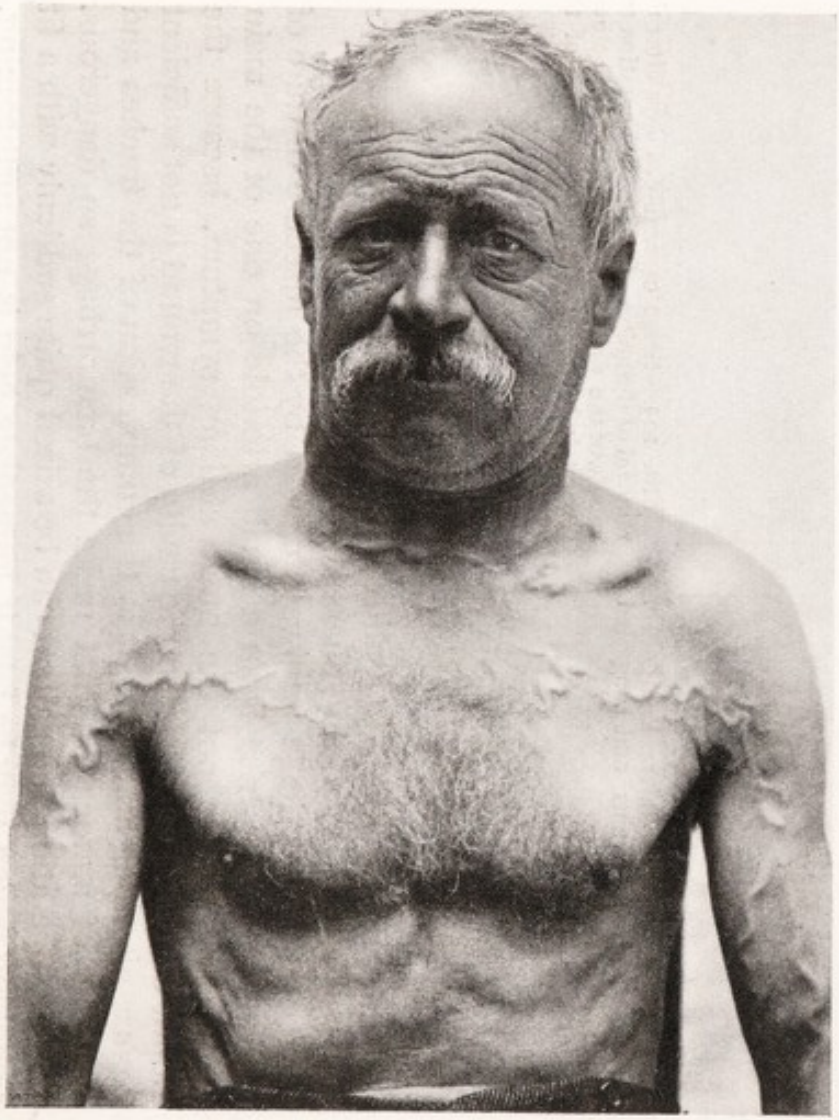


FIG. 106.—Retrosternal goitre, with Medusa head, and puffed-up face.

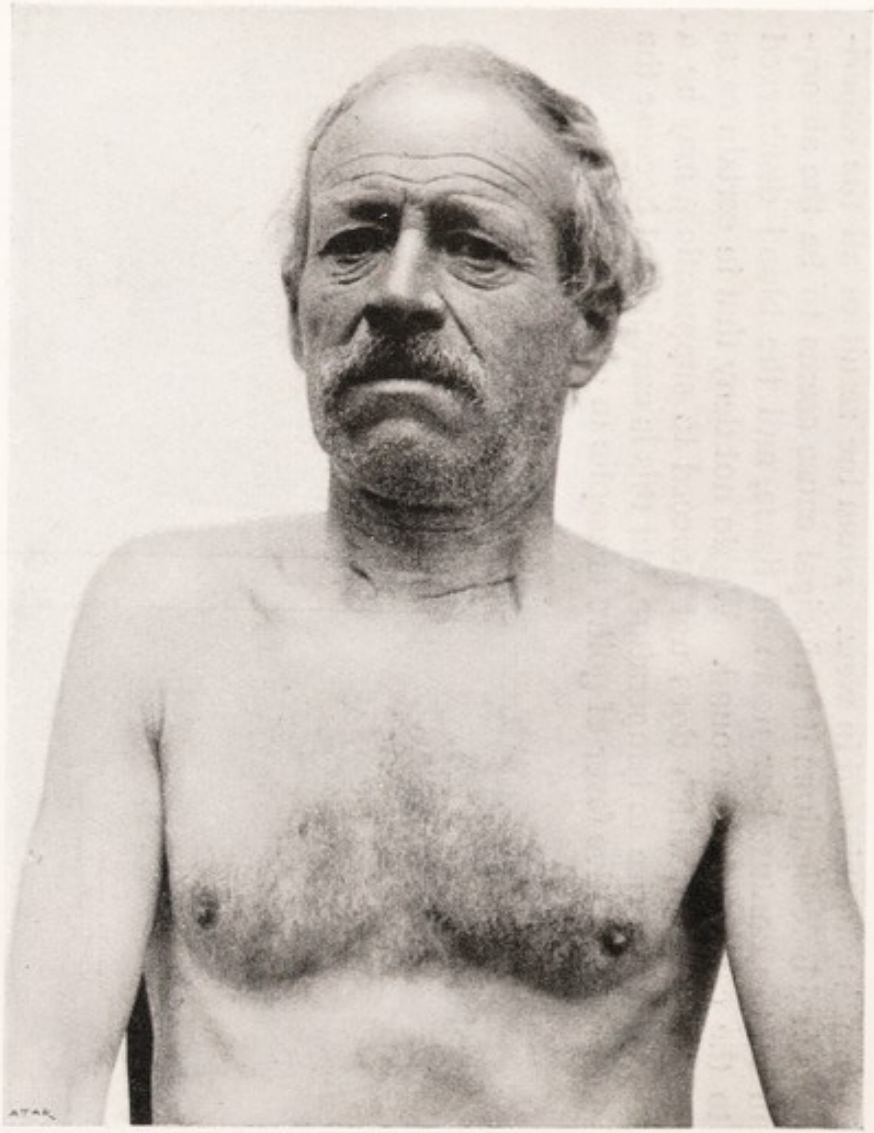


FIG. 107.—Same case, six months after operation. Veins and face no longer congested.

The wound should be opened quickly, the extravasated blood emptied, the stump of the vessel compressed and subsequently ligatured. It is as well to know that severe hæmorrhages nearly always arise from the pedicle of the superior artery. Their origin is easy to understand. The superior thyroid artery was drawn towards the wound during the operation, and if the usual method was followed, ligatured and cut. The trunk receded into the dome of the cavity, and by a slow but continuous traction the tissues succeeded in freeing themselves from the constriction of the ligature material. An infallible method of preventing this accident is always to tie the superior thyroid artery (in the same way as the inferior) in *continuity*. In this way at least the extremity of the trunk of the superior artery is left in place, even when hemithyroidectomy has been performed.

If for any reason these precautions cannot be taken, one should be careful to tie a second ligature above the first ligature of the thyroid artery, in continuity of the trunk. It is due to the observance of these simple precautions that none of our surgical cases have been victims of great arterial hæmorrhage with sudden compression of the trachea.

In other cases hæmorrhage consists merely of the slow oozing arising from the parenchymatous tissue. This moderate oozing rarely causes a hæmatoma on the first day, but frequently does so after two, three or four days. The hæmatoma may become large enough in rare cases to cause an attack of dyspnœa. When the hæmatoma appears slight and ceases spontaneously, it can be left to become absorbed naturally. If, on the other hand, it increases, some of the sutures should be removed to allow the clots to escape. If the oozing continues while the wound is being re-opened, attention should be given to the stump of the thyroid artery. In other cases, after the wound has been opened, a tube is introduced, and some hæmostatic preparation such as "coagulene" is given, either by intravenous or subcutaneous injection. In only three cases of all those that came under our care was there any need to give any attention to the stump of the artery after operation. In all the others the hæmatoma was relieved by emptying the cavity of the wound.

The best prophylactic measure is adequate hæmostasis during the operation, supplemented by an accurate suturing of the thyroid wound, so as to prevent bleeding. The control of the venous hæmostasis by the simple method of increasing venous pressure should never be neglected after the operation.

We have observed forty-seven cases of post-operative hæmatomata in 1,000 cases operated on, including those of minor degree. In thirteen cases the formation of the hæmatoma was followed by some slight infection and a temporary sinus.

This relatively high percentage (4·7) of hæmatomata is accounted for by the fact that even the slightest cases are included, and above all by the widespread practice of bilateral enucleation. The less frequent occurrence of hæmatoma where a unilateral excision is made is counteracted by the much greater frequence of relapses after this operation, as we shall see later.

III.—INFECTIOUS COMPLICATIONS FOLLOWING OPERATION FOR GOITRE.

Although the infectious complications following an operation for goitre have diminished, they have not entirely disappeared, and it is useful for the practitioner to know their course and clinical signs.

The following types should be distinguished.

(a) *A Serious Septic Phlegmon, accompanied by Inflammation of the Mediastinum.*—This very exceptional occurrence is characterized by the rapid change in the general condition. The pus has a fœtid smell and the tissues quickly become gangrenous. In one case only have we met this complication. Here there was an accidental wound of an almost microscopic œsophageal diverticulum. A less acute form once set in after a tracheotomy, which had to be performed during the operation. The treatment consists in rapid and extensive opening of the focus, and if possible irrigating it with Dakin's liquid or peroxide of hydrogen.

(b) *Immediate Purulent Infection.*—The slight infiltration of the tissues, which is usual for the first few days after the operation, increases instead of diminishing from the third day. Pain on pressure and soreness are noticeable, the skin becomes tense and shiny and presents a more or less phlegmonous appearance. The temperature goes up to 101·3° or 102·2° F., and if the edges of the unhealed wound are separated on the fourth or fifth day, a certain amount of pus will exude. The pathogenic cause is nearly always staphylococcic, although it may sometimes be streptococcic.

In rare cases we have seen dermatitis due to disinfection of the skin by tincture of iodine, looking like the beginning of a phlegmon.

(c) *Subacute Diffuse Infection.*—The edges of the wound unite normally, but the diffuse infiltration of the deep tissues does not subside in the usual time. The general condition, although it does not become alarming, does not improve as it should, and the temperature remains somewhat high and exhibits inexplicable exacerbations. The insertion of the drainage tube at the end of four or five days does not give vent to ordinary pus, but to a cloudy serous blood-stained fluid. Suppuration sets in slowly after six or eight days. It is caused by necrosis of the thyroid tissue, as a result of the ligatures being too bulky or the hæmostatic sutures being too close together. This necrosis is complicated by a slight infection.

(d) *Late Abscess.*—Everything appears to be progressing normally, when after two or three weeks the temperature goes up and follows the course of fever due to an abscess. The appearance of a spherical swelling, sensitive to pressure, indicates the course to be taken. The abscess is opened either through the operation scar or by making an incision where it points. Sometimes the abscess subsides to a small lump the size of a nut, rising to the level of the scar and slowly exuding a minimum amount of ropy pus.

(e) *Hæmatoma with a Secondary Infection.*—The formation of an ordinary hæmatoma, of such a size as to need emptying, has already been dealt with. This may be followed during the first days by a discharge of a serous blood-stained fluid, which later becomes sero-purulent, and finally distinctly purulent. The cavity has become infected by the bacteria which are always to be found on the epidermis.

These different forms of infection are at first treated by opening the affected part and inserting a drainage tube. Disinfection by means of chemicals appears to be quite unnecessary, except in the first case where Dakin's fluid and peroxide of hydrogen are used. Generally as soon as the cavity is sufficiently drained the temperature goes down. It is not necessary to reopen the wound widely in order to bring this about. The insertion of one or two tubes into the operation scar is generally enough to ensure the flow of pus, and makes very little difference to the appearance of the scar when healed. The chief trouble with these infections is the sinus which persists until all the necrosed tissue and all unabsorbed suture and ligature material have been completely eliminated. This last point makes it necessary for care to be taken after the third week (never earlier) with ligature material and sutures that have become loose.

During the last few years we have used for this purpose a small instrument that was invented for twisting the ends of silver threads in metal sutures. It is inserted like a probe, then rotated a little, but if the hooks are felt to be catching in the tissues, it must not be forced. This is inserted at various points along the direction of the sinus of the infected cavity, and nearly always succeeds in removing the foreign body causing the trouble. This proceeding is harmless as long as it is not resorted to before the third week, and carried out with an instrument the hooks of which have a total diameter of less than six millimetres (fig. 103).

The scar resulting from these infections often has the unsightly appearance of being fixed to the trachea, because it moves with it during the process of swallowing.

The following is a brief survey of the infectious complications observed among the thousand cases from which our latest statistics are compiled (1915-1920).

The total number of primary infections—without any hæmatoma—was sixteen out of 1,000 cases operated on. This figure does not include the rare cases in which an abscess was formed after the patient had left the clinic. The infection proved fatal in two cases. Once because of an almost microscopic œsophageal diverticulum, not noticed at the time of operation (already referred to), and the other case after tracheotomy, owing to the complete compression of the trachea. In thirteen cases a hæmatoma was followed by the formation of a temporary sinus.

It must be said that these statistics were compiled during conditions very unfavourable for asepsis. Change of staff, influenza, &c., were all too frequent occurrences.

CHAPTER XI

THE PROGNOSIS OF THE OPERATION FOR GOITRE.

THE percentage of cases in which operation proved fatal—according to the statistics compiled by Roux from 1871-1880—varied between 12·5 and 13·9. The percentage of cases operated on in Switzerland from 1911-1915, where operation proved fatal, had fallen to 0·66. The percentage of cases from 1871-1875 was worked out from a total of 8 operations performed, while from 1911-1915 the results of 7,809 operations were taken. These figures show in a general way what great progress has been made in operative surgery during the last fifty years. Infection and hæmorrhage have become very infrequent causes of death after operation. At first many patients were sacrificed because of the lack of knowledge and experience common to all pioneer work. Besides this the dangers of operation were so great that only the most severe cases of goitre received surgical treatment. The æsthetic aspect of the operation did not exist at all. For this reason most of the cases that came for surgical treatment were difficult ones. This state of affairs has altered considerably since 1890. That the operation has become more popular is shown by the fact that the number of operations performed in 1915 was ten times as great as that in 1890.

The statistics compiled by Roux, showing the actual causes of death after the operation, are reproduced here diagrammatically. We are struck at once by the large proportion of deaths from *pneumonia*. A surgeon who, without bearing in mind the statistics, consents to operate on old and bronchial patients suffering from obstructive goitre, runs the risk of having to deal with fatal pneumonia. However, the number of mishaps decreases as the operation assumes a prophylactic rather than a curative character. Leaving this type of pneumonia out of the question it seems that some prophylactic precaution should be taken immediately before the operation (pre-operative treatment of the cardio-vascular and renal system). By using a local anæsthetic the occurrence of pneumonia due to general anæsthesia is prevented. This is certainly a progressive step. A patient who has recently been suffering from a catarrhal condition of the air passages should not be operated on. After the operation, expectoration can be made easier by giving the patient any sedatives that may be necessary, and also optochine if there is the slightest cause (0·2 to 1·2 gr. every two hours). Care should be taken that the patient does not get cold while being brought from the operating table to bed. These few precautions should certainly help to make the prognosis more favourable. Nevertheless pneumonia which proves fatal may set in quite unexpectedly at the time of year when the pneumococcus is most virulent, or when the patient's constitution has previously suffered from some form of debility such as heart fatigue, kidneys in the early stage of sclerosis, the beginnings of glycosuria, &c.

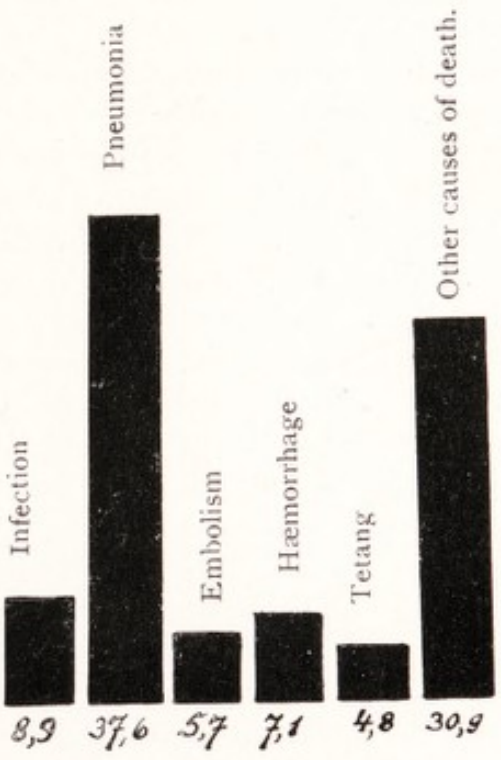


FIG. 108.—Table showing the causes of death after operation for goitre, in 7,809 cases treated by Swiss surgeons from 1911-1915.

Infections of the wound take the second place. Pneumonia occurs four times as often as these, which are to be feared in those rare cases where it has been necessary to perform tracheotomy *during the operation*.

Hæmorrhage is fourth in order of frequence. Pneumonia occurs five times as often as this, which might be a much rarer thing if the

practice of ligaturing the arterial trunks in *continuity* were more widespread, and if the terminal ligature of the superior thyroid artery were omitted altogether. Of this we feel quite certain.

Fatal *pulmonary embolism* occurs with a frequency one-tenth of that of pneumonia. It is as well to note here that the danger of embolism is much greater after an operation for hernia than it is after goitre.

Tetany is fatal even less frequently than embolism.

The remaining conditions cause 30 per cent. of the fatal cases: cardiovascular affections, cirrhosis of the liver, nephritis, diabetes, &c.

Our own observations agree very nearly with the results shown by the general statistics. *Pneumonia* is responsible for a third of the fatal cases. We have considered whether the bilateral operation might increase the danger, and we have noticed that out of six cases which succumbed to pneumonia four were operated on with the bilateral incision. On the other hand we see that we have a slightly smaller percentage of fatal cases than the Swiss surgeons in general, because, at the time when the statistics were compiled most of them were (and still are) using the unilateral method of operation, following Kocher's rules. What part the bilateral operation plays in causing pneumonia is doubtful. We have had *one* case under our care which succumbed to *pulmonary embolism*, and *one* other which succumbed to *inflammation of the mediastinum*. This latter infection was caused by an œsophageal diverticulum, probably post-goitrous. This case does not come under the usual category of goitres. We have never lost a case through *hæmorrhage* alone, although loss of blood may have had something to do with one or other of the occurrences grouped together in Roux's statistics as *other causes of death*. This group includes cases of cardiac affection, Bright's disease, cirrhosis, pathologic obesity with overstrain, and fatty degeneration of the heart. In these cases something must be done in order that the patient may be spared sudden choking or slow suffocation. Operation often relieves the condition and justifies both the patient's and the surgeon's courage. Sometimes, especially in cases of large intrathoracic goitre, the trauma of the operation proves too much for the patient, and he dies of shock during the following twenty-four or thirty-six hours, before sufficient time has elapsed for pneumonia to set in. Such are the conditions which cause death in half of our fatal cases. On three occasions the patient was brought to the operating table choking *in articulo mortis*, in the last stages of exhaustion, where in spite of immediate operation and artificial respiration it was impossible to save him. A large proportion of these bad cases naturally drift to a hospital. We must add that 50 per cent. of the patients who died after operation were over 60 years of age. That explains why our

death-rate, 0·95 per cent. of all the cases treated since 1895, is slightly higher than the average figure given by the latest general statistics for 1911-15. We do not think it right to abandon all hope even for such cases as appear to be beyond any hope. There are some patients even in the seventh decade who can be rescued if their dyspnœa is really due to the pressure of the goitre. It is a part of the surgeon's art to recognize its limitations, and for this purpose knowledge, prudence and feeling are required in equal degree.

Generally speaking, we can say that the number of deaths after operation for goitre (which is neither Graves' disease nor cancer) is under 1 per cent., provided the surgeon is accustomed to the technique. The proportion approaches 1 per cent. if the surgeon operates on obstructing and intrathoracic goitres in patients over the age of 60 suffering from heart disease, obesity and Bright's disease.

CHAPTER XII.

OPERATION IN CASES OF RELAPSE.

I.—GENERAL OBSERVATIONS CONCERNING RELAPSE.

BEFORE speaking of *recurrence* the meaning of the term must be understood.

In *true recurrence* masses of diffuse or nodular goitre reappear on the side operated upon, when the lobe in question had apparently been completely removed.

In *false recurrence* there is a formation or further development of diffuse or nodular goitrous tissue in the lobe that was not operated on.

The occurrence of one or the other of these conditions is dependent on the technique of the operation, the type of goitre and the age of the patient.

Let us deal with these points seriatim :—

(1) It is evident that the *type of operation must have some influence.* The surgeon who favours the unilateral excision or some similar method will have a minimum of real recurrences. The lobe that is removed will not grow again. The results, however, are not as good as they appear at first sight because there will be more cases of false recurrence.

The more radical surgeon who only leaves a fragment of each lobe will encounter a minimum of true and false recurrences, but at the same time he will run the inevitable risk of seeing his patients become hypothyroidic or attacked by tetany.

The surgeon who cautiously operates on both lobes will not encounter hypothyroidism or tetany among his cases but they will sometimes suffer from true recurrences, the frequency with which these occur depending on the care of the surgeon and above all on the age of the patient when first operated on.

From this it appears quite useless to attempt to establish any statistics that would be of general value.

We have tried to ascertain approximately how often these two types of recurrence occur, and for this purpose we examined 250 of our own patients. The examination was carried out during the two and a half years following the operation.

In 185 cases the thyroid region was normal or had not increased in size since the operation.

In twelve cases diffuse swelling of the neck was found.

In twenty-nine cases one or more nodules at least the size of a nut were present in the region of operation, and in twenty-eight cases these were found on the side which had *not been treated surgically*. These figures correspond to those obtained from the first set of cases which were operated on after we had given up Kocher's principle of unilateral operation. This proved to us that we had been too apprehensive and induced us to go further in that direction.

(2) In order to study the *influence of age* on the causation of recurrences, whether true or false, we have investigated the last 101 cases of recurrence that we operated on. In nine-tenths of these cases the primary operation had not personally been done by the author.

The following table gives the most interesting figures yielded by this small statistical enquiry :—

(i) Age at the time of first operation :—

Under 21	...	...	...	58	per cent.	of the	cases
,, 31	...	...	...	81	,,	,,	,,
,, 41	...	...	...	94	,,	,,	,,

(ii) Age at the time of the second operation :—

Under 21	...	...	...	18	per cent.	of the	cases
,, 31	...	...	...	53	,,	,,	,,
,, 41	...	...	...	77	,,	,,	,,

(iii) Limits of time during which recurrence occurred.

The first operation was performed between the ages of 8 and 56.

The second operation between the ages of 14 and 64.

(iv) *Interval* :—

(*a*) Duration of the interval between the first and second operations : 1 to 35 years.

(*b*) Average duration of interval : ten years.

(*c*) The recurrence occurred before the eighth year in 50 per cent. of the cases.

The frequency of recurrences and pseudo-recurrences diminishes with the age of the patient ; three-fifths of the recurrences occur in cases operated on before the age of 20, and 94 per cent. after operations performed on patients under 40. There is hardly ever a recurrence after an operation on a patient *over* the age of 40.

(3) The third influential factor is the *histological character of the goitre*. An investigation of the same cases supplies ninety-four histological conditions. The following is a classification :—

Diffuse colloidal goitre	6	per cent.	(4·8)
Nodular colloidal goitre	36	,,	(37·5)
Diffuse parenchymatous goitre ...	0	,,	(2·6)
Nodular parenchymatous goitre ...	31	,,	(48·0)
Mixed goitre	25	,,	(36·4)

(The figures in brackets refer to the relative frequency of the type in question in the cases in Bâle and Berne, and are taken from Mlle. Woelz's work.)

The general distribution of the histological types corresponds approximately with that in Bâle and Berne, although there are more intermediate and mixed forms than parenchymatous nodular goitres.

No case of diffuse parenchymatous goitre suffered a recurrence because it reappears in the form of nodular parenchymatous goitre. Colloidal diffuse goitre appears again in the same form or as colloidal nodular goitre.

The fact that from 4·5 to 6 per cent. of the operations performed for goitre are cases where a recurrence has occurred, indicates the importance which attaches to true or false recurrence in cases operated on during the last twenty or thirty years. It is for a future generation to give an opinion of the results obtained from the more radical treatment which has been in vogue during the last few years.

II.—OPERATIVE INDICATIONS IN CASES OF RECURRENCE.

When should one operate on a case of recurrence ? The indications are practically the same as those for goitre in general : Compression of the trachea, obstruction of the veins at the level of the head and neck, æsthetic considerations. The decision is always more difficult than for a first operation.

The *laryngoscopic examination*, which is indispensable before any operation on a goitre, has a special significance in these cases, because it frequently happens that paralysis of the posterior crico-arytenoid,

or even complete paralysis of one cord, is made up for by the other cord, in such a way that the voice gives no indication of the mishap which has occurred since the first operation. These cases should only be operated on after most careful consideration, especially when the goitre reappears on the side opposite the paralysis. It is only when compression of the trachea and vessels is evident that one is justified in exposing the other recurrent to the risk of injury, however slight it may be.

Unfortunately, *direct control of the parathyroid glands* is not yet possible. At the most the first operation may suggest some indications as to its state. For instance, the complete removal of one of the lobes, hemithyroidectomy, would result in the probable loss of one or two parathyroids. A thin layer of tissue left on the posterior surface of the lobe, in accordance with Kocher's practice, might perhaps save the little glands for the time being, but one cannot say what would happen later in the scar of the stump, especially in cases where the isthmus has been cut. When the trachea can be felt directly under the skin, on the side that was operated upon, one can be quite sure that in the first operation hemithyroidectomy was performed, and accordingly the parathyroids of the other side should be treated with care. On the other hand, a mesial trachea with thyroid or goitrous tissue present on either side, probably is an indication of the fact that the parathyroid apparatus is intact.

As far as the *thyroid substance* itself is concerned, the operation on a case of recurrence demands great care. Where myxœdema is present, unless there is urgent need, the operation should not be performed. However, this is a rare coincidence, although a condition is often found where a recurrence occurs together with symptoms of cretinism. The reader is referred to what is said regarding this subject in Chapter XV. The best control—although only relative—is the determination of the basal metabolism.

III.—SURGICAL TECHNIQUE.

Let us now consider the technique of the operation performed on a case of recurrence.

If the new goitre can be reached by making an incision in the old scar this should be done, although this may not be the incision we would make in the ordinary way.

Palpation and radiographic examination enable us to decide beforehand on the general plan of the operation. It is quite easy to operate on a lobe that has hitherto received no surgical treatment. This seems to be the sole advantage of a unilateral incision in the first operation. It is more difficult where the lobe has already been

tampered with, especially when the small muscles have been cut and the exposed lobe left to heal without any stitching to bring its edges together. The sutures themselves may cause scarred masses and extensive adhesions if they are too massive in their arrangement or if the catgut is too coarse.

According to Sarkissiantz's observations made in Roux's clinic, the ligature of the arterial trunks itself causes the formation of much connective tissue. We have not been able to verify this by experiment on the dog, but probably the conditions are not identical.

The shorter the interval between the two operations the more troublesome are the adhesions—the first few weeks excepted. Excessive vascularization in exophthalmic goitre extends beyond the gland itself, and there is much bleeding in spite of the ligatures of the vessels made at the time of the first operation. This condition may be responsible for almost insuperable difficulties. In these circumstances, to avoid a fatal shock, the surgeon should wait a favourable opportunity before operating.

The following are a few general rules. Whatever is bleeding should be carefully tied, and transfixion used rather than the unreliable terminal ligatures. The edge of the sternomastoid must be completely and rapidly exposed at the beginning of the operation in order to penetrate the space of the small muscles and to explore the course of the inferior thyroid artery.

If accessible and intact it should be tied. The goitre should then be cut down upon, and its posterior surface reached as quickly as possible. The lobe is freed, great care being taken, owing to the proximity of the recurrent nerve. If possible the lobe should be removed. If removal of the lobe is impracticable owing to the risk of implicating the recurrent nerve, one must be satisfied with enucleation or resection. In cases of diffuse goitre amenable to resection, the superior pole, or at least the antero-external branch of the superior thyroid artery, should be ligatured. The resection should be melon-sliced, or in any other shape adaptable to the type of the goitre, but it is important to leave a fair layer of thyroid tissue on the posterior surface or at the upper pole of the lobe. The edges of the thyroid wound should be brought together, and the layer of muscles in front of the gland replaced as carefully as possible. Besides aiming at the preservation of the normal contour of the neck after the operation, the observance of this precaution tends to prevent the unsightly adhesion of the scar to the thyroid body, which causes a dragging movement of the scar in the act of swallowing, and with every ascent of the larynx.

It must not be imagined that every operation on a case of recurrence presents all these difficulties. In most cases the operation is

perfectly straightforward, except for the difficulty caused by the obliteration of the original planes of cleavage. The really difficult operations are encountered in Graves' disease, and in those cases where the interval between the two operations is under a year but over three months. From what we have just said it follows that an operation on a case of recurrence after extensive resection is more difficult than a subsequent operation on a case of false recurrence after hemi-thyroidectomy.

CHAPTER XIII.

THE OPERATION IN INFLAMMATORY CONDITIONS OF THE THYROID.

I.—ACUTE INFLAMMATORY AFFECTIONS.

It is necessary to distinguish the *non-suppurating* from the *suppurating* affections. The former usually attacks a comparatively healthy gland, and may be designated as a "simple thyroiditis." Its causes include rheumatic polyarthritis, influenza, tonsillitis, scarlet fever, measles and malaria. Most generalized infections are capable, at some time or other, of determining a metastasis in the thyroid. The question of operation hardly ever arises in these cases, for the swelling usually subsides towards the end of the first week, and after leaving one lobe it invades the other. If, however, there be any antecedent pressure on the trachea, a diffuse inflamed goitre may increase this to such an extent that surgical intervention may become urgent, viz., resection of one lobe, simple incision of the isthmus, or tracheotomy, as circumstances dictate. We have discussed this matter in detail in a monograph on acute thyroiditis, published in 1904.

The position is, however, quite different in cases of suppuration of the thyroid, whether the gland had been healthy or diseased previously. We have already said that the tendency to suppurate mainly concerns the goitrous nodule; inflammatory affections of a previously healthy thyroid, or of a diffuse hypertrophied gland, are not so apt to suppurate. If the underlying cause of the inflammation is known, it is quite easy to arrive at the diagnosis of suppuration. Inflammation due to rheumatism, malaria, or measles does not proceed to suppuration; but if it is due to scarlet fever, typhoid fever, or puerperal fever, suppuration is the almost invariable sequence, and it is also frequent after

influenzal inflammation. Otherwise, the diagnosis depends upon the general course of the affection, persistence of the fever beyond the first week, infiltration of the skin and subcutaneous tissue, and the appearance of a soft centre surrounded by a dense zone of induration. The main difficulty in diagnosis arises from old cysts surrounded by a thick fibrous capsule in which secondary inflammation has occurred. We shall refer to this condition later on.

In acute cases associated with definite infiltration of the perithyroid tissues, the only operation needed is *incision of the suppurating focus and drainage*. If the centre is not softened, an incision "en cravate" of a few centimetres is made in the skin in the middle of the infiltrated area; the dissection is carried down to the gland and the cut vessels are tied as required. The superficial veins of the anterior jugular anastomosis and the capsular veins are encountered, but no important arteries are met with. When the true capsule of the thyroid has been exposed it is desirable to make a deep exploratory puncture with a large cannula. If pus is struck, Kocher's forceps should be plunged in the direction indicated by the needle, and when the abscess cavity is reached the instrument is withdrawn as the cavity is widened. The operation is completed by the insertion of a rubber tube of adequate size.

FIG. 109.—Acute inflammation of an old goitre, with spontaneous perforation of skin and œsophagus.

There are some cases in which a diagnosis of suppuration is made from the general clinical symptoms and is confirmed by puncture, although there is no definite infiltration of the perithyroid tissue. These are the cases wherein suppurating foci are enclosed within a goitrous cystic nodule, and the intrathyroid capsule of the cyst has formed a barrier which protects the surrounding tissues. These *subacute forms* occur in old-standing goitres, and their ætiology is very variable. In these cases it is possible to penetrate to the intraglandular capsule of the nodule as if it were a non-suppurating goitre, and it is quite easy to *enucleate* the nodules, much to the surprise of the

operator. These nodules may be as large as a fist or an infant's head. Owing to the inflammatory œdema the plane of cleavage in these cases is more accessible than in ordinary goitre, and the compression of the vessels renders the venous hæmorrhage quite insignificant. In such a case we do not adopt preliminary hæmostasis. After having enucleated the cyst without opening it, the wound is closed as in an ordinary goitre, but a little more complete drainage is provided. In some cases the wound heals by first intention; in others there is a slight oozing, which, however, never leads to any trouble, owing to the drainage.

FIG. 110.—Skiagram of preceding case. Calcareous concretion. The probe indicates the course of the external sinus and the arrow that of the œsophageal fistula.

If the case has been healed originally by drainage only and a chronic goitrous sinus has developed, it becomes necessary to enucleate the infected lobe. This operation is more difficult than in subacute cases because the adhesions will have become denser in the interval. Enucleation will often be combined with resection and even excision of the lobe. The same applies to a sinus which develops spontaneously in a diseased thyroid of old standing. The cause of the persistence of the suppuration is generally due to the presence of calcareous nodules. In these cases one should always bear in mind the possibility of an œsophageal fistula (see figs. 109 and 110).

The breathing always becomes easy immediately after the opening of the abscess or the enucleation of the lobe, and we have never been compelled to perform a tracheotomy, either in an acute thyroiditis or in chronic disease of the gland.

II.—CHRONIC INFLAMMATORY AFFECTIONS.

In some cases of subacute or chronic *simple thyroiditis* which run a very long course, there is a persistence of pain. In this type of case

we have, on rare occasions, performed resection of a lobe. This operation is done according to the ordinary method of resection and requires no further description.

Some cases of persistent non-suppurating diffuse thyroiditis are *tubercular* in character. The whole lobe and sometimes the whole gland is transformed into lardaceous tissue, in no way resembling ordinary tubercular tissue. It is, however, the variety of tuberculosis which Poncet has classified as inflammatory tuberculosis, and it comes within the same group as fibroid tubercle of the liver or kidney. It cannot be diagnosed without a microscopic examination. It is not rational to operate on these cases; they should be treated by radiotherapy after the diagnosis has been established by examination of a small portion which has been excised.

In some cases *tertiary syphilis* is responsible for diffuse dense infiltration of the gland. The diagnosis is made from the history and the examination of the blood. Some of these cases may be mistaken for a malignant tumour. Whenever there is the slightest suspicion that a doubtful tumour may be syphilitic, specific treatment should be carried out tentatively.

Chronic suppurating thyroiditis, whether starting in a healthy or diseased gland, is nearly always *tubercular*. If the affection is definitely unilateral, excision of the lobe is indicated. If both sides are affected, we prefer repeated punctures and X-ray treatment, or climatic treatment. Systematic histological examination of all goitres operated on would often reveal localized and circumscribed tubercular lesions in goitres which give no rise to such suspicion, either on clinical or macroscopical examination.

CHAPTER XIV.

MALIGNANT GOITRE.

I.—GENERAL REMARKS. SYMPTOMS. HISTOLOGY.

NOTWITHSTANDING the progress made in Histology we are still compelled to use the general term of "malignant goitre," because it is impossible to differentiate the different histological types of cancer clinically; indeed it is not possible to distinguish cancer from sarcoma. We will first briefly describe the clinical symptoms of malignant goitre, without going into any details of pathological anatomy.

Clinical diagnosis is quite out of the question when malignant degeneration exists in a well encapsuled innocent goitre. We only

become aware that we have operated on a malignant goitre after histological examination of a section, or if metastatic deposits occur.

The following are the *earliest symptoms of malignancy:* The rapid growth of a goitrous nodule after the age of 30 and in the absence of pregnancy the firm consistence of the nodule, and its lack of mobility. This triad of symptoms is soon followed by nerve lesions, viz., radiating pains, paralysis of the recurrent nerve and of the ocular branches of the sympathetic causing contraction of the pupil and narrowing of the palpebral fissure. The goitre becomes more and more fixed, compressing the trachea and invading the skin.

If the type of neoplastic tissue is very different from the normal structure of the thyroid, the symptoms are quite characteristic, but if the histological type resembles that of an innocent adenoma the nature of the case remains indefinite. The mildest form of malignancy is presented by those *cases which look innocent but which are associated with secondary deposits.* Then comes the type described by Langhans as *wuchernde Struma* or *proliferating goitre.* In structure it resembles an innocent adenoma with solid plaques parallel with the periphery and curling towards the centre. Its malignancy is betrayed by the size and irregularity of these plaques, the penetration of the neoplastic cells into the capsule and the vessels and by the frequency of karyokinesis. Sometimes histological examination is indecisive, and the clinical progress must be followed before malignancy becomes evident. In other cases the goitre assumes the form of a *papilloma;* but histological examination is indecisive here also, because there is no polymorphism of cells or invasion of the capsule and vessels to betray its true nature. Finally, there are the various forms of *epithelial cancer,* which are neither adenomatous nor papillomatous.

We make no reference to certain very rare forms, such as cancroid of the thyroid or malignant tumour of the parathyroids. These can only be identified by microscopical examination.

Sarcomata also appear under diverse forms, which defy clinical diagnosis. Endotheliomata of the thyroid, first described by Hedinger, occur quite frequently, and these tumours are allied to sarcomata.

Metastatic deposits from malignant growths in other organs occur but rarely in the thyroid (hypernephroma, melanosarcoma). We have observed one case wherein the only secondary deposit of a hypernephroma occurred in the thyroid, and it resembled a primary carcinoma of the gland.

Some authorities hold that obliteration of the shadow of the trachea in a skiagram is a characteristic feature of malignant goitre, but this really indicates nothing more than anteroposterior com-

pression of the trachea and may quite well be caused by an innocent goitre situated in the middle line.

Later on, we shall discuss the differential diagnosis of malignant goitre and certain forms of old diseased thyroids.

II.—DIFFERENTIAL DIAGNOSIS.

It is necessary to refer to certain difficulties in diagnosis which do not always receive the attention they deserve.

We have already mentioned the fact that chronic diffuse thyroiditis, in its simple and its tubercular form, is very suggestive of malignant goitre; but the mistake is not likely to be made by those who have frequent opportunities of seeing this type of case. In thyroiditis the swelling is not great, the consistence is uniformly hard, and the lobe retains its normal shape. These points should suffice to enable a novice even to distinguish between the two conditions.

Tertiary syphilis of the thyroid may also resemble malignant goitre. Before undertaking operative measures, the history must be investigated and the Wassermann test performed, and if indications are positive, vigorous specific treatment must be instituted. But time must not be wasted, lest a new growth be allowed to drift into a condition wherein it is no longer operable.

Tuberculosis in its nodular form rapidly breaks down into an abscess, so that the diagnosis does not remain long in doubt. A tuberculous goitre is, however, much more rare than a malignant goitre.

The chief diagnostic difficulties are caused by certain old cystic goitres with thick walls, in which hæmorrhage has taken place or in which a subacute metastatic infection has occurred—events which impart to the goitre an aspect of activity. The patient usually comes to the surgeon after the temperature has fallen to normal, and the leucocytosis has disappeared. The immobility of the tumour, its recent increase in size and the age of the patient raise suspicions of malignant goitre. One would hardly suspect that the goitre is innocent, but has been awakened into activity by hæmorrhage or infection, unless the history is very precise. The difficulties of diagnosis are further increased by the possibility of infection taking place in a pre-existing malignant goitre. We have seen this combination in three cases in which operation showed the presence of a sarcoma together with infection. More than once we have seen a malignant neoplasm develop in the wall of an old hæmorrhagic cyst.

III.—INDICATIONS FOR OPERATION.

Operation is the treatment of choice so long as it can be undertaken with reasonable chance of success.

The operation for malignant goitre does not differ in principle from that for innocent goitre if one only performs complete hemi-thyroidectomy, including the capsule, so long as the neoplasm has not overstepped the limits of the true capsule. When the new growth has exceeded these limits and diagnosis has become certain the operation will correspond to that for the removal of any malignant tumour. In this latter case one must be prepared to sacrifice the trachea, recurrent laryngeal, jugular vein and even the carotid, according as these structures are invaded by the growth. Involvement of the carotid should always cause the operator to hesitate, because after the fiftieth year, and sometimes even before, ligature of this vessel results in grave if not fatal cerebral disorders. The immediate results of operation in these advanced cases are so unsuccessful, and the subsequent results even more so, that well-regulated radiotherapy and radium treatment are much to be preferred to these extensive and mutilating dissections. X-rays through a copper or zinc filter of 0·5 to 1 mm., and radium applied in sufficient quantity on and in the tumour will exhaust the patient much less than resection of the trachea and will be equally efficacious. It seems that the future lies with a combination of these different methods which appear to have much more influence over sarcomatous than carcinomatous growths. The immediate results are sometimes brilliant, but present experience makes one very guarded about prognosing a radical cure.

The only way of avoiding the alternative between a mutilating operation and simple palliative treatment is to operate on the goitre before one is sure that it is malignant.

IV.—THE OPERATION FOR MALIGNANT GOITRE.

We pass on to details of the operative technique.

The collar incision will generally be made. It should be placed somewhat higher than in most innocent goitres so as to give free play in all directions. In certain cases the old angular incision of Kocher or the lateral ascending collar incision of Girard may be used with advantage. When the platysma has been incised one makes straight for the sternomastoid either to detach its insertion above the sternum, or to resect it should it be adherent to the goitre. The small thyroid muscles should be divided above and below, and left in contact with the goitre. Then one proceeds to the upper pole of the goitre and divides the superior vessels after having placed a double ligature on their proximal end and a single ligature on the side of the gland. This done, the tumour is raised up and the inferior thyroid artery is found as quickly as possible without paying any heed to the para-thyroids and the recurrent nerve.

If the internal jugular vein is adherent to the tumour it must be

resected after having ligatured it proximally to avoid any risk of air embolism. If the carotid is also adherent it should be resected in patients below forty, and in older patients one should cautiously attempt to free it. Then the lower pole is raised and the inferior vessels are divided after double ligature. The goitre is then separated towards the mid-line, detached from the trachea and resected, leaving a wide margin round the malignant tissue. Before the isthmus is taken away the antero-internal branch of the superior thyroid artery of the opposite side is ligatured in continuity.

When the new growth extends into both lobes the position is very uncertain. The choice between incomplete excision on the one hand and total thyroidectomy with the risk of myxœdema and tetany on the other is not always easy. It has already been said that the possibility of giving radiotherapy and the desire not to burden the last months of a patient's life with the miseries of a tracheotomy tube will often determine one in favour of prudent opportunism.

Sometimes the superior thyroid artery is not accessible at the beginning of the operation; one must then invert the order of procedure and attack the tumour either through the isthmus or by quickly detaching the lower pole. It is almost superfluous to point out that the neoplasm will always appear more mobile before the operation than during it, and that the most able surgeon will desist from interfering with a tumour immured in the upper aperture of the thorax. He will also hesitate to perform the operation when the mobility of the tumour appears to be doubtful. Two types of immobility must be distinguished: in the first the goitre is fixed by neoplastic infiltration which obliterates all the planes of cleavage. Here the surgeon is perfectly justified in hesitating. In the second type, the fixation is due to the lower part of the tumour being locked in the upper aperture of the thorax. If the operator is bold he may be able to overcome the difficulties and will be rewarded with unexpected success. Radiographic examination will sometimes enable one to foresee the second class of difficulty. In other cases only operation, at first exploratory, will show if removal of the tumour is possible.

Mention has been made above of the difficulty in diagnosing between malignant goitre and certain forms of recent and old-standing thyroiditis. We have also seen that the presence of pus does not exclude malignant new growth—nevertheless on the solution given to this question depends one's treatment, especially in regard to the great cervical vessels and nerves. Only excision of a fragment of tissue during operation and the immediate examination of a frozen section thereof will enable one to take a precise line of conduct. Repeated experience has shown that in the case of malignant new growth complicated by inflammation, interpretation of

the microscopic appearances may be very difficult, even to skilled pathologists.

The operative difficulties arising from stenosis of the trachea are overcome in the same way as in similar cases of innocent goitre; but one would decide on tracheotomy much more readily in malignant goitre than in the innocent variety.

Immediate *post-operative treatment* is the same as for ordinary goitre in the simple cases, and as for resection of the larynx, of the trachea or of the pharynx in the advanced cases. The subsequent treatment can be summed up in three words: radiotherapy, arsenic—and morphia in case of recurrence.

CHAPTER XV.

THE SURGERY OF THYROID DEFICIENCY.

I.—DIAGNOSIS OF HYPOTHYROIDISM.

How can hypothyroidism be recognized? The clinical picture of the different hypothyroid conditions is too well known, thanks to the classic work of Ord, J. Reverdin, Kocher, Horsley, Hertoghe, Moebius

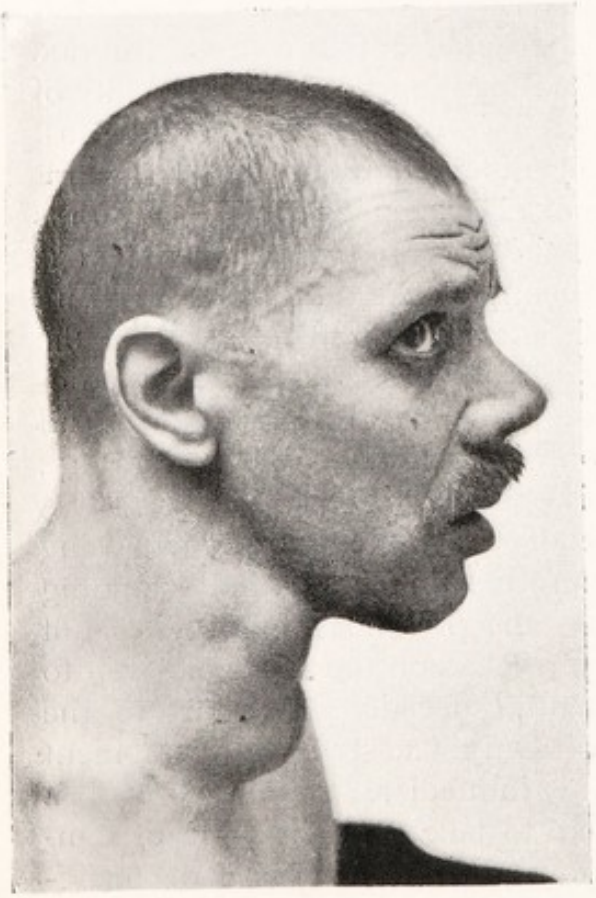


FIG. 111.—Cretinism with goitre.

FIG. 112.—Cretinism without goitre.

and too many others to detain us here, although daily experience teaches that there are still many problems to be solved in this region. We are thinking particularly of **cretinism** which, despite the important work of Iphofen, Maffei, Troxler, Lebert, St. Lager, Baillarger, Kocher, Bircher, Wagner, Stolz, McCarrison and the Sardinian, Lombard and French Commissions, is far from having given up all its secrets.

Endemic cretinism shows only in a minority of cases the clear picture of hypo- or athyroidism. On the contrary it is the resultant of a number of factors :—

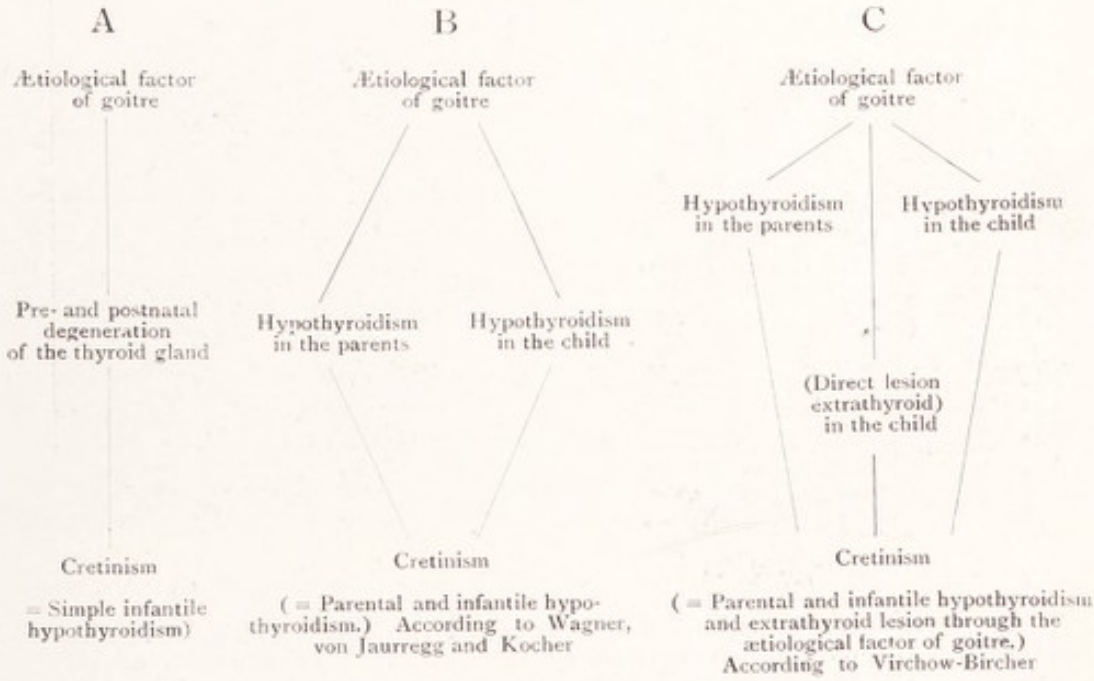
(1) Hypothyroidism in the father, giving rise to inferiority of spermatozoa.

(2) Hypothyroidism in the mother, more frequent than the former, giving rise to (*a*) original inferiority of the ovum, (*b*) intra-uterine disorders of nutrition following on thyroid deficiency in the mother.

(3) Deficiency of and vitiated thyroid function in the child, showing itself chiefly in extra-uterine life.

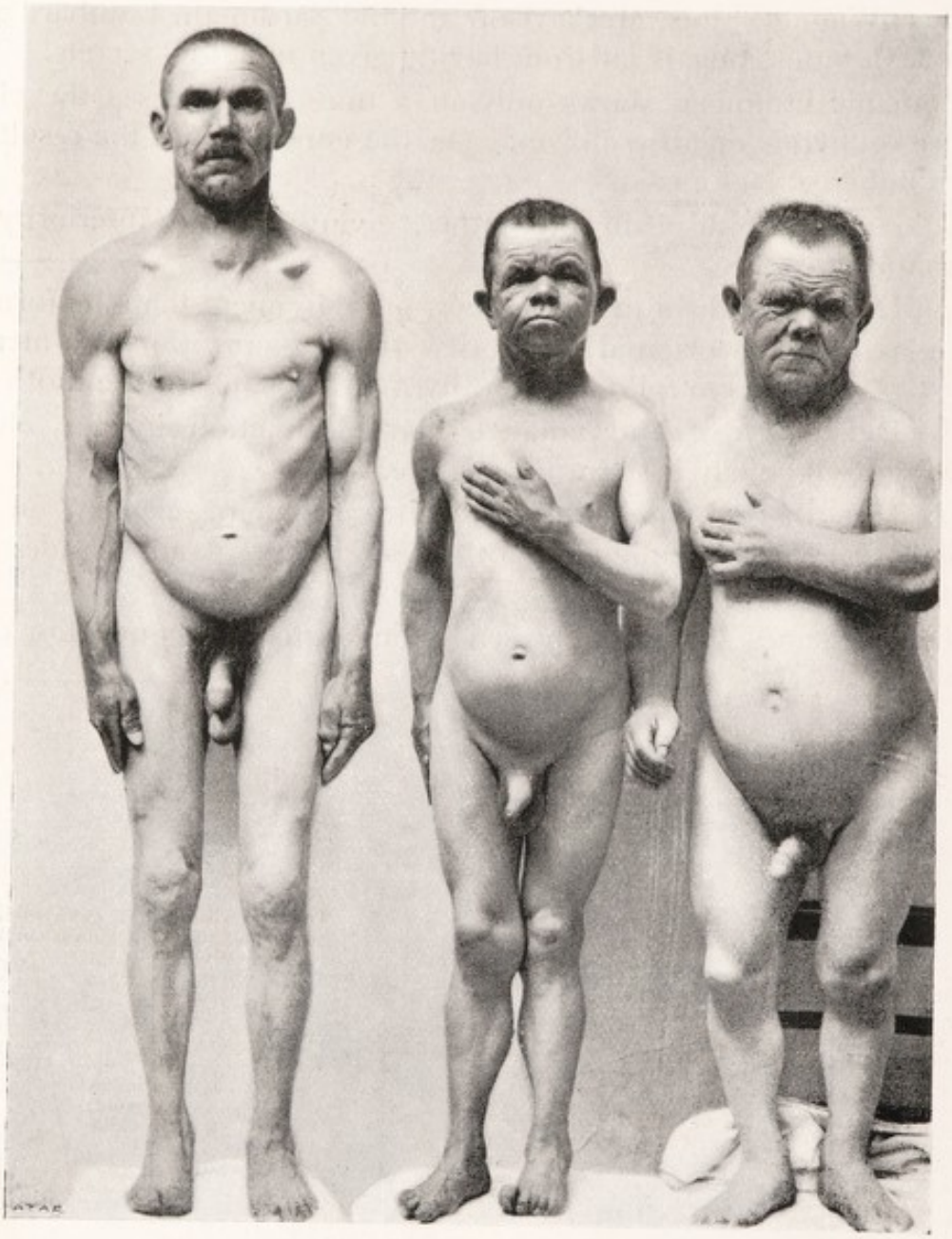
(4) Hypothetic influence of the goitre-producing element on the whole organism, including the other endocrine glands besides the single thyroid lesion.

The schemes below represent the different conceptions of cretinism :—



The question of thyroid deficiency is forthwith decided if digital examination detects the practically complete absence of the two lobes of the thyroid and the finger can pass uninterruptedly down the anterior surface of the trachea. The clinical picture accompanying

these anatomical findings may be associated with simultaneous deficiency in other endocrine glands. The case of the goitrous cretin is quite different, for the full complement of the classical symptoms of



(*a*) (*b*) (*c*)

FIG. 113.—Cretinism with and without goitre. (*a*) Cretin with goitre. Height 158 cm. Genital glands and pilary system normal. (*b*) Cretin with atrophied thyroid. Height 133 cm. Testicles atrophied; maldeveloped pilary system. (*c*) Ditto. Height 135 cm.

thyroid insufficiency (disturbed growth of bones, skin affections, nervous disorders) is not always present. This dissociation of essential symptoms has been long recognized and never fails to strike those

who have the opportunity of examining a large number of cretins. Figs. 111-113 demonstrate the difference between the dwarfed cretin with an atrophied thyroid, and the goitrous cretin who is often of average height or only a little below it. The differences in the skeleton, in the hairy growth and in the development of the genital organs are very apparent. Figs. 114-118 illustrate the principal phases

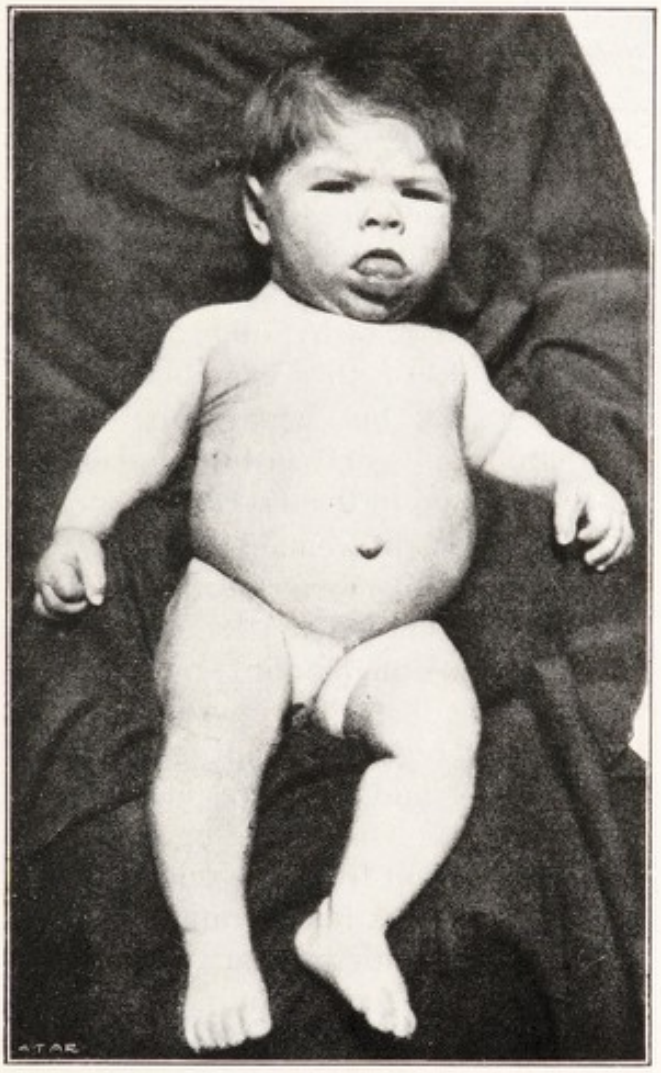


FIG. 114*a*.—Cretin with atrophied thyroid, aged 2 years.

FIG. 114*b*.—Cretin without goitre, aged 6 years.

of development of the cretin with an atrophied thyroid. The case illustrated, for the sake of comparison, in fig. 116 belongs to the series published in 1883 by Kocher of cases which had undergone complete thyroidectomy. The dissociation of symptoms, of which we have just spoken, suggests to us the idea of a hypodysthyroidism in which the *hypo* and the *dys* elements participate equally.

The **slighter forms of hypothyroidism** occur in patients whose glands have been damaged by an inflammatory affection or by endemic goitre. Objection has been taken, with some justification, to the inclusion into this group by Hertoghe and his followers, of conditions whose hypothyroidic origin has not been proved. The truth is that we have no absolute criterion of hypothyroidism. The *examination of the blood* to ascertain the total red cell count and the differential count of the white cells, affords us no decisive indication—as already noted in Chapter VI. An investigation of the *biological characters of the blood* yields interesting results in severe cases. In mild cases of hypothyroidism the result of this examination is negative, but very probably useful results may in future also be obtained in this type of case.

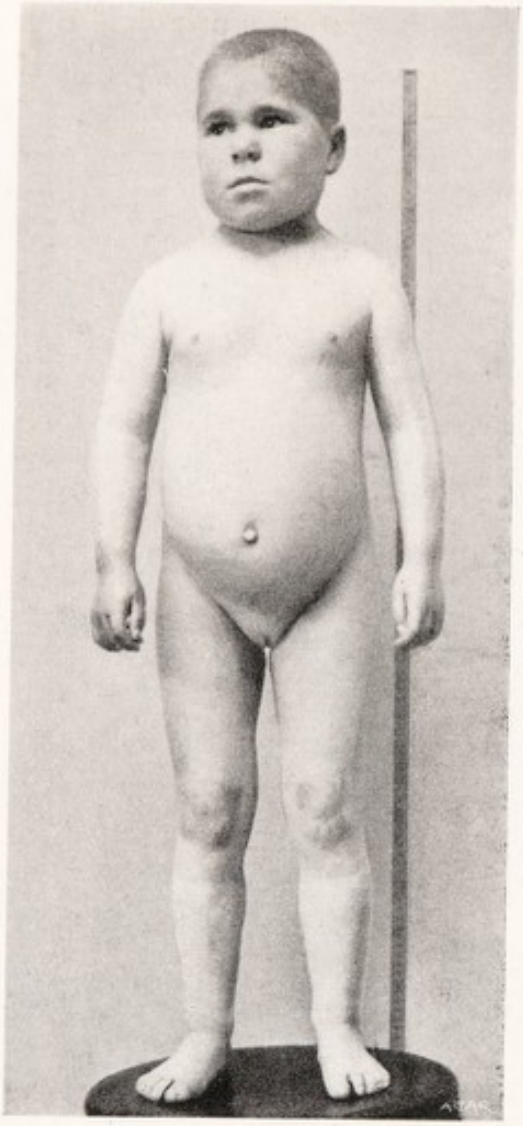


FIG. 115.—Cretin without goitre, aged 14 years.

There still remains the *examination of the metabolic rate*. We have known for some time that the metabolic rate is diminished in hypothyroidism, both in regard to nitrogenous material and the respiratory exchange. These investigations are important from the scientific point of view, but are much too complicated for ordinary clinical practice. The determination of the respiratory exchange which, in Europe, has hitherto been regarded as a matter of purely scientific research, has of late been employed by American physicians in their practical work. It is, however, an investigation which it is difficult or impossible to carry out in most cretins. The experiment requires that the patient should remain at rest in Jaquet's apparatus for two hours, and this is an ordeal which a cretin will not tolerate. On the other hand, we have convinced ourselves that the test can be carried out, by means of Tissot's spirometer, even on certain cretins of the second degree, after the preliminary exercises.

There is no doubt that there is a great decrease in the metabolic rate in severe cases of hypothyroidism; the American authorities (Janney, Plummer, Gardener) estimate this to be about 20 to 40 per cent., and this is confirmed by our own experiments. In the case of the dwarfed cretin this diminution of the metabolic rate may be absent and does not always correspond to the degree of the changes in the skeleton. The accuracy of Rubner's formula—the height-weight formula of American authors—in regard to the extreme figures of weight and height still awaits verification. The test for the metabolic rate must be carried out thoroughly, especially in cases of slight hypothyroidism wherein the clinical diagnosis is doubtful. It is necessary that the inherent sources of error should be eliminated, as far as possible, in each case by repeated examinations, and it is desirable that we should know more than we do at present of the limits of normal metabolism for each age period, including infancy. The tables hitherto ascertained do not apply to early or later infancy, and we think that it is quite impossible to obtain any information of value concerning the respiratory metabolism before the age of 6-8, because a young child will not maintain the absolute repose which is requisite, especially if there be any psychical abnormality.

FIG. 116.—Post-operative cachexia, after removal of thyroid, patient aged 26.

We are in a position to state that the diminution of the metabolic rate is greater in acquired thyroid insufficiency—myxœdema—than in cretinism, for in the latter condition there has been sufficient time for the metabolic rate to have returned to its normal.

We have hitherto been referring to cases whose symptoms have suggested the idea of thyroid insufficiency, or what amounts to the same thing, of a dysthyroidism associated with insufficiency. We

now have to consider individual **disturbances of certain systems or organs** in their relation to the thyroid.

In the first place there are the cases of *imbecility and idiocy* which one is tempted to ascribe to thyroid inadequacy, in default of any other plausible causation.

What are the relations between (1) the idiocy of cretinism; (2) Little's disease; and (3) the nervous cretinism described by McCarrison?

There is a current idea that the *motor and sensory* disorders of the cretin are diffuse in character, and that definitely localized lesions are absent. Most cretins are too dull to permit of any detailed or precise neurological examination. It is only from an examination of the *reflexes* that any accurate results can be obtained. One of the first observations which strikes us in connection with cretinism is the very frequent exaggeration of the tendon reflexes, especially those of the patella. This sign has been recognized for a very long time, and Scholz has noted this exaggerated knee-jerk in 52 per cent. of the cases. We have observed this exaggeration in 50 per cent. of the 213 cases of cretinism. It has usually been accompanied by an exaggeration of the tendon and periosteal reflexes of the upper limb, and it keeps pace to a certain extent with the severity of the general symptoms of cretinism; but there are very numerous exceptions. The condition of the thyroid, whether atrophied or goitrous, does not appear to play any decisive rôle.

These facts impelled us to examine the reflexes in a series of forty goitrous cretins under observation in hospital who were subsequently operated on. The results may be tabulated as follows:—

	Absent	Feeble	Normal	Greatly increased
Muscle tonus as recognized on palpation	...	11	23	6
Muscle tonus as recognized on passive movements	...	9	19	12
Trousseau's sign	38	...	...	...
Chvostek's sign	20	17	...	...
Idiomuscular contraction	11	21	...	...
Muscular tenderness	...	20	17	...
Plantar reflex	...	8	25	5
Abdominal reflexes	2	15	22	9
Tendo Achillis reflex	...	14	18	7
Patellar reflex...	...	5	13	21
Periosteal reflexes of upper limb ...	3	5	15	13
	Plantar flexion		Dorsal extension	
Babinski's sign	28	...	9	...

In this series also the *patellar reflex* was exaggerated in more than half the cases (52 per cent.). The *periosteal reflexes* were less frequently exaggerated (32 per cent.). These figures are a contrast to the comparative frequency (35 per cent.) of the decrease of the Achilles reflex. *Skin reflexes* are very variable even among persons who are supposed to be normal, and in our small series the cases wherein these reflexes were exaggerated are balanced by those in which they were decreased.

Is the exaggeration of the tendon and periosteal reflexes an

FIG. 117.—Cretin with atrophy of the thyroid, aged 40 years.

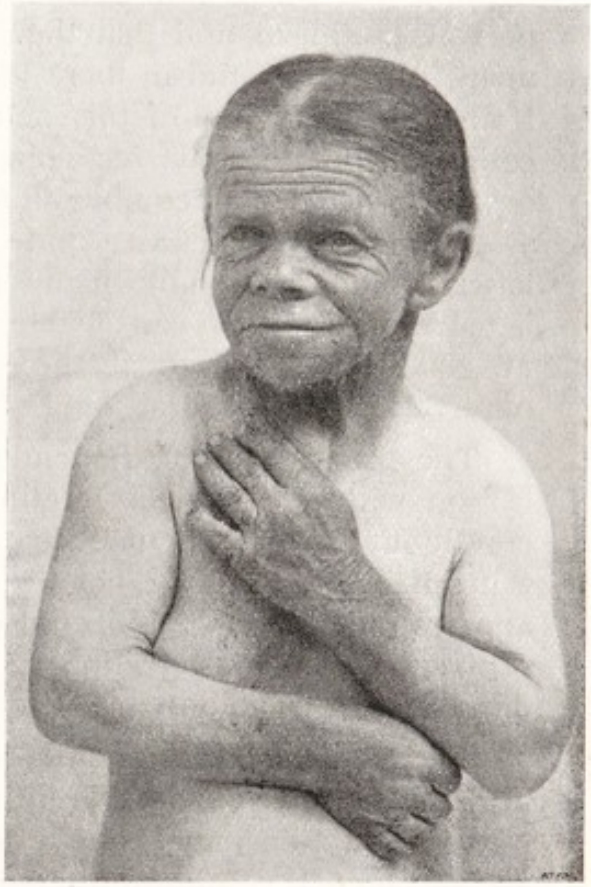


FIG. 118.—Cretin with atrophy of the thyroid, aged 62 years.

integral part of the clinical picture of cretinism, or is it an *accessory phenomenon* due to secondary cerebral lesions, such as hydrocephalus? We cannot reply categorically to the question from our own observations, but the latter explanation appears to us more plausible than the former, in view of the inconstancy of the sign and its more frequent occurrence in advanced cases. But it may be stated confidently that the classical picture of cretinism never presents any general spasticity like that of Little's disease, despite the tremors of

the thigh muscles, which are sometimes almost epileptoid in character. This fact has an important bearing on the explanation of the syndrome termed by McCarrison *nervous cretinism*.

According to McCarrison one-third of the cases of cretinism in the Himalayas is of this type, which is a *combination of ordinary cretinism* with the clinical pictures of *cerebral diplegia and tetany*. The cases published by him certainly present the physiognomy of cretinism; their attitude resembles Little's disease and their movements are very suggestive of tetany. Crookshank has described cases of this kind in England. He thinks that these cases have hitherto been regarded as examples of Little's disease, but that they are really instances of nervous cretinism, and that they can be improved by thyroid treatment. In true cretinism there are neither focal lesions nor diplegia. If there be any lesion of this nature, it is most probably not due to cretinism, but to some recognized variety of encephalitis or myelitis, or to an accidental combination of a thyroid disorder with some systemic nervous disease, quite independent of the thyroid. This latter condition is quite likely to occur in countries where goitre is endemic, and is very liable to lead to mistakes in diagnosis. M. Naville has arrived at the same conclusion as a result of his observations in Geneva.

The exaggeration of the tendon reflexes in the cretin has no association with the nervous cretinism of McCarrison. In this latter condition there is an inadequacy of cerebral inhibition, and not a state of hypermotility. The explanation of McCarrison's syndrome appears to be due to the fibroid degeneration of the parathyroids in subjects of nervous cretinism. Thus the pathology of this latter disease is to be found in a thyroid-parathyroid inadequacy.

To establish the *differential diagnosis*, it is necessary to take into account the state of the thyroid as well as all the other points just referred to. The metabolic rate should also be determined if the age and mental condition of the patient permit of this test. In cases of doubt the therapeutic use of thyroid may be employed as a test, but no conclusion should be drawn that the nervous symptoms are of thyroidic origin unless the results of the test are quite definite.

The diagnosis of *mongolism* should not be difficult. It is easy to recognize the Mongol features, and the hypermotility of the patient is very characteristic. In our opinion the existence of "mongoloid cretinism" is very doubtful.

In regard to the relation between *slight functional disorders of the nervous system* and thyroid inadequacy, it may be said that there is hardly any symptom which has not been attributed to this latter cause—since the researches of Hertoghe. One need only mention

lassitude, fatigue, feeling cold, sleepiness, loss of memory, headache, arthritis, myalgia, transient œdema, constipation, obesity, and premature baldness. It is, of course, possible that the thyroid may be responsible for each of these symptoms, but they are of such frequent occurrence that some discretion is required before attributing them to this cause. The most conclusive criteria may be derived from careful palpation of the gland and the investigation of the respiratory exchange; but even then the results may be equivocal. The question can be settled by therapeutic experiment if the result of treatment is definite.

In regard to *deaf-mutism*, the relation of this condition to endemic cretinism is quite clear, because of their frequent coincidence, and because of the frequent occurrence of deaf-mutism in countries where goitre is endemic. In proportion to the population, Switzerland has three times as many deaf-mutes as any other European country. In any case of deaf-mutism wherein there is a morbid condition of the thyroid gland, it may be assumed that the latter is the cause of the former, if there be no other obvious explanation of the deaf-mutism. But if there be no disorder of the thyroid and there be no other symptoms of cretinism, the cause must remain doubtful. It may be said, *en passant*, that the researches of Siebenmann and his pupils have shown that the deaf-mutism of the cretin is not due to any abnormality of the ear, but to a lesion of the nerve organ of perception.

A similar problem arises in certain cases of *dwarfism*. Is the condition due to rickets, disorder of the pituitary or of the thyroid, or is the stunted growth due to some other cause? The differential diagnosis depends upon the details of the development of the skeleton, and upon any other symptoms which may be present. A dwarfed cretin may still retain a certain amount of intelligence, and on the other hand, some cretins are complete idiots although they are not dwarfs. Possibly the determination of the respiratory exchange and biological tests of the blood may cast light on some of these obscure points.

We shall discuss, in a separate chapter, the association of the symptoms of hypo- and hyperthyroidism.

II.—OPERATIONS INTENDED TO RELIEVE THYROID INADEQUACY.

At first sight, thyroid grafting appears to be the rational treatment for all conditions of hypothyroidism. Since the first attempts of Schiff in this direction, the operation has been practised, in all its modifications, by von Eiselsberg, Cristiani, Kocher, Bircher, Payr, Voronoff and others. The work has been taken up again quite recently by Lexer,

in a very thorough manner. This surgeon has arrived at the conclusion that heteroplasty, i.e., the implantation of a thyroid of an animal into man, is quite useless, and that good results can be expected only from autoplasty and homoplasty. In his view, autoplasty is the one procedure which can give an ideal result in the sense that the graft "takes" and that it assumes the specific function of the gland, it being the only thyroid tissue in the body. The success of other methods is said to be due to the persistence of gland "rests" which are stimulated into functional activity by the distant graft. It is in this way that he explains the success of homoplasty, i.e., the grafting of the human gland of another person (Kocher). The unfavourable opinion of heteroplasty held by Lexer and most other authorities is at variance with a result obtained by Voronoff with the graft of the thyroid of one of the higher apes on man. The future will, however, decide.

Many methods of *operative technique* have been suggested—viz., subcutaneous, subserous, intraperitoneal, intrasplenic grafts, also grafting into the bone marrow (medullary cavity of the tibia). The best results have been obtained by means of an intrasplenic graft and into the head of the tibia (Kocher, Payr). Kocher insists upon the importance of thyroid treatment before and after operation. In 1914 Voronoff grafted into the anatomical site of the thyroid, a procedure which we had adopted without being aware of Voronoff's operation.

The description of the operative technique need not detain us long. In order to succeed three essentials are requisite: (1) perfect hæmostasis; (2) strict asepsis; (3) immediate implantation of the graft.

Years must elapse before the permanent success of the grafting can be assured. It often happens that the graft only acts as a drug, in that it is gradually absorbed and when completely absorbed its effect terminates. Before one can speak definitely of a positive result, it must be established that the disorder is hypothyroidic in origin, and that good health is subsequently maintained without the aid of any additional thyroid treatment. These two essential conditions must be carefully considered in estimating the true value of the results hitherto published.

Carrel, Enderlen and Hotz have paid special attention to grafting, assisted by vascular suture. Except for temporary improvement during the period of absorption, the results were negative.

Drug treatment consists of the daily administration of one of the numerous preparations of thyroid, which acts most satisfactorily in young patients.

TABLE OF DOSES OF SOME FORMS OF THYROID PREPARATIONS.

Preparation	Usual dose	Dose calculated for fresh gland	Dose calculated for dry gland	Iodine content
Thyroxine of Kendall	0·002 grm.	...	2·00 grm.	65 per cent. = 1·3 mg.
Thyracrine (= Iod-thyreo-globuline of Oswald)	0·05 grm. (in tablets of 0·3 grm.)	1·5 grm.	...	0·3 per cent. = 0·15 mg.
Thyreoglandol (Hoffmann and Laroche)	Tabloids of 0·1 grm. ,, 0·3 ,, Ampoules of 1 ,,	0·1 grm. 0·3 ,, 1 ,,	...	—
Thyroidine (Byla)	Cachets of 0·1 grm. ,, 0·15 ,, ,, 0·25 ,, Pills of 0·1 ,, Ampoules of 0·05 ,,	0·5 grm. 0·75 ,, 1·25 ,, 0·5 ,, 0·25 ,,	...	0·002 mg. per 0·1 grm. of thyroidine
Thyroidine (Burroughs Wellcome)	Tabloids of 0·05 grm. ,, 0·1 ,, ,, 0·3 ,,	0·05 grm. 0·1 ,, 0·3 ,,	...	0·01 mg. per 0·1 grm. of thyroidine
Thyroidine of Parke, Davis	0·3 grm.	0·25 grm.	...	...
Gl. thyr. sicc. Thyroidea-Opton	0·1 grm. 0·1 ,,	...	0·1 grm. 0·1 grm.	0·3 per cent. = 0·3 mg. 0·4 ,, = 0·4 ,,

Our experiments on the rat show that thyracrine and thyreoglandol are more active than thyroxine calculated on the basis of the same weight of fresh gland (Branovacki).

The experimental and clinical results of **parathyroid grafting** are similar to those already stated for thyroid grafting. The only chance of real success is offered by an autoplastic graft, but the matter has very little practical importance. Homoplasty should be attempted if the opportunity arises, because a certain amount of success stands to its credit in rare cases (von Eiselsberg).

III.—THE OPERATION FOR GOITRE IN CASES OF THYROID INADEQUACY.

In countries where goitre is very endemic, the necessity occasionally arises to operate on cretinoid patients or genuine cretins, owing to symptoms of compression. As the thyroid gland is already inadequate, any diminution of it by operation is apparently contra-indicated. A similar difficulty arises in cases of recurrence of goitre in patients who are already at the lowest level of euthyroidism. The

operation of *dislodgment of the goitre* has been suggested in these circumstances. Bonnet was its pioneer, and it was popularized by Kocher and Wœlfler. It is impossible to give precise directions for the performance of this operation, because each case is a rule to itself. Its principle depends upon isolating as effectually as possible the lobe which is causing the obstruction and which it is desired to preserve. This is done by the aid of ligatures, by cutting through the isthmus and one of its vascular roots, the other root being carefully safeguarded. The lobe is then manipulated sideways, upwards and downwards according to the indications present, and is then fixed by a few catgut sutures in the lateral region of the neck, at the side of the sternomastoid, if possible.

This proceeding is much more likely to be successful than the transplantation of a graft of the goitre into another part of the body (peritoneal cavity, spleen, medullary cavity at the tibia). But if for any reason the dislodgment *in situ* appears to be impracticable, the method of transplantation must be adopted.

In our own practice, we do not hesitate to remove a considerable portion of goitrous tissue in cretins. These patients are often provided with a large amount of goitrous tissue, which, according to modern views, is practically functionless—or, what is more likely possesses a disordered function. At any rate, it is better for a cretin to breathe freely than to keep his goitre intact. The principle, *primum vivere, deinde philosophari* is also applicable to cretins.

Are the mental faculties of a cretin influenced by any considerable removal of goitrous tissue? In order to answer this question, we have investigated the remote results of operations for goitre on fifty cretins who have been under our care during the last few years. The patients usually express their satisfaction with the operation. Even the deaf mute is full of vivacious gratitude to the operator, in contrast to many a euthyroidic patient who looks upon the operation as a "social duty." There are institutions which contain hundreds of cretins, and those who have been operated on are emphatic in recommending those of the other inmates whom they think suitable subjects, to undergo the operation. In order to compare their mental faculties, before and after operation, the opinions of the attendants must be considered. Among fifty-six cases operated on, thirty-four showed no change in their psychical condition. The attendants were however able to observe a notable improvement in thirteen cases, some of this improvement being doubtless due to the liberation of the trachea. In nine cases, the intellect and capacity for work appeared to have diminished, despite the improvement in breathing which resulted from the operation.

The maintenance of the *statu quo* on the part of these patients may be due to the fact that enough thyroid tissue remains to secure the diminished functional capacity of the nervous system (mild cases), or to the fact that they are already so bad at the time of the operation that their symptoms cannot become worse (severe cases).

It is more difficult to explain the improvement which the attendants noted in about one-third of the cases, unless it is to be attributed entirely to the easier respiration. One explanation may be that the goitrous tissue of the cretin originates some inhibition, which is decreased by the reduction in size of the goitre. Some support is found for this view in the presence of inhibitory substances in the blood of the adult as compared with that of the child, a point which Carrel admits. Another explanation assumes that there is a comparatively healthy portion of thyroid in the cretin which is being compressed. Removal of the goitre relieves this pressure, and the function of the healthy compressed portion of thyroid is restored. It is quite possible that this explanation may be true in some cases, but it has no general application. We are aware of cases of cretinism wherein the entire gland has undergone a uniform change and where there can be no question of the compression of a healthy portion.

The aggravation of the mental state in a little more than one-fifth of the cases is easily explained on modern views. The gland which was already inadequate before the operation becomes even less useful after some of its tissue has been removed. This of course means that the goitrous tissue of such cretins was partially functional.

We have stated the facts and for the moment will not attempt to provide them with any definite interpretation ; but we are bound to say the interpretation is facilitated by adopting the hypothesis of a cretinoid dysthyroidism. This dysthyroidism varies in different cases, and the result of operation will be the more favourable as the pathological element preponderates over the physiological.

How are we to distinguish those cases which may undergo considerable removal of goitrous tissue without any deterioration from those wherein this tissue is still useful and functional ? The answer to this question can only come from a detailed study of the clinical, histological and biological characters of each case.

M. Chaitan has made a comparative study of the blood of thirty-nine cretins, before and after operation. In twenty cases no change was observed. In fifteen cases there was more than a 25 per cent. increase of lymphocytes after the operation, and in four cases there was a decrease of more than 25 per cent. There was thus a very predominant increase.

We have not hitherto been able to establish any constant relation between the state of the blood, the histological type of the goitre and the physical and psychical characters of the cretinism.

CHAPTER XVI.

THE SURGERY OF HYPERTHYROIDISM AND EXOPHTHALMIC GOITRE.

I.—DIAGNOSIS.

BEFORE one can make a diagnosis one must have a definition of the disease it is desired to diagnose. The clinical picture of Graves' (or Flajani's or Basedow's) disease has been and is described so often and so variously that it becomes more and more difficult to reduce it to simple proportions. The creation of numerous subdivisions in accordance with the particular author's theoretical conceptions is not conducive to clarity, so that we shall not attempt here to give an account of the many divergent views but confine ourselves solely to the practical aspect. The reduction of the volume of the thyroid affected by Graves' disease to the limits of a normal gland (about 25 c.c.) ensures preservation of the function of the gland while the chief symptoms of the disease disappear, whatever the nervous temperament of the patient or the condition of his other endocrine glands may be. This fact alone is sufficient to make the thyroid the centre of the discussion. That the nervous system, or rather the nervous predisposition of the patient, plays a considerable part no one can deny, any more than one can deny the importance of the supra-renals in Graves' disease ; but these various factors enter into play only on the basis of an excessive or deranged thyroid function. Even if one wished to regard this deranged function as primarily a disorder of the nervous system the function of the thyroid would still form the main plank in the pathological condition.

We may note by the way that too much importance must not be attributed to the emotional element in the causation of Graves' disease. The careful researches of Roussy and Connie on the effect of the war on the incidence of Graves' disease in the French army show that it played a very small part in the ætiology.

There is no need to enlarge upon those cases presenting the classic syndrome : vascular goitre, exophthalmos, tremors, tachycardia, accompanied or not by well-known ocular symptoms the importance

of which has been much exaggerated, or by diarrhœa and attacks of profuse perspiration. Clearly, the general examination of these cases must be completed by the laboratory investigations mentioned in Chapter VI. The cases presenting real difficulty in diagnosis are the *abortive types* with an incomplete syndrome: general excitability together with muscular weakness, cardiovascular instability, unexplained wasting, insomnia, or mental changes showing themselves by alternating fits of excitement and depression, &c.

All these symptoms lead one to suspect Graves' disease when there is exaggerated pulsation in the carotid arteries. This sign, without being pathognomonic, rarely leads one astray. The pulse in hyperthyroid conditions nearly always exceeds 80, not only at the time of examination but in the morning before rising. Examination of the heart and lungs will often enable one to say at the outset whether the tachycardia is of cardiac or pulmonary origin, or whether it is likely to be due to the thyroid. There remain those cases suspected of having a tuberculous or cardiovascular lesion and in whom the first stages of Graves' disease cannot be excluded by the clinical symptoms alone, including Goetsch's test. The best criterion in such cases is furnished by the respiratory metabolism. According to Sturgis and Tompkins the metabolism will be increased by at least 15 per cent. in 80 per cent. of cases of Graves' disease in whom the pulse is more than 90.

For the differential leucocyte count and the photo-chemical examination of the serum (Kottmann) reference can be made to Chapter VI.

The distinction between the vagotonic and sympathicotonic forms need not detain us. The frequency of mixed forms deprives this differentiation of any absolute value and, so far, of any practical application.

As to the differential diagnosis between true exophthalmic goitre and toxic adenoma, palpation of the goitre generally determines: there being a diffuse goitre in the former, a nodular goitre in the latter. It must be remembered that nodules are occasionally found in the classic Graves' disease, yet they only represent an accessory element. Real toxic adenoma is generally quite easy to distinguish from diffuse Graves' goitre with a few occasional nodules.

The clinical picture of toxic adenoma is generally less serious than that of diffuse Graves' disease, and exophthalmos is absent or only very slightly noticeable. However, it does not seem justifiable at present to define a distinct syndrome as appertaining to toxic adenoma. We have seen very grave attacks of tachycardia and most marked wasting supervene in a case of toxic adenoma in which a comparative

examination of the adenoma and the glandular tissue showed the iodine content of the former to be three times as great as of the latter. Its action on the rat was also much more powerful than that of the glandular tissue.

Examination of the blood by experiments on the rat have given so far very consistent results in the two forms, but it is too complicated to use in ordinary practice.

II.—TREATMENT.

Without wishing to attribute a real ætiological basis to the various therapeutic measures used in thyroid disease, it is convenient to distinguish those which form symptomatic treatment, the effect of which hardly survives the period of their use.

A short résumé of such *symptomatic measures* will be given.

It is quite understood that in speaking of hyperthyroidism in subjects of Graves' disease one keeps in mind the possibility of their being hyperdysthyroidism.

Treatment aims at *restraining the thyroid secretion* by direct action on the gland, and also to *render the excess of secretion harmless* to the organism.

The first of these objects has been attempted by *chemical methods*, notably by the administration of sodium phosphate (Trachewsky, Kocher). We have often tried this drug treatment without being able to convince ourselves of its efficacy. Other observers claim to have obtained more favourable results, but always palliative in nature. The administration of the nucleoprotein elaborated in the thyroid itself (Oswald)—a product equally rich in phosphorus—has been tried by Kocher who attributes to it an action antagonistic to that of iodothyrine. This measure does not appear to have conclusive results so far, and Oswald himself in his experiments has not been able to convince himself of this antagonism.

Neutralization of the secretory product of the gland has been attempted by two processes based on diametrically opposed theories.

One of the groups of organotherapeutic or serotherapeutic remedies is based on the idea that the serum of an athyroid animal contains an excess of substances capable of *neutralizing the thyroid secretion*. This notion forms the rational basis for the antithyroid serum of Moebius (Merck), for the preparations of milk of thyroidectomized goats (Lanz), for Parke, Davis' thyroidectine, for hemoethyroidin and similar preparations. The experimental proofs cited up till now in support of such medication do not appear to be absolutely conclusive. Diminution in the sensibility of the rat to lack of oxygen, brought about by injection of the serum of an athyroid cretin, would seem to lend colour to this theory. We have succeeded

in neutralizing the specific action on the rate of blood from a case of Graves' disease by the addition of a given quantity of the blood of an athyroid cretin—following up the idea of Ballet, Henriquez and Burghart. According to some, the antithyroid preparations should produce a passing antitoxic effect on certain cases of Graves' disease, whereas according to others they should be without effect. We are rather sceptical of this treatment, because the experimental neutralizing dose is over a hundred times greater than the usual therapeutic dose.

Other preparations are based on the theory of *immunization* or the production of antibodies in the animal treated by the thyroid products. In 1903, Dexmoor and van Lint prepared a cytolytic and antitoxin serum, that is to say capable of destroying simultaneously both the thyroid cell and the product of the gland circulating in the blood stream. These experiments have had no practical outcome. Similar attempts have been made by Lépine and Beebe. Both have thought themselves able to show that in an animal treated by thyroid products antibodies are formed able to counteract the pathological effects of excessive thyroid secretion. This conception has been contradicted by numerous writers.

It is well to recall the fact that the products of secretion of the endocrine glands closely resemble *hormones*. Now according to Bayliss and Starling, Biedl and Gley, the characteristic of hormones is their inability to act as antigens and to give rise to the production of antibodies. Their entrance into the circulation does not provoke a reaction tending to destroy them (Gley). This fundamental idea is supported in connection with the thyroid by experiments conducted on the rat by Dr. Doubler on our advice, using the method of Asher-Streuli. It appears to us at the start unlikely that the principle of antibodies can be profitably applied to the therapeutics of exophthalmic goitre.

The administration of carefully regulated doses of thyroidine, advised by certain authors, is based on the hypothesis of a deranged function, in the sense of a relative dysthyroidism. It is impossible to deny the probability of this rationale, but its application appears to be difficult if not dangerous in practice.

Among other authors Neisser, Loewy and Zondek may be mentioned as recommending small doses of *iodine preparations*. This method, the theoretical basis of which is not evident (unless it be to correct a deranged thyroid function) is contra-indicated because of the harmful effect of even very small doses in most cases of Graves' disease.

The trials made with *extracts of other endocrine glands*—practically all have been used—have never emerged from the experimental stage. Their action—if it exists at all—is purely palliative. It should be

recalled in this connection that preparations of pituitary are used in small doses to combat tachycardia. Extract of thymus has been used for more than twenty years in the treatment of Graves' disease, and the recent experiments of Hawk seem to show that it counteracts thyroid extract in its effect on metabolism. This idea would of course contradict the theory of thymus disease being the cause of Graves' disease. Pluriglandular extracts also have their advocates which proves that we are still in the age of an empiricism which threatens to rub shoulders with quackery.

There remains the *non-specific medical treatment*. Here again empiricism has free rein and no medicament has any real effect on the cause of the disease, unfortunately unknown to us. Sodium phosphate, to which it was thought possible to attribute some specific action, and iodine, have already been mentioned. All the sedatives have been tried and *bromides* seem to be the best. *Parasiticide medication* : *quinine and salicylate* seem to be indicated in Graves' disease following on rheumatic or malarial thyroiditis. Moreover, quinine has a sedative effect on the heart. The *intestinal antiseptics*, thymol, β-naphthol, bismuth salicylate, also recommended for the treatment of simple goitre, should find their use particularly indicated here if excitation of the thyroid is due to auto-intoxication from the bowel. Experiments performed on rats by Dr. Doubler have not succeeded in producing thyroid excitation by injections of indol and skatol. Needless to say, the negative result of these experiments (which were also too few) should not discourage those who are trying to attack thyroid diseases through the channel of intestinal infection. Treatment of this kind has much more chance of being ætiological than the administration of all the sedatives. The use of *fermented milk* (yoghourt, kephir, &c.) comes under this category.

As to *general tonics*, *arsenic* without being a specific has preference.

As to *digitalis* and similar preparations, some of the most experienced surgeons, such as Kocher and Ochsner, advise against their use in exophthalmic goitre. In our experience these drugs have no effect on ordinary thyroid tachycardia, and are therefore of no use in Graves' disease unless it be complicated by organic cardiac disorder. On the other hand, they are indicated for use as preparatory treatment for and adjuvant to surgical measures whenever there is a real deficiency of cardiac muscle. But here also we believe that a carefully conducted operation, divided into several stages, is the best treatment for the heart condition. We have too often seen hearts on which cardiac tonic had no effect regain a practically normal function, to have the least doubt on the matter.

Whereas *hydrotherapeutic measures and electrical applications* may have some success in mild cases, it is generally held that these means

fail completely in the serious cases. Hygienic measures directed towards care of the nervous system, absolute rest, mainly vegetarian diet, abstinence from coffee, tea and alcohol appear to work wonders in acute attacks of hyperthyroidism, without the help of any other therapeutic measure. Nevertheless, this treatment does not *cure* the patient, who relapses as soon as he returns to his normal life and its exigencies.

As to *climatic* treatment, it is known that the seaside is unfavourable for Graves' disease, whereas an altitude of from 3,000 to 5,500 feet has a beneficial effect. The harmful effect of residence by the sea appears to be explained by the toxic action of iodine on a hyperthyroid subject, while the favourable effect of mountain life is a purely empirical fact, the action of which is not yet understood (lack of iodine, actinic effects . . ?).

It is almost superfluous to add that *psychical treatment* of cases of Graves' disease is of the greatest importance, and it is to the undoubted credit of Crile that he constantly emphasizes it. Physical calm and mental rest constitute the best non-operative means of reducing the basal metabolism. However, we do not believe that "trust in physiology and philosophy," even combined with intestinal antisepsis and extract of hemp, can replace a well-conducted operation in a really serious and intractable case.

We come to means of local treatment. Application of cold to the gland itself by means of a *collar of cold running water*, as well as ice or cold plaster applied over the heart, can render valuable aid in acute attacks of hyperthyroidism, but they do not constitute a real curative treatment.

It is otherwise with *X-ray and radium treatment*. There is no doubt that the epithelial cells of the thyroid can be altered and even destroyed by the action of X-rays, and thus their function can be modified and eventually abolished.

As to the *method* of applying the rays, some, especially Béclère, use moderate doses at frequent weekly intervals, while others prefer large doses given at intervals of three or four weeks. Several authors advise simultaneous application over the upper part of the sternum, thus obtaining an action on the thymus or aberrant portions of thyroid glandular tissue.

The results obtained by a certain number of authors: Halsted, Boggs, Pfander, Knox, Hubbeny, Clagget, Aikens, Béclère, Mackenzie, Means and Eaul, &c., have been good in a large number of cases. Means and Eaul have shown a gradual diminution in the basal metabolism as definite proof of the action of the rays. Béclère finds that in cases where the syndrome of Graves' disease is just present radiotherapy is always perfectly successful, and that in well-marked cases

it is successful in 90 per cent. He advocates operation only in certain toxic goitres. Other authors like Wallace, Franck, Hildebrand, Berkman, Ch. Mayo, emphasize the frequency of failures, and especially of relapses after X-ray treatment. We have ourselves seen some failures or very inefficient results after long intensive treatment, and also the recurrence of all the symptoms after a few careful applications. Crile, judging his results by means of the respiratory exchange, places the efficacy of radiotherapy between that of simple ligature and that of resection of the gland.

These methods of treatment unfortunately have several serious *drawbacks*. First is the impossibility of strictly regulating the dose. The destructive effects show themselves slowly, and the action of the rays is markedly cumulative. This is apart from the fact that a result apparently favourable at the beginning may, owing to the prolonged action of the rays, eventually turn out to be excessive. In all cases the dosage is much less precise than is operative treatment, and myxœdema has already been seen as a result of radiotherapy.

The second drawback is due to the manner in which radiotherapeutic treatment complicates a subsequent operation. The inherent difficulties of an operation for exophthalmic goitre are increased to such an extent by the X-rays as almost to render such treatment impossible. This may occur without the rays having effected even a relative cure. It is a grave mistake to think, like Seymour, Means and Eaul, that the difficulty and risk of an operation are lessened by preliminary X-ray treatment. The contrary is the fact.

We think it may be definitely stated from our observations on the living subject that the fibrous adhesions—to say nothing of the lardaceous consistency of the tissues—seen after prolonged X-ray treatment, exceed anything ever found in an exophthalmic goitre that has not been subjected to treatment. It has nothing to do with an increase of connective tissue due to the natural development of the lesion. The adhesions after radiotherapy are only to be compared, in certain cases, to those produced by previous surgical intervention in an exophthalmic goitre, if they are not even more marked.

One of the disadvantages of radiotherapy which it should be possible to avoid nowadays, but which is not effectively guarded against, is the disgraceful pigmentation of the skin and the appearance of small teleangiectases. We have seen the skin of the neck all thickened and infiltrated and the Graves' disease not cured in a patient who preferred to have X-ray and radium treatment in order to avoid a fine linear scar. One should not have to mention complete necrosis of the skin and underlying tissues down to the trachea save as historical curiosities, but the mishap has occurred even at the present day.

We must note, finally, as a fourth drawback, acute aggravation of all the symptoms coming on after an apparently careful application of X-rays. Radiotherapy shares this danger, though to a minor degree, with the operative treatment. Perfection of technique will doubtless render possible more accurate dosage. However, one can never prevent the fibrous changes in the perithyroid tissue, and the difficulty caused thereby in a subsequent operation. For this reason we advise against the use of X-rays or radium in all cases in which one is liable to have to resort to the knife eventually.

There are cases in which one endeavours for one reason or another to avoid operation at all costs. Here radiotherapy undoubtedly constitutes the most effective means of lessening the function of the gland, but a means the harmlessness of which has certainly been exaggerated.

The application of X-rays to the thymus may be of use in certain cases, but it is a step in the dark, because slight degrees of hypertrophy of the thymus cannot be recognized by any method of diagnosis, and the relationship between the thymus and exophthalmic goitre (Garré, Capelle, von Haberer, Bircher, &c.), while forming a subject for interesting researches, is still by no means clear.

In regard to *injections of boiling water* (Porter) or of *quinine and urea* (Watson), destined to produce a partial necrosis of the thyroid tissue, these are methods too irrational and too violent to replace operative treatment.

There remains *surgical treatment*, considered by some few surgeons to be the only remedy, and looked on as an anachronism by certain physicians for internal disorders.

To which method of treatment should preference be given in any individual case?

The question is easy to answer in cases where the "goitre" element predominates, or where there is marked compression of the trachea. Here operative treatment is always indicated unless it be rendered inadvisable by some heart condition.

The cases remaining after deducting this class may be divided into three groups:—

(1) *Mild Cases.*—The syndrome of Graves' disease is either incomplete or little marked. The symptoms develop slowly. The general condition of the patient is little affected, and the patient is even able to follow his occupation. In these cases bromides, rest and residence at a high altitude often decrease the symptoms sufficiently to allow the patient to lead a practically normal life.

The operation can be postponed so long as the patient's condition remains stationary. Is it necessary to treat these cases with X-rays? We think not. It is better to be content with sedative methods of

treatment than to compromise in advance by ill-advised radiotherapy an operation that may eventually have to be performed. If sedative treatment does not suffice to keep the patient in a practically normal condition, the case becomes one of the next class, and operation appears to be indicated.

(2) *Medium Cases.*—The syndrome is fairly well marked, and the patient alternates, as it were, his periods of treatment with attempts to resume a normal existence. The heart as yet shows no symptoms of real insufficiency. These cases are visibly relieved when obliged to take complete rest. Mountain life apparently improves them, but they relapse as soon as they try to adapt themselves to a normal mode of life.

These are the cases in which surgical treatment seems to be clearly indicated if the patient does not wish to devote his life to the cure of his malady. Whenever a patient is in a state of acute hyperthyroidism dietetic treatment for a week or fortnight, together with the use of bromides and quinine, must precede the operation.

(3) *Serious Cases.*—The syndrome of Graves' disease is clearly marked and the heart has suffered. The pulse is not only rapid but also irregular, and attacks of cardiac failure are seen. The patient is not bedridden, but is unable to follow a regular occupation. He does not attempt to do so, his whole time being devoted to the treatment. From this stage the disease passes imperceptibly to that in which complete cardiac failure destroys all hope of useful intervention. In this class of serious cases must be included those which develop quickly, even before any cardiac affection is apparent. The more rapidly the picture of exophthalmic goitre develops the worse the prognosis. We go so far as to say that a Graves' disease which has developed in a few months is more to be feared than one causing the most serious heart trouble, but in which the symptoms have been developing over a number of years.

In this third class operative treatment is fully indicated provided there is no marked circulatory failure, but one must not operate during acute exacerbation of the symptoms. The preparation of the patient, bromides, quinine, sodium phosphate, light diet, rest and the requisite climatic treatment will take longer than in the cases of the preceding group.

We have considered above the serious disorders of compensation : hydrothorax, ascites, œdema, as being contra-indications for operative treatment. But one should add here in parentheses that there are some cases of cardiac failure—œdema, pleural effusion, ascites—which can be relieved or even cured only by carefully graduated operative measures. Of course, one will first exhaust the medical methods of

treatment, but one must not abandon an operation if the œdema and effusions do not clear up.

We have seen the excretion of urine mount rapidly from 600 to 1,600 c.c. after ligature of the two upper poles and excision of the goitre; whereas medical treatment lasting for several months: complete rest, cardiac tonics, diuretics, quinine—failed to restore the heart and kidneys to normal function.

In cases of Graves' disease operation forms the most effective diuretic and restorative measure. The personal experience of the surgeon will decide if, after the failure of other methods, it may be risked. If the surgeon or the patient cannot make up their minds to have it, radiotherapy should be tried.

We must deal briefly with the *influence of the type of goitre on the operative indications.*

Without wishing to make a fundamental distinction between nodular parenchymatous (adenomatous) goitre with Graves' syndrome (toxic adenoma of American writers) and the classic diffuse goitre of Graves' disease, we believe with Plummer and Boothby that the symptoms of toxic adenoma are, on the whole, less severe than those of classic exophthalmic goitre, and that the operation in these cases is relatively simple, provided that the rest of the parenchyma is not diseased. One should not waste time with half measures, but should resort to the only quick and effective mode of treatment. It is much easier to come to a decision because the prognosis of the operation in toxic adenoma is no more serious than in any other goitre, so long as the heart is sound. The difficulties in regard to therapeutic indications are more pronounced in ordinary cases of exophthalmic goitre.

No mention has been made so far of the part played by the respiratory exchange in the indications for operation. It is certain that the figure for the respiratory exchange and the variations of this figure in a given individual afford very useful and important information as to the degree of hyperfunction of the gland in the different stages of the disease, but it is no less certain that these findings can only be used in conjunction with the clinical facts. There can be no question of arranging the indications for operation schematically merely on the basis of the figure for the basal metabolic rate, as some hoped at first. It is very interesting to know that such is also the view of Plummer and of Boothby, the authors who have given most attention so far to the problem of metabolism. It is certain that this method of investigation will become more common as improved technique places apparatus suitable for routine work at the disposal of practitioners. Further clinical experience will show whether the small type of apparatus with closed circuit of Krogh and Benedict

will be adaptable for this purpose. Research work at present still seems to be making use of complete analyses of the respired gases.

III.—GENERAL PLAN OF OPERATIVE TREATMENT.

Unlike the operation for simple goitre which, with rare exceptions, can be undertaken at one sitting, that for exophthalmic goitre needs a well-thought-out plan of campaign if one wishes to avoid mishaps. This plan is generally simple in case of *toxic adenomata*. Here the operation will correspond in principle with that for simple goitre, with this difference, that one will be less sparing in the matter of ligatures and in sacrifice of thyroid tissue.

Sometimes, however, this toxic type of goitre needs treatment by stages, just like a classic case of exophthalmic goitre.

In *diffuse exophthalmic goitre* the first thing is not to operate during an acute attack of hyperthyroidism. The duration of the preliminary treatment will depend on the results of confinement to bed and general sedative measures.

The operation should be perfomed in two or three stages if it seems that a radical cure at one sitting would be too great a strain on the resistance of the patient. It is here that the experience of the surgeon comes in, because it is impossible to draw up any mathematical scheme to regulate the mode of treatment. Neither the percentage of lymphocytes, nor the pulse rate, nor the rise in the basal metabolic rate can furnish such a chart.

There are different methods of dividing the operation into stages:

(1) One of the lobes is resected and the resection of the other is postponed for several weeks or months. This *resection in two stages* is suitable for medium cases with large thyroids. One must be careful not to interfere with the second lobe during the first operation, otherwise the subsequent operation may be unnecessarily complicated. There need be no fear of making an extensive resection of the first lobe, but one should be careful of the posterior surface—a dangerous area—in order not to compromise the vitality of the parathyroids. This method will be one of necessity in a case where one at first intended to do the bilateral operation, but where the patient has been so severely tried during the first part that it would be unwise to continue.

(2) The second method is that of *preliminary ligature* followed after a variable interval by operative removal of the goitre. The ligatures may be applied in various groups, all of which we have tried.

Let us commence with those cases where the condition of the patient allows of the application of two ligatures at one sitting. *Ligature of the two inferior thyroid arteries* would control the vascular

supply most effectively; tying the *two superior thyroid arteries* by polar ligature blocks the chief vasomotor nerves at the same time. The latter also has the advantage of leaving the perithyroid tissue more intact. It would seem that ligature of the *two arteries of one lobe* would be a better guarantee of hæmostasis at the subsequent operation, but such is not the case. Ligature of the two principal vessels is an excellent method of obtaining *immediate hæmostasis*, but a very bad one to ensure *subsequent hæmostasis*. Preliminary ligature results in the opening up of the collateral circulation, and at the second operation the surgeon finds, instead of two vessels easy to tie, a host of small collaterals, the bleeding from which is far more difficult to control than that in an untouched gland. Roux has rightly emphasized this fact, and we have noticed it ourselves in operating on exophthalmic goitres. We only perform multiple ligatures of $3\frac{1}{2}$ to 4 arteries in exceptional cases in which we abandon from the first the idea of a subsequent excision, restricting ourselves to *ligature of the two upper poles* by small classic incisions, *whenever we discount an ultimate excision of thyroid tissue*.

Ligature of the two upper poles reacts favourably on the cardinal symptoms of the disease, especially on the pulse-rate and nervous condition, and investigation of the basal metabolism has confirmed this fact, long since established by clinical observation.

In the more serious cases it is better to apply the ligatures at two sittings, at an interval of one or two weeks.

Preliminary ligature having been decided on, two new questions arise :—

(i) *When should the goitre be removed?*

As soon as the patient has completely recovered from the first step. The shorter the interval the less time will the collateral circulation have had to develop, and the easier it will be to effect hæmostasis. The study of the metabolism will be a useful control of the heart's action and the change in the body weight. We prefer not to make the interval longer than two to six weeks.

(ii) *Should the resection be bilateral at first, or is it still necessary to proceed by stages?*

Clearly one would prefer to complete the removal at one operation if possible, in order not to have to submit the patient to a third ordeal; but here again great caution must be exercised and one should perform the operation in stages if the goitre is large. It must not be forgotten that the post-operative shock is in large measure a function of the quantity of thyroid tissue removed.

Nothing has been said as yet of *operations on the cervical sympathetic*. There is no doubt that section or resection of the sympathetic trunk can exercise a considerable influence on the blood supply, and

hence on the function of the gland. Such intervention, however, involves a mutilation the extent of which may be seen in cases where the sympathetic has been divided accidentally in the course of operation. As we believe it is possible to obtain a more certain result, avoiding any mutilation, by ligature of the large arterial vessels which includes the principal nerve filaments to the gland, we prefer to adopt this latter method to that of section or resection of the sympathetic, and we think most surgeons are of our opinion. We are not unmindful of the interesting anomalies of pigmentation of the superior cervical ganglion in Graves' disease, but we agree with Wilson, who has studied them specially, that they are secondary lesions.

IV.—THE OPERATION.

(*a*) *Preparations.*—There is nothing to add to what has been already stated in Chapter X, except that we avoid the use of tincture of iodine, restricting ourselves to a careful toilet with soap, benzine and alcohol, followed by painting with picric acid (5 per cent. alcoholic solution).

(*b*) *The anæsthetic.*—The problem of the anæsthetic is more debatable here than in cases of simple goitre. It is advisable to avoid general anæsthesia as far as possible. Morphia together with novocain generally affords sufficient analgesia, but it must not be forgotten that these are also toxic products. One has seen accidents, sometimes fatal, caused by the use of novocain even when the recognized dose has not been exceeded. There seems to be no doubt that subjects of Graves' disease are abnormally susceptible to most of these drugs. We have not used nitrous oxide with incomplete narcosis, recommended by Crile, and consequently we are unable to give a personal opinion of the method.

As to injections of a solution of urea and quinine into the thyroid tissue immediately before resection, we think they are less effective than a quick operation, with special care not to damage the tissues more than necessary. It seems to us that the excellent operative results of Crile, the advocate of the quinine and urea injections, are due to the realization of this latter condition.

After the local anæsthesia we induce a slight narcosis with ether or chloroform in those patients who are obviously too agitated to undergo the operation while conscious. Often it is enough to administer a few drops of ether when the ligatures are being tied, and when the goitre is being disengaged. The rest of the operation causes no pain, the glandular tissue itself being insensitive.

(*c*) *The operation.*—Typical exophthalmic goitre has four characteristics in varying degrees:—

(1) The rich vascular supply, not only of the thyroid, but also of the perithyroid tissue extending to the muscles. Everything is ready to bleed, and there are big arterioles which are never seen in the normal subject.

(2) The friability of the thyroid vessels. The large arterial trunks are easily ruptured by the ligatures when they have been too conscientiously dissected out from the surrounding connective tissue. This is in contrast with the following:—

(3) The frequent obliteration by adhesions of the plane of cleavage round the thyroid. The goitre often gives one the impression of being welded to the thyroid fascia by a real inflammatory process. It is difficult to disengage it, and there is a risk of tearing the capsular veins. Such are the cases in which it is a distinct advantage to tie the inferior thyroid artery outside the small vessels, the veins and the adhesions.

(4) The more or less sticky yet friable consistency of the glandular tissue, sometimes leading to difficulty in suturing.

This group of characteristics is more marked in certain cases as a result of pre-operative X-ray treatment. There is no need to repeat what has already been said on this subject.

Disengaging the goitre before resecting it is the best method in exophthalmic as in simple goitre, but perithyroid adhesions may necessitate resection of the gland *in situ*. One may have to divide the small muscles rather than retract them more often than in simple goitre.

The size of the principal vessels is roughly proportional to the volume of the gland, in Graves' disease as in simple goitre. It is for this reason that a diffuse colloid goitre of moderate size but having more or less the syndrome of Graves' disease, such as constitutes most of the exophthalmic goitres operated on to-day, has smaller vessels than the majority of large adenomatous goitres in endemic goitrous regions, and even than many goitres in cretins.

(*d*) *Drainage.*—We always insert a drain after the operation, and when both sides have been dealt with we prefer to use two tubes rather than one, in order to obviate as far as possible any post-operative resorption.

(*e*) *Post-operative precautions.*—A case of Graves' disease shows the post-operative phenomena of acceleration of pulse rate and rise of temperature to a much greater extent than simple goitre. These symptoms may resemble an acute attack of hyperthyroidism. In some particularly serious cases we have seen in addition a state of mental disorder lasting for several days or weeks.

How can one avoid or deal with such a condition, which even nowadays may end fatally?

There is no need to repeat what has been said about the choice of a time for operation and about the preliminary dietetic and drug treatment.

There is no sure remedy for post-operative hyperthyreosis. One must therefore try the various measures capable of affording relative assistance. In this connection may be recalled such physical methods as cold applications to the whole body in order to lower the temperature, the ice collar intended more especially to lessen resorption in the field of operation, and the ice plaster applied over the heart.

As chemical and organotherapeutic measures one could enumerate the whole arsenal of remedies mentioned in the chapter dealing with the non-operative treatment of Graves' disease. As sedatives we use sodium bromide and the veronal group of preparations. Digitalin and strophanthin are invaluable as cardiac tonics, despite their inefficiency in regard to the thyroid acceleration of the pulse. Quinine and quinidine must be placed foremost in regulating the heart function. Preparations of pituitary help to overcome the fall in arterial tension. It is most important to ensure an abundant diuresis. Hence it must be seen that the patient obtains a large amount of fluid by the usual channels—stomach, rectal and subcutaneous.

The critical period during which, in certain exceptionally serious cases, an hour-to-hour struggle may be fought, rarely lasts longer than the fifth day. It is generally on the fourth day that the decline of the attack sets in, even in those cases in which the temperature and pulse remain above normal for a few days longer. Rest in bed is indicated for a longer period than in ordinary goitre, and the more marked the post-operative recrudescence of symptoms the stricter one must be in this matter. The diet should be milk and vegetarian during the whole period of convalesence. Fruit, especially oranges, is generally much appreciated by the patients.

There remains to be mentioned the *complementary operation on the thymus*. The frequent persistence of the thymus in Graves' disease—40 per cent. of cases at autopsy—has induced some surgeons, especially Garré and von Haberer, to recommend its removal in cases where the operation on the thyroid has not furnished the desired result. This advice has been followed by but few operators, and so far there is no collection of observations enabling one to give an authoritative opinion on the subject.

V.—RESULTS OF THE OPERATION.

As to the *immediate prognosis* of the operation, the mortality, which was originally ten times greater than that of simple goitre, has got progressively smaller, and now tends to approach the figure for the

latter. The reasons for this improvement lie in the better preparation of the patient, more common division of the operation into stages and the larger number of operations for slight cases. In our own practice we had eight deaths in a first series of eighty operations, and only one in the following series of sixty operations. This latter fatality occurred in a very grave case treated by ligatures after having been very much aggravated by untoward X-ray treatment which we advised against. In connection with these figures we should remark that in Switzerland exophthalmic goitre forms only about 4 to 5 per cent. of goitres among the indigenous population.

The good results of operative treatment show themselves first by a decrease in pulse rate and the patient's starting to put on flesh. Tremors and exophthalmos decrease more slowly, and the complete result is not attained till after about six months. Often the patients return to normal life in spite of some persistence of one or other of the symptoms: slight irregularity of the pulse, or slight exophthalmos. This is the final result in about three-quarters of the cases.

In certain cases the result is most satisfactory at first, but after six months or a year relapse sets in, both local and general. The local relapse shows itself in a new increase in the volume of the thyroid, the general relapse by the reappearance of the classic symptoms of the disease. We are obliged to set to work again to remove what is left of the gland. It has already been said that these second operations are often difficult; they are to be reckoned among the most delicate in this region.

The differential leucocyte count is of but very limited value as a means of accurately controlling the effect of the operation. The subjective symptoms may show a very pronounced improvement, while the lymphocytosis may still be present. Increase of body weight, decrease of pulse rate and of basal metabolism furnish more exact figures which may be used as a means of control. Above all, they are much more readily affected than the leucocyte count by the operation.

The fall in the pulse-rate, the improvement in the cardiac action, the increased diuresis where there is cardio-renal inadequacy, the rapid diminution of basal metabolism, the complete change in the temperament of patients who for months and years have exhausted, in vain, all therapeutic resources, cannot be due to post-operative treatment nor to spontaneous cure, as Bram suggests. The change must obviously be the result of the one new factor, i.e., the operation.

One question remains. Does the operation produce a permanent cure? The vicious circle is broken and more effectually than by any conservative treatment, but the abnormal sensitiveness of the individual to the products of excessive or of vitiated thyroid secretion is not destroyed. The patient is not so likely to relapse as after treatment

by diet, drugs or X-rays, but a relapse is *possible*, more especially if the thyroid tissue which one is compelled to preserve takes on active growth or is stimulated by careless iodine medication. A theoretical consideration must be interposed here, by way of parenthesis. The cure by operation—at any rate in regard to symptoms—is easily explained on the assumption of a simple hyperthyroidism associated with an abnormal thyroid sensitiveness. If on the other hand we assume the existence of a "hyper"- combined with a *dysthyroidism*, we are bound to conclude that a little of the latter is not harmful, or that the operation has effected a change in the constitution of the gland. The latter explanation is however disproved by histological examination in many successive operations. The element of dysthyroidism persists despite the operation, and may give rise to a recurrence. But this is no argument against operation, as long as medical treatment is incapable of curing the goitre and suppressing the patient's sensitiveness to thyroid. At the present time, treatment by medical and dietetic measures attenuates the symptoms of the disease, but the patient requires constant professional attention. His whole life must be devoted to treatment. The fundamental basis of the malady is neglected in order to attain a temporary benefit. It is true that surgery is unable to deal with the absolute origin of the disease any more than medicine, but it surpasses the latter in being able to restore to the patient the capacity for work and something of the joy of life. The term of health which surgery is able to impart to the invalid may possibly result in some greater influence on the underlying pathology of the disease than repeated courses of medical treatment, which are so often discouraging owing to their lack of success.

We have just seen that despite operation the patient really remains a subject of Graves' disease, until the lapse of time obliterates the latent defect. Can this eventuality be anticipated by means of a dietetic regimen ? We believe that there is some possibility of effecting this and therefore we advise our patients who have undergone operation to avoid, in their food and their general conduct of life, everything which is prejudicial to the health of the nervous system ; but these measures apply to a constitution which is practically cured and not to one whose health is always an uncertain factor. It is herein that we realize the advances made by Rehn, Kocher, Halsted and other advocates of the operative treatment of Graves' disease.

We must make a brief reference to the subject of thyroid treatment where inadequacy results from too vigorous or too prolonged application of X-rays or from too extensive an operation. Local treatment, whatever be its nature, if it is to succeed, should aim at obliterating the function of just enough thyroid tissue to bring the

patient to the verge of hypothyroidism. The victim of Graves' disease, unlike a euthyroidic person, is unable to accommodate himself to an excess of thyroid secretion. His sensitiveness to thyroid causes him to react abnormally, even to a trifling excess of the secretion in his blood. Indeed such a patient may present the cardio-vascular and the psychical symptoms of hyperthyroidism, while he may actually be bordering on an absolute insufficiency of thyroid. This thyroid sensitiveness is notoriously a very variable factor. It is therefore impossible to lay down any dogmatic scheme for post-operative thyroid therapy. But the following general rules will be applicable :—

(1) There should be no haste in administering thyroidine, because the diminution of function which usually follows upon the operation on the goitre becomes spontaneously compensated in the course of a few months. This recovery restores the function to normal, and may even overstep it. If this recovery does not take place the operation threatens to be a failure.

(2) The nervous sensations which are experienced by patients with Graves' disease in common with other nervous patients after operation must not necessarily be ascribed to hypothyroidism. The significance of these symptoms can be appraised after estimating the basal metabolism, a test which should be repeated, if necessary. The differential leucocyte count is not a reliable guide, it is rarely unequivocal and is very susceptible of change. The experiments of Asher-Goetsch, and Brams' test of tolerance towards quinine, may prove to be useful.

(3) If there is a decrease in the basal metabolism many months after the operation, there will be justification in instituting a careful treatment by thyroid for any symptoms which are thought to be due to inadequacy of the gland.

It is impossible to set down definite rules in regard to dosage. The best method is to feel one's way with small doses, and to increase them as the case demands. In this connection, it is desirable to mention the fact established by Plummer and Kendall that the effect of one dose of thyroxine manifests itself for three weeks, and that it is therefore able to produce a cumulative effect. It is a wise precaution to employ the very small doses recently recommended by Leopold Lévi (1 mg. of the dried gland). This, however, will not be necessary in all cases, and in practice we see that much larger doses are perfectly well tolerated, for a considerable time, without the least rise in the pulse-rate. The question of minimal doses still requires investigation ; but the general rule holds good that the pulse-rate needs strict watching, whatever be the dose.

CHAPTER XVII.

COMBINATION OF HYPOTHYROIDISM WITH HYPERTHYROIDISM.

THE most difficult chapter from the theoretical standpoint is that dealing with those cases in which the symptoms of both hypothyroidism and hyperthyroidism are present. This combination has been known for some time, but it is to Sattler (1909) that we owe the first considered analysis of the cases observed. He points out that there is a naturally-formed division into three groups which we shall enumerate in their order of frequency.

I.—HYPERTHYROIDISM OF GRAVES' DISEASE PROCEEDING TO MYXŒDEMA.

The facts regarding this group are too well known to demand much attention here. The change from hyperthyroidism to myxœdema is due in most cases either to spontaneous degeneration of the gland (thyroiditis), or to over-treatment of Graves' disease (radiotherapy, operation). It happens exceptionally that the change from Graves' disease to myxœdema, or, at least, to thyroid deficiency, takes place without inflammation having supervened, or excessive therapeutic measures having been adopted. This is shown by the following case :—

A woman of 35, treated for Graves' disease for two years by competent practitioners. Exophthalmos, goitre, tachycardia, tremors. Gradual diminution of these symptoms, except the goitre. Puffy features. Basal metabolic rate *minus* 10 per cent. Operation for compression of the trachea: the whole thyroid was found converted into a mass of small cysts, no normal tissue being present. The degeneration of the gland must have passed rapidly through an excitatory phase to one of anatomical and functional deficiency.

II.—CRETINOID HYPOTHYROIDISM PROCEEDING EVENTUALLY TO HYPERTHYROIDISM.

This type is considerably rarer than the foregoing. We have observed it in these two forms :—

(*a*) The gland is slightly deficient—in part at least—from youth, and the patient shows certain stigmata of cretinism in his physical development and in his features. His intellectual development may

also be retarded. Towards puberty the goitre assumes an obviously vascular character, and certain symptoms of cardiovascular instability make their appearance. Histologically the goitre resembles a case of Graves' disease, but, on the other hand, the basal metabolic rate is not much increased. This incomplete manifestation of Graves' disease is but an incident grafted on the original deficiency, which latter plays the chief part in determining the subsequent development of the goitre. It is true that one might be tempted in these cases to speak of the co-existence of two groups of symptoms to the exclusion of simple "hypo-" or "hyper"-thyroid states, but we prefer to reserve our judgment on the matter.

(*b*) Here one is dealing with patients who are more or less cretinoid in whom pronounced Graves' disease appears. These cases are rare, but they exist. This is an example which appears to belong to this group :—

A woman, aged 44, living in an endemic cretinous district, had suffered since early youth from practically complete deafness. Educated in a home for deaf mutes. Slightly cretinoid facies, defective intelligence. Diffuse goitre present, which started to enlarge at age of 44. Symptoms of Graves' disease. Basal respiratory exchange + 18 per cent. Removal of the large diffuse colloid goitre reduced the respiratory exchange to − 11 per cent. Iodine content calculated for the dried gland 0·067 per cent. (about 18 mg. for the whole gland !).

The appearance of the symptoms of Graves' disease is sometimes due, in such a case, to iodine or thyroid medication. It is a known fact which we have personally verified that the cretin with a goitre sometimes reacts to prolonged iodine treatment by manifesting symptoms of hyperthyroidism. The cretinoid facies remains despite the Graves' disease, and the co-existence of apparently opposing symptoms by no means proves their simultaneous origin. These cases, too, can be explained by the idea of simple "hypo-" or "hyper"-thyroidism. A deficiency of function has, in the course of years, branded the organism with stigmata which a subsequent excess of function is unable to remove.

III.—SIMULTANEOUS DEVELOPMENT OF HYPO- AND HYPERTHYROID SYMPTOMS.

If these cases really existed they would entirely dispose of the theory of the unity of the thyroid secretion. Now Kaufmann, who continued the work of Sattler till 1912, believes that the majority if not all of these cases belong to one or other of the two preceding classes. There would thus be co-existence of certain symptoms but not simultaneous development of them. Personally we have not seen

any cases capable of being placed with certainty in this third class, the order of appearance of the symptoms always having enabled the cases to be put in either the first or second class. Determination of the respiratory exchange and biological analysis of the blood will perhaps enable us in the near future to say whether certain cases which one believes to belong to the first two groups should be definitely classed with the group in which the two syndromes appear together.

In connection with this, one should remember the *thyroid instability* described by Leopold Lévi. According to its author's definition this syndrome comprises the association in one individual of slight signs of hypo- and hyperthyroidism. Lévi endeavours to emphasize by this term the "non-permanence of thyroid function, its latitude and variability." There would thus not be simultaneous production strictly speaking, but rapid alternation resulting in apparently opposing symptoms being superimposed on each other. It has already been remarked that in the normal individual such oscillations are impossible, his reserve of thyroid tissue and its secretory products being too wide, and the capacity of the organism to adapt itself being too great to allow of such a phenomenon. Of all the endocrine organs the thyroid lends itself least to this. Cases are known where there is no doubt of the existence of such rapid oscillations, but they are all subjects who have been operated on for Graves' disease.

One essential fact results from what has been said, namely, that thyroid instability cannot exist unless the individual has already an abnormal thyroid sensitiveness. It is not just the thyroid apparatus that is at fault but primarily its bearer. This thyroid sensitiveness is above all *positive:* the patient reacts normally either to an *increase* or to an absorption of the thyroid secretion. Is it also *negative?* Is there a pathological reaction to small degrees of diminution? We do not know, but it is quite possible. Perhaps the threshold of absorption for the gland is upset at the same time. We think that the most reliable examples of thyroid instability are furnished by old cases of Graves' disease operated on at a very early stage. Nevertheless it appears to be an undoubted fact that in many cases of Graves' disease the first stage of the disease is characterized by a phase of instability which does not actually constitute a separate malady. In any case, laboratory workers should investigate the matter a little more, so that the idea of "thyroid instability," as left by its originator, should not fall into the category of what may be called "romance" in pathology.

This chapter cannot be concluded without mentioning once more the explanation of the co-existence of hypo- and hyperthyroid symptoms given by Janney. He agrees with Klose that the secretory product leaves the gland before it is completely formed. This in-

complete product, essentially toxic, would cause symptoms of Graves' disease, while the absence of a normally constituted secretion would lead to simultaneous presence of symptoms of hypothyroidism. One has only to push the argument a little further to see the weak point of this explanation : the appearance and intensity of the hypothyroid symptoms should go hand-in-hand with the hyperthyroid symptoms, according to this theory. One should be able to postulate an absolute antagonism between the preliminary toxic product and the final physiological product. Now both clinical and laboratory experience go to show the contrary. Up to a certain point Janney's theory recalls Cléret's interpretation of Graves' disease : intoxication caused by an abnormal product of secretion combined with hypofunction of the thyroid. So far it does not appear that the key to the co-existence of hypo- and hyperthyroid symptoms is to be found in this direction. The relation between the normal products of the gland—both within the gland and in the blood—and those in Graves' disease is too close, as shown by biological experiment (in tortoise and rat), to admit of this theoretical antagonism between the two groups of products.

BIBLIOGRAPHICAL APPENDIX.

We venture to think that the addition of an appendix containing a brief bibliography of Goitre will be of value to the reader. Owing to limits of space, the bibliography is not so full as we might desire. We have selected from the constantly increasing flood of publications those which are of fundamental importance, especially those of the last two decades, and those which deal with the questions treated of in the book. We have included references to works which contain bibliographical information, however incomplete, in order to assist the reader who wishes to make further bibliographical investigations. We crave the indulgence of those authors whose works we have been unable to notice in this appendix.

THE WORKS OF THE AUTHOR AND HIS PUPILS ON THE PHYSIOLOGY AND PATHOLOGY OF THE THYROID.

ABBREVIATIONS:

t = volume No. = number.
f = fasciculus p. = page.

1. **de Quervain, F.** — Ueber die Veränderung des Centralnervensystems bei experimenteller Cachexia thyreopriva de Thiere. *Virch. Arch.*, 1893, t. 133.
2. — Ueber akute, nicht eiterige Thyreoiditis. *Arch. f. klin. Chir.*, t. 67, f. 3, 1902.
3. — Die akute, nicht eiterige Thyreoiditis und die Beteiligung der Schilddrüse an akuten Intoxikationen und Infektionen überhaupt. *Mitt. Grenzg. Med. u. Chir.*, II. Suppl. Bd., 1904.
4. — De l'influence de l'alcoolisme sur la glande thyroïde. *Sem. Méd.*, t. 25, 1905.
5. — Thyreoiditis simplex und toxische Reaktion der Schilddrüse. *Mitt. Grenzg. Med. u. Chir.*, t. 15, f. 3, 1905.
6. — Die Chirurgie des Halses, in Lehrb. d. Chirurgie von Wilms and Wullstein, 1908-1922, 1-8 Aufl.
7. — Parastruma maligna aberrata. *D. Ztschr. f. Chir.*, t. 100, p. 334, 1909.
8. — Zur Technik der Kropfoperation. *D. Ztschr. f. Chir.*, t. 116, p. 574, 1912.
9. — Weiteres zur Technik der Kropfoperation. *D. Ztschr. f. Chir.*, t. 134, 1915.
10. — Preliminary hæmostasis in goitre operations. *Surg., Gynec. and Obst.*, t. 23, 1916.
11. — Spezielle chirurgische Diagnostik. Vogel, Leipzig, 8 Aufl., 1922. Traité de diagnostic chirurgical. Atar et Maloine, 2e éd., 1922.
12. — Evoluzione e stato attuale della operazione del gozzo. *Rif. Méd.*, No. 9, 1922.
13. — Relationship between histological structure and biological activity of goitre tissue. *Surg., Gynec. Obst.*, t. 34, 1922.
14. — La prophylaxie du goitre. *Rev. suisse d'Hyg.*, 1922.
15. — Schilddrüse und Iod mit Rücksicht auf die Kropfprophylaxe. *Schw. med. W.*, No. 35, 1922.
16. — Ueber den respiratorischen Gaswechsel bei der Struma vasculosa im Kindesalter und nach Implantation von Kropfgewebe bei Kretinen. *Schw. med. W.*, No. 38, 1922.
17. — Zur pathologischen Physiologie der verschiedenen Kropfarten und ihrer Einwirkung auf das biologische Verhalten des Blutes. *Schw. med. W.*, No. 1, 1923.

18. **de Quervain, F.**—Ueber den Schutz der Epithelkörperchen. *Beitr. z. klin. Chir.*, t. 128, f. 1, 1923.

19. — Instruction concernant la mensuration du corps thyroïde, publiée par la commission du goitre principalement à l'usage des examens scolaires. Bühlmann, Berne, 1922. (Rédigé par l'auteur avec collaboration de la Sous-commission d'Enquête.)

20. — Crétinisme, états hypothyroïdiens et système nerveux. *Arch. suisses de Neurologie*, t. XII, f. 1-2, 1923.

21. **Aeschbacher, S.** Ueber den Einfluss krankhafter Zustände auf den Iod- und Phosphorgehalt der normalen Schilddrüse. *Mitt. Grenzg. Med. u. Chir.*, 1905.

22. **Luthi, A.**—Ueber experimentelle venöse Stauung in der Hundeschilddrüse. *Mitt. Grenzg. Med. u. Chir.*, 1905.

23. **Sarbach, J.**—Das Verhalten der Schilddrüse bei Infektionen and Intoxicationen. *Mitt. Grenzg. Med. u. Chir.*, 1905.

24. **Hoessly, H.** — Ueber Störungen der Larynxinnervation im Anschluss an 250 Kropfoperationen. *D. Ztschr. f. Chir.*, t. 134, 1915.

25. — Ueber Nervenimplantation bei Recurrenslähmungen. *Beitr. z. klin. Chir.*, t. 99, 1916.

26. **Woelz, E.**—Vergleichende Untersuchungen über die Häufigkeit der verschiedenen Kropfformen in Basel und in Bern. *Schw. med. W.*, 1921, No. 27.

27. **Doubler, F. H.**—Ueber den respiratorischen Gaswechsel bei der Struma vasculosa im Kindesalter und nach Implantation von Kropfgewebe bei Kretinen. *Schw. med. W.*, 1922, No. 38.

28. **Hara, Yuzo.**—Untersuchungen über die pathologische Physiologie des Kropfes mittels der Asher'schen Methode der Empfindlichkeit der Ratte gegen Sauerstoffmangel. *Mitt. Grenzg. Med. u. Chir.*, t. 36, f. 4, 1923.

29. — Die Wirkung des Iodes auf den respiratorischen Gaswechsel. Ibidem, t. 36, f. 4, 1923.

30. **Branovacky, M.**—Der physiologische Wert der verschiedenen Kropfarten unter gleichzeitiger Berücksichtigung des biologischen Experiments und des Iodgehaltes. Thèse de Berne, 1923. Paraîtra dans *Mitt. Grenzg. Med. u. Chir.*

31. **Pedotti u. Branovacky.**—Ueber vergleichende Untersuchungen der Schilddrüsenfunktion mittelst der direkten Bestimmung des Gaswechsels und der Untersuchung des Blutes im Asherschen Rattenexperiment. *Schw. med. W.*, No. 21, 1923.

32. **Kerzmann, H.**—Vergleichende Untersuchungen über die Häufigkeit des Kropfes in kindlichem Alter im Neuenburger Jura und in der Stadt Bern. Diss., Bern, 1921.

Chaitar, S. — Ueber die Beeinflussung des Kretinismus durch die Entfernung von Kropfgewebe. *Diss.*, Bern, 1923.

II.—BIBLIOGRAPHICAL LIST.

(1) Works on the Subject in General.

Asher, L.—Prinzipielle Fragen zur Lehre der inneren Sekretion. *Klinische Wochenschrift*, 1. Jg., 1922, No. 3.

Baillarger.—Enquête sur le goitre et le crétinisme. Baillière, Paris, 1873.

Barker, L.—Endocrinology and metabolism. 5 vol. D. Appleton and Co., New York and London, 1922.

Bérard, L.—Corps thyroïde. Baillière, Paris, 1908. *Ztbl. f. Chir.*, t. 35, No. 25, 1908,

Berry, J.—Diseases of the thyroid gland. Blakiston's Son and Co., Phila., 1901.

Biedl, A.—Innere Sekretion, ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie. Urban und Schwarzenberg, Berlin, 1922, 4. A.

Boothby, W. M., Plummer, H. S. and Wilson, L. B.—Diseases of the parathyroid and thyroid glands. Oxford Univ. Press. N. Y., 1922.

Crile, G. W. and associates.—The thyroid gland. W. B. Saunders, Phila., 1922.

Crotti, A.—Thyroid and thymus, Lea and Febiger, Phila. and N. Y., 1923. 2me éd.

v. Eiselsberg.—Die Krankheiten der Schilddrüse. *D. Chir. Lief.* 38, Enke, Stuttgart, 1901.

Endocrinology.—Los Angeles, 1917-1922, t. 1-6.

Ewald, C. A.—Die Erkrankungen der Schilddrüse, Myxoedem und Kretinismus. 2. Aufl., Wien, 1909.

Fabre, J. P. A.—Traité du goitre et du crétinisme et des rapports qui existent entre ces deux affections. Labé, Paris, 1857.

Falta, W.—Die Erkrankungen der Blutdrüsen. Springer, Berlin, 1913,

Foster, N. B.—Diseases of the thyroid gland. *Nelson's Liv. Med.*, N. Y., t. 3, p. 304, 1920.

Gauthier, L.—L'opothérapie thyroïdienne. Baillière, Paris, 1913.

Gley, E.—Quatre leçons sur les sécrétions internes. Baillière, Paris, 1920.

— Les sécrétions internes. Baillière, Paris, 2e éd., 1921.

Hertzler, A. E.—Diseases of the thyroid gland. *Endocrin.*, t. VI, f. 6, 1922.

Kocher, Th.—Ueber Krankheitserscheinungen bei Schilddrüsenerkrankungen geringen Grades. Nobelkonferenz. Stockholm, 1910.

Lebert, H.—Die Krankheiten der Schilddrüse und ihre Behandlung. Breslau, 1862.

Lereboullet, P.—Sympathique et glandes endocrines. Maloine, Paris, 1921.

Lévi, L.—Les doses en thérapeutique thyroïdienne. Maloine, Paris, 1918.

— Opothèrapie endocrinienne, ses applications journaiières. *Edit. du Livre de France*, Paris, 1922.

Lücke.—Krankheiten der Schilddrüse. Pitha-Billroth, *Handb. d. Chir.*, t. 3, 1875.

McCarrison, R.—The thyroid gland in health and disease. Baillière, Tindall and Cox, London, 1918.

Messerli, F.—Le goitre endémique. Lausanne, 1916.

Niépce, B.—Traité du goitre et du crétinisme. Baillière, Paris, 1851.

Ochsner, A. J., and Thompson, R. L.—The surgery and pathology of the thyroid and parathyroid glands. St. Louis, 1910.

Pende, N.—Endocrinologia, patologia e clinica degli organi a secrezione interna. Vallardi, Milano, 1920.

Porta, L.—Delle malattie e delle operazioni della glandiola tiroidea. Milano, 1849.

de Quervain, F.—Die Chirurgie des Halses, in Lehrb. d. Chir. von Wilms und Wullstein, 1908-1922, 1-8. Aufl.

Richadson, H.—The thyroid and parathyroid glands. Blakiston, Phila., 1905.

v. Rodt, W. E.—Beitrag zur Geschichte der Schilddrüse. *D. Ztschr. f. Chir.*, t. 116, p. 629, 1912.

Taussig, S.—Kropf und Kretinismus. Eine epidemiologische Studie. G. Fischer, Jena, 1912.

(2) Anatomy.

Briau, E.—L'innervation du corps thyroïde, recherches anatomiques et physiologiques. Baillière, Paris, 1898.

Chemin, A.—Contribution à l'étude des restes chez l'adulte de l'ébauche thyroïdienne médiane. Cadoret, Bordeaux, 1895.

Clerc, E.—Die Schilddrüse im hohen Alter vom 50. Lebensjahr an, aus der norddeutschen Ebene und Küstengegend sowie aus Bern. *Frankf. Ztschr. f. Path.*, t. 10, p. 1, 1912.

Elkes, Ch.—Der Bau der Schilddrüse um die Zeit der Geburt. Diss., Königsberg i. Pr., 1903.

Enderlen und Hotz.—Beiträge zur Anatomie der Struma und zur Kropfoperation. *Ztschr. f. angew. Anat. u. Konstitutionslehre*, t. 3, 1918.

Erdheim, J.—Ueber einige menschliche Kiemenderivate. *Ziegl. Beitr. z. path. Anat.*, t. 35, f. 2, p. 366, 1904.

Getzowa, S.—Ueber die Gl. parathyreoidea, intrathyr. Zellhaufen und Reste des postbr. Körpers. *Virch. Arch.* 188, 1907.

Hesselberg, C.—Die menschliche Schilddrüse in der fötalen Periode und in den ersten 6 Lebensmonaten. *Frankf. Ztschr. f. Path.*, t. 5, p. 322, 1910.

Isenschmid, R. — Zur Kenntnis der menschlichen Schilddrüse im Kindesalter, mit besonderer Berücksichtigung der Herkunft aus verschiedenen Gegenden im Hinblick auf die endemische Struma. *Frankf. Ztschr. f. Path.*, t. 5, f. 2, 1910.

Lübcke, O.—Beiträge zur Kenntnis der Schilddrüse. Diss. Rostock. *Virch. Arch.*, t. 167, p. 490, 1902.

de Quervain, F.—Zur Techkik der Kropfoperation. *D. Ztschr. f. Chir.*, t. 116, p. 574, 1912.

— Weiteres zur Technik der Kropfoperation. *D. Ztschr. f. Chir.*, t. 134, p. 475, 1915.

Sanderson-Damberg.—Die Schilddrüsen zom 15-25. Lebensjahr aus der norddeutschen Ebene und Küstengegend, sowie aus Bern. *Frankf. Ztschr. f. Path.*, t. 6, f. 2, p. 312, 1911.

Sobotta, J.—Anatomie der Schilddrüse (in *Handb. d. Anat. d. Menschen. hrsg. v. Bardeleben*), t. 6, 1915.

Stierlin, R.—Ueber morphologische Anomalien der Schilddrüse. *Schw. Rundschau f. Med.*, 1912, No. 26.

Streckeisen, A.—Beiträge zur Morphologie der Schilddrüse. Diss., Basel. *Virch. Arch.*, t. 103, p. 131, 215, 1886.

Truffert, P.—Le cou, anatomie topographique. Les aponévroses, les loges. L. Arnette, Paris, 1922.

(3) Physiology (see also 5, 6, 15).

Abderhalden, E., und Schiffmann, O.—Studien über die von einzelnen Organen hervorgebrachten Substanzen mit spezifischer Wirkung IV. *Arch. f. d. ges. Physiol.*, t. 183, p. 197, 1920; VIII. ibidem, t. 195, p. 167, 1922.

Abelin, J.—Nachweis der Stoffwechselwirkung der Schilddrüse mit Hilfe eines eiweissfreien oder iodarmen Schilddrüsenpräparates. *Biochem. Ztschr.*, t. 80, f. 5 u. 6, 1917.

— Beiträge zur Kenntnis der physiologischen Wirkung der proteinogenen Aminwirkung auf den Stickstoffwechsel schilddrüsenloser Hunde. *Biochem. Ztschr.*, t. 93, f. 3 u. 4, 1919.

— Beiträge zur Kenntnis der physiologischen Wirkung der proteinogenen Amine. II. Mitteilung. Wirkung der proteinen Amine auf den Gaswechsel. *Biochem. Ztschr.*, t. 101, f. 4, 5 u. 6, 1920.

— Beiträge zur Kenntnis der physiologischen Wirkung der proteinogenen Amine. IV. Mitteilung. Einfluss von Dijodtyramin und Tyramin auf die Entwicklung der Froschlarven. *Biochem. Ztschr.*, t. 102, f. 3 u. 4, 1920.

— Beiträge zur Kenntnis der physiologischen Wirkung der proteinogenen Amine. Vegetatives Nervensystem und Stoffwechsel. *Biochem Ztschr.*, t. 129, f. 1 u. 2, 1922.

Abelin, J., und Jaffé, J.—Beiträge zur Kenntnis der physiologischen Wirkung der proteinogenen Amine. III. Mitteilung. Ueber den Einfluss der proteinogenen Amine, Phenyl, u. p. Oxyphenylaethylamin auf den Kohlehydratstoffwechsel. *Biochem. Ztschr.*, t. 102, 1920.

Adler, L.—Ueber den Angriffspunkt der Blutdrüsenhormone bei der Wärmeregulation. Weitere Untersuchungen an Winterschläfern. *Arch. f. exp. Path. u. Pharm.*, t. 87, f. 5 u. 6, 1920.

— Schilddrüse und Wärmeregulation. Untersuchungen an Winterschläfern. *Arch. f. exp. Path. u. Pharm.*, t. 86, f. 3 u. 4, p. 150, 1920.

Allen, B. M.—The relation of normal thyroid gland development to bodily growth and differentiation in Rana, Bufo and Amblystoma. *Anat. Rec. Phila.*, t. 14, 1918.

Asher, L.—Kritische Bemerkungen zur Geschichte und Methodik der Schilddrüsenphysiologie, *Arch. f. d. ges. Phys.*, t. 139, 1911.

— Die physiologischen Wirkungen des Schilddrüsensekretes und Methoden zu ihrem Nachweis. *D. med. W.*, No. 34, 1916.

— Die Wirkungen des Schilddrüsenhormons. *Therap. Halbmon. Hefte.*, t. 34, No. 8, 1920.

Asher, L., und Flack, M.—Beiträge zur Physiologie der Schilddrüse. Die innere Sekretion der Schilddrüse und die Bildung des inneren Sekretes unter dem Einfluss von Nervenreizung. *Ztschr. f. Biochemie*, XVI. Mitteilung, t. 55.

Backmann, Hs.—Beiträge zur Physiologie der Schilddrüse. Untersuchungen zur Frage, ob nach Exstirpation von Schilddrüse und Nebenschilddrüse biologisch nachweisbare toxische Stoffe im Blute aufreten. XXX. Mitteilung. *Ztschr. f. Biochemie*, t. 67, 1917.

Bassinger, H. R.—The alleged detoxicating power of the thyroid gland. *Jour. Infec. Diseases, Chgo.*, t. 20, p. 131, 1917.

Bensley, R. R.—Influence of Diet and Iodides on Hyperplasia, in opossums in captivity *Am. Journ. Ant. Phila.*, t. 19, p. 57, 1916.

Blum, F.—Gefässdrüsen und Gesamtorganismus. Studien über ihre gegenseitigen Beziehungen unter Anwendung einer neuen Versuchsanordnung. *Arch. f. d. ges. Physiol.*, t. 105, p. 625, 1904.

Blum, F., und Grützner, R.—Studien zur Physiologie der Schilddrüse. 1.-6. Mitteilung. *Zeitschrift für Physiol. Chemie.*, t. 85-92, 1913-14.

Brown, N. W.—Determination of relative activity of the thyroid lobes. *Endocrin.*, t. 5, p. 29, 1921.

Cameron, A. T., and Carmichael, J.—The comparative effects of thyroid and of iodine feeding on growth in white rats and rabbits. *J. Physiol.*, London, t. 54, p. 74, 1921.

Cannon, W. B., and Smith, P. E.—Some conditions affecting thyroid activity. *Endocrin.*, t. 4, p. 386, 1920.

Cléret, M.—Etude sur la pathogénie du goitre exophtalmique. Thèse de Paris, 1911.

v. Cyon, E.—Beiträge zur Physiologie der Schilddrüse und des Herzens. *Arch. f. d. ges. Physiol.*, t. 70, 1898.

— Die Gefässdrüsen als regulatorische Schutzorgane des Zentralnervensystems. Springer, Berlin, 1910.

Duran, M.—Das Verhalten von normalen, mit Schilddrüsensubstanz gefütterten und schilddrüsenlosen Ratten gegen reinen Sauerstoffmangel. *Biochem. Ztschr.*, t. 106, f. 4-6, 1920.

Eiger, M.—Der biologische Nachweis der innern Sekretion der Schilddrüse im Blute der mit Schilddrüsenextrakten gefütterten weissen Ratten. *Ztschr. f. Biol.*, t. 67, H. 6, 1917.

Endocrinology, the bulletin of the Association for the study of internal secretions. Los Angeles, t. 1-6, 1917-22.

Eppinger, Falta, H. W., und Rudinger, C.—Ueber die Wechselwirkungen der Drüsen mit innerer Sekretion. *Ztchr. f. klin. Med.*, t. 66, p. 1, 1908.

Fenger, F.—On the seasonal variation in the iodine content of the thyroid gland. *Endocrin.*, t. 2, p. 98, 1918.

Fuhr, F.—Die Exstirpation der Schilddrüse. Eine experimentelle Studie. *Habilit. Schrift*, Giessen, 1886.

Gley, E.—Exposé critique des recherches relatives à la physiologie de la glande thyroïde. *Arch. de Physiol.*, avril, 1892.

— Toxicité des extraits d'organes, tachyphylaxie, anaphylaxie (dans Mélanges biologiques), livre jubilaire du prof. Ch. Richet, Paris, 1912.

— Conception et classification physiologiques des glandes. *Rev. Scient.*, t. 52, 1893.

— Essais de philosophie et d'histoire de la biologie. Masson et Cie., Paris, p. 123, 1900.

Gley, E., et Cléret, M.—Recherches sur la pathogénie du goitre exophtalmique. Action cardiovasculaire du sérum sanguin des malades atteints de goitre exophtalmique. *Jour. de physiol. et de pathol. gén.*, t. 13, 1911.

Gley, E., et Quinquaud, A.—Contribution à l'étude des interrelations humorales. *Arch. internat. de physiol.*, t. 1, p. 152, janv., 1914.

Gröbly, W.—Ueber das Nukleoproteid der Schilddrüse. *Mitt. Grenzg. Med. u. Chir.*, t. 30, f. 3, p. 403, 1918.

Gudernatsch, J. F.—Studies on internal secretions. IV. Treatment of tadpoles with thyroid and thymus extracts. *Anat. Rec. Phila.*, t. 11, p. 357, 1917.

— Feeding experiments on tadpoles. I. The influence of specific organs given as food on growth and differentiation. *Arch. f. Entwickl. Mech.*, t. 35, p. 475, 1912.

— Feeding experiments on tadpoles. II. A further contribution to the knowledge of organs with internal secretion. *Am. Jour. of Anat.*, t. 15, p. 431, 191.

Halsted, W. S.—Reconsideration of the question of experimental hypertrophy of the thyroid gland and the effect of excision of this organ upon other of the ductless glands. *Am. Jour. of the med. sc.*, t. 147, No. 1, 1914.

Herring, P. T.—The influence of the thyroids on the functions of the suprarenals. *Endocrin.*, t. 4, p. 577, 1920.

Hofmeister, F.—Experimentelle Untersuchungen über die Folgen des Schilddrüsenverlustes. *Beitr. z. klin. Chir.*, t. 11, f. 2, 1894.

Horsley, V.—Die Funktion der Schilddrüse. London, 1891. *Festchrift für Virchow.*

— Remarks on the function of the thyroid gland, critical and historical review. *Brit. med. Journ.*, 1892.

Hoskins, E. R., and Hoskins, M. M.—The interrelation of the thyroid and hypophysis in the growth and development of frog larvæ. *Endocrin.*, t. 4, Jan.-March, 1920.

Isenschmid, R.—Histologische Veränderungen im Zentralnervensystem bei Schilddrüsenmangel. *Frankf. Ztschr. f. Path.*, t. 21, f. 3, 1919.

Kocher, A.—Ueber die Wirkung von Schilddrüsenpräparaten auf Schilddrüsenkranke. *Mitt. Grenzg. Med. u. Chir.*, t. 29, p. 309, 1918.

Lanz, W.—Versuche über die Wirkung einiger Schilddrüsenpräparate auf den Stoffwechsel und das Blutbild von Myxoedem und Cretinismus. *Mitt. Grenzg. Med. u. Chir.*, t. 29, p. 285, 1918.

Lenhard.—The influence upon tadpoles of feeding desiccated thyroid gland in variable amounts and of variable iodine contents. *Jour. of experim. med.*, t. 22, 1915.

Ligneris, des.—Experimentelle Untersuchungen über die Wirkung des Iods auf die Hundeschilddrüse, sowie über die Hyperplasie dieser Drüse. Diss., Bern, 1907.

Monéry, A.—Recherches nouvelles sur la fonction iodée de la glande thyroïde. Métabolisme de l'iode. Lyon, 1903.

Moussu, G.—Recherches sur les fonctions thyroïdienne et parathyroïdienne. Asselin et Houzeau, Paris, 1897.

Nagel, W. A., und Roos, E.—Versuche über experimentelle Beeinflussbarkeit des Iodgehaltes der Schilddrüse. *Arch. f. Anat. u. Physiol.*, 1902.

Oswald, A.—Beiträge zur Schilddrüsenfrage (Ueber den Iodgehalt der Schilddrüsen). Diss., Basel. Trübner, Strassburg, 1897.

— Ueber die Wirkung der Schilddrüse auf den Blutkreislauf. *Arch. f. d. ges. Physiol.*, t. 166, p. 169, 1916.

Pézard, A.—Le conditionnement physiologique des caractères sexuels secondaires chez les oiseaux. Thèse de Paris, 1918.

Pineles, Fr.—Klinische und experimentelle Beiträge zur Physiologie der Schilddrüse und der Epithelkörperchen. *Mitt. Grenzg. Med. u. Chir.*, t. 14, f. 1 u. 2, 1904.

Plummer, H. S., and Boothby, W. M.—Specific dynamic action of thyroxin. *Am. Jour. Physiol. Balt.*, t. 55, p. 295, 1921.

Prins, A. L.—Ueber den Einfluss des Iodes auf die Schilddrüse. Diss., Freiburg i. Br., 1895.

de Quervain, F.—Ueber die Veränderung des Zentralnervensystems bei experimenteller Cachexia thyreopriva der Thiere. *Virch. Arch.*, t. 133, 1893.

Richardson, Henry B.—Beiträge zur Physiologie der Schilddrüse. Wirkung innerer Sekrete, insbesondere von Schilddrüsensekret und Adrenalin auf das überlebende Säugetierherz. *Ztschr. f. Biochemie*, t. 67, f. 2, 1916, XXIV. Mitteilung.

Rogoff, J. M.—A method for the standardization of thyroid preparations. *Jour. Pharm. and Exp. Therap., Balt.*, t. 10, p. 199, 1917.

Rogoff, J. M., and Marine, D.—Attempts to produce a substance with thyroidlike activity by the artificial iodization of proteins. *Jour. Pharm. and Exp. Therap.*, t. 10, p. 321, 1917.

Rogowitch, M. N.—Sur les effets de l'ablation du corps thyroïde chez les animaux. *Arch. de Physiol.*, Par., 1888.

Romeis, B.—Versuche über den Einfluss von Fett und Lipoidsubstanzen sowie von enteiweissten Extracten der Schilddrüse auf Entwicklung und Wachstum. *Arch. f. d. ges. Physiol. Berl.*, t. 173, p. 422, 1919.

— Quantitative Untersuchungen über die Wirkung von Thyroxin, Dijotyrosin, Iodothyrin und Iodthyreoglobulin. *Berl. Klin. W.*, f. 1, p. 1262, 1922.

Schmid, E.—Der Sekretionsvorgang in der Schilddrüse. *Arch. f. mikrosk. Anat.*, t. 47, 1896.

Seidell, A.—Further experiments upon the determination of iodine in thyroid. *Jour. of biol. chem.*, t. 10, f. 2, 1911.

Seidell, A., and Fenger, F.—Seasonal variations in the iodine content of the thyroid gland. *J. Biol. Chem., N.Y.*, t. 13, p. 517, 1912-13.

Streuli, Heinrich.—Beiträge zur Physiologie der Schilddrüse. Die Wechselwirkung von inneren Sekreten und die Beziehung dieser Wirkung zum Problem der Erregung und Hemmung. XXII. Mitteiluug. *Ztschr. f. Biochemie*, t. 66, f. 4 u. 5.

Swale, V.—Innere Sekretion und Drüsen ohne Ausführungsgang. *Ergeb. der Physiol.*, t. 9, p, 454, 1910, u. t. 9, p. 218, 1911.

Swingle, W. W.—Iodine as the active principle of the thyroid gland. *Endocrin.*, t. 2, p. 283, 1918.

— Studies on the relation of iodine to the thyroid. II. Comparison of the thyroid glands of iodine-fed and normal frog larvæ. *J. Exp. Zool. Phila.*, t. 27, p. 417, 1919.

Tschistke, A.—Ueber die Wirkung des im Schilddrüsencolloïd enthaltenen Nukleoproteïdes bei M. B. *D. med. W.*, t. 37, p. 2217, 1911.

Van Dyke, H. B.—A study of the distribution of iodine between cells and colloid in the thyroid gland. II. Results of study of dog and human thyroid glands. *J. Biol. Chem. Balt.*, t. 45, p. 325, 1921. III. The effect of stimulation of the vago-sympathetic nerve on the distribution of iodine in the dog's thyroid gland. *Am. J. Physiol. Balt.*, t. 56, p. 168, 1921.

Waser, Alois.—Beiträge zur Physiologie der Schilddrüse. Das relative weisse Blutbild nach Injektion von Eisen und Schilddrüsenpräparaten. XLI. Mitteilung. *Ztschr. f. Biochemie*, t. 71, 1920.

Wuth, O.—Ueber biologische Wirkungen proteinogener Amine. Zugleich ein Beitrag zur Frage der Acetonitrilreaktion. *Biochem. Ztschr. Berl.*, t. 116, p. 237, 1921.

(4) Pathological Anatomy (exclusive of Graves' disease, inflammations and malignant goitre). (See also 14, 15, 16, 17.)

Bérard, L., et Alamartine, H.—Contribution à l'étude de la classification anatomique des tumours thyroïdiennes. *Rev. de chir.*, t. 32, f. 4, 1905.

Coudray, P.—De l'influence des maladies infectieuses sur la glande thyroïde. Thèse de Montpellier, No. 89, 1909.

Crispino, M.—La tiroide nella infezione ed intossicazione sperimentale. Estratto dal *Giorn. dell'Ass. Nap. dei Med. e Nat.*, t. 12, Punt. 3, 1902.

Garnier, M.—La glande thyroïde dans les maladies infectieuses. Thèse de Paris, 1899.

Giraud, G.—Le corps thyroïde des tuberculeux, recherches histologiques et chimiques. Thèse de Paris, 1908.

Goetsch, E.—Further studies on the pathological and clinical significance of diffuse adenomatosis of the thyroid gland. Assoc. for the Study of Int. Secr., Boston, June, 1921.

Halsted, W. St.—Hypertrophy of the thyroid gland. Revision of experiments made 25 years ago. *Proc. Soc. exp. biol. med.*, t. 10, f. 3, 1913, u. *Ztbl. d. exp. Med.*, t. 5, p. 254, 1914.

Hellwig.—Die diffuse Colloidstruma. *Mitt. Grenzg. Med. u. Chir.*, t. 32, p. 508, 1921.

Hitzig.—Beiträge zur Histologie und Histogenese der Struma. *Arch. f. klin. Chir.*, t. 47, f. 2, p. 464, 1894.

Kloeppel, F.—Vergleichende Untersuchungen über Gebirgsland- und Tieflandschilddrüsen. *Ziegl. Beitr.*, t. 49, p. 579, 1910.

Klose, H.—Die chirurgische Topographie des wachsenden Kropfes. *D. Ztschr. f. Chir.*, t. 157, f. 3 u. 4, p. 157, 1920.

Lanz, O.—Ausführungen über die Klassifikation der Kropfgeschwülste. *Niederl. Tidjsch. v. Geneesk.*, t. 1, 1917. *Ref. d. m. W.*, p. 540, 1917.

Lüthi, Alb.—Ueber experimentelle venöse Stauung in der Hundeschilddrüse. *Mitt. Grenzg. Med. u. Chir.*, t. 15, f. 3 u. 4, p. 247, 1905.

MacCarty, W. C.—Pathologic anatomy of goitre (a macroscopic and microscopic study of fresh material from 2,500 cases). *N.Y. State Jour. med.*, t. 12, p. 595, 1912.

— Goitre and its relation to its structural and physiologic units. *Surg. Gynec. Obst. Chgo.*, t. 16, p. 406, 1913.

Michaud, L.—Die Histogenese der Struma nodosa. *Virch. Arch.*, t. 186, 1906.

Muller, L. R.—Beiträge zur Histologie der normalen und der erkankten Schilddrüse. *Beitr. z. path. Anat. u. z. allg. Path.*, t. 19, p. 127, 1886.

de Quervain, F.—Ueber akute, nicht eiterige Thyreoiditis. *Arch. f. klin. Chir.*, t. 67, f. 3, 1902.

— Die akute, nicht eiterige Thyreoiditis und die Beteiligung der Schilddrüse an akuten Intoxikationen und Infektionen überhaupt. *Mitt. Grenzg. Med. u. Chir.*, II. Suppl., Bd. 1904.

— De l'influence de l'alcoolisme sur la glande thyroïde. *Sem. med.*, t. 25, 1905.

— Thyreoiditis simplex und toxische Reaktion der Schilddrüse. *Mitt. Grenzge. Med. u. Chir*, t. 15, f. 3, 1905.

Roger et Garnier.—La glande thyroïde dans les maladies infectieuses. *Presse méd.*, 1899, No. 31.

Sarbach, J.—Das Verhalten der Schilddrüse bei Infectionen und Intoxikationen. *Mitt. Grenzge. Med. u. Chir.*, t. 15, f. 3 u. 4, 1905.

Torri, O.—La tiroide nei morbi infetivi. *Il Policl.*, t. 7, C, f. 3, 1900.

Valentin, Fr.—Der Einfluss letaler Verbrennungen auf das histologishe Bild der Schilddrüse. Diss., Bern, 1908.

Wegelin, C.—Zur Histogenese des endemischen Kropfes. *Corr. Bl. f. Schw. Aer.*, f. 9 u. 10, p. 321 u. 376, 1912.

— Die Einteilung der Kröpfe. *Schw. Kropfkomm.*, 21. I. 1922.

— Ueber die Ossifikationsstörungen beim endemischen Kretinismus und Kropf. *Corr. Bl. f. Schw. Ae.*, t. 46, p. 609, 1915.

v. Werdt, F.—Lymphfollikel in Strumen. *Frankf. Ztschr. f. Path.*, t. 8, f. 3, 1913.

Wilson, L. B.—A study of the thyroids from cases of toxic non-exophthalmic goiter. *Am. Jour. Med. Sc. Phila.*, t. 147, p. 344, 1914.

— The pathological changes in the sympathetic system in goiter. *Am. Jour. Med. Sc. Phila.*, t. 152, p. 799, 1916.

— The pathological classification of lesions of the thyroid gland. *Am. Clin. Med. Balt.*, t. 1, p. 44, 1922.

Wilson, L. B., and Kendall, E. C.—The relationship of the pathologic histology and the iodine compound of the human thyroid. *Am. Jour. Med. Sc. Phila.*, t. 151, p. 79, 1916.

Wilson, L. B., and Young, T. O.—Further study of the histopathology of the autonomic nervous system in goiter. *Jour. Lab. and Clin. Med. St. Louis*, t. 2, p. 295, 1917.

Wölfler, A.—Ueber die Entwicklung und den Bau des Kropfes. Berlin, 1883.

(5) Pathological Physiology (see also 6, 14, 15).

Aeschbacher, S.—Ueber den Einfluss krankhafter Zustände auf den Iod-und Phosphorgehalt der normalen Schilddrüse. *Mitt. Grenz. Med. u. Chir.*, t. 15, p. 269, 1905.

Ballmer, F., Bauer, J., und Streit, A.—Komplementbildungsversuche bei endemischen Kropf. Hyg. Inst. u. med. Klinik, Innsbruck. *Ztschr. f. Immun. Forsch.*, p. 546, 1912.

Bircher, M. E.—Technik der Basalstoffwechselbestimmung, mit Demonstration ihrer Anwendbarkeit an einem Fall von operativem Hypothyreoidismus. *Schw. med. W.*, t. 4, No. 6, 1923.

Blum, F.—Neues und Altes zur Physiologie und Pathologie der Schilddrüse. 23. Kongr. München 1906 f. inn. Med., und Münch. med. W., p. 890, t. 53, 1906.

Blum, F., et Marx, A. V.—Zur Physiologie der Schilddrüse und der Epithelkörperchen, *Arch. f. d. ges. Physiol.*, t. 159, 1914.

Boothby, W. M.—The fundamental classification of disease by the basal metabolic rate. *Jour. Am. Med. Ass. Chgo.*, t. 76, p. 84, 1921.

Breitner, B.—Zur Frage nach dem Wesen des Kropfes. *Mitt. Grenzg. Med. u. Chir.*, t. 24, f. 3, p. 590, 1912.

— Experimentelle Untersuchungen über das Wesen der Schilddrüsenerkrankungen. *Wien. Med. W.*, t. 13, p. 342, 1913.

Chapman, T. L.—Factitious toxicity of previously simple goiter. *Minnesota Med.* (St. Paul), f. 4, p. 148, 1921.

Courvoisier.—Ueber den Einfluss von Iodthyreoglobulin und Thyreonukleoproteid auf den Stickstoffwechsel und das Blutbild von Myxoedem und Basedow. *Mitt. Grenzg. Med. u. Chir.*, t. 29, p. 245, 1917.

Eiger, M.—Der biologische Nachweis der inneren Sekretion der Schilddrüse im Blute der Schilddrüsenvene sowie auch in der Blutbahn der Basedowkranken. *Ztschr. f. Biol.*, t. 67, f. 6, 1917.

Fonio, A.—Ueber den Einfluss von Basedowstruma- und Kolloidstrumapräparaten und Thyreoidin auf den Stickstoffwechsel und auf das Blutbild von Myxoedem unter Berücksichtigung ihres Iodgehaltes. *Mitt. Grenzg. Med. u. Chir.*, t. 24, f. 1, p. 123, 1912.

Frey, H.—Ueber den Einfluss von Iod, Iodkalium, Iodothyrin und iodfreiem Strumapräparat auf den Stickstoffwechsel, auf Temperatur, Pulsfrequenz und auf das Blutbild von Myxoedem. *Mitt. Grenzg. Med. u. Chir.*, t. 28, p. 348, 1916.

Goetsch, E.—Hypersensitiveness test with especial reference to "diffuse adenomatosis" of the thyroid gland. *Endocrin.*, t. 4, p. 389, 1920.

— Recent advances in the diagnosis and treatment of thyroid disease based on the use of the epinephrin hypersentiveness test. *N. Y. State Jour. of Med.*, Sept., 1920.

Graham, A.—A study of the physiological activity of the adenomata of the thyroid gland, in relation to their iodine content, as evidenced by feeding experiments on tadpoles. *Jour. of the experim. med.*, t. 24, p. 345, 1916.

Herzfeld und Klinger.—Chemische Studien zur Physiologie und Pathologie. Zur Funktion der Schilddrüse. *Münch. Med. W.*, t. 65, p. 647, 1918.

Janney, N. W.—Concerning the pathogenesis of the thyrotoxicosis. Part I. *Endocrin.*, t. 6, f. 5, 1922.

— Studies in thyroid therapy. III. The effects of the thyroid hormone as determined by metabolic and dietetic investigation. *Arch. Int. Med. Chgo.*, t. 22, p. 187, 1918, and *Abst.* 327, *Endocrin.*, t. 2, p. 345, 1918.

Kendall, E. C.—Experimental hyperthyroidism. *Jour. Am. Med. Ass. Chgo.*, t. 69, p. 612, 1917.

Kendall, E. C. and Associates.—Series of papers on isolation and identification of thyroxin. Collected Papers of the Mayo Clinic. W. B. Saunders, Phila., t. 7, p. 393 and p. 422, 1915; ibidem, t. 8, p. 513, 1916; ibidem, t. 9, p. 417 and 424, 1919.

Kocher, Th.—Die Pathologie der Schilddrüse. 23. Kongress f. inn. Med., München, 1906.

Kottmann, K.—Beiträge zur Physiologie und Pathologie der Schilddrüse. I. Mitteilung: Ueber die Beeinflussung der Blutgerinnung durch die Schilddrüse (von Anna Lidsky), *Ztschr. f. klin. Med.*, t. 71, p. 344, 1910.

— Ueber den Fibringehalt des Blutes im Zusammenhang mit der Schilddrüsenfunktion Gleichzeitig ein Beitrag zum Fibringehalt des normalen menschlichen Blutes. *Ztschr. f. klin. Med.*, t. 71, p. 362, 1910.

— Kolloidchemische Untersuchungen über Schilddrüsenprobleme. *Schw. med. W.*, t. 1, f. 30, 1920.

Lépine.—Médication thyroïde. *Sem. méd.*, pp. 57 et 333, 1896.

Lévi, A. — Etudes sur la physiopathologie du crops thyroïde et de l'hypophyse. Paris, 1908.

Lévi, L., et de Rothschild, H.—Etudes sur la physiopathologie du corps thyroïde et de l'hypophyse. Doin, Paris, 1908.

— Nouvelles études sur la physiopathologie du corps thyroïde et des autres glandes endocrines. Doin, Paris, 1911.

— La petite insuffisance thyroïdienne et son traitement. Doin, Paris, 1913.

Lobenhoffer. — Beiträge zur Lehreder Sekretion in der Struma. *Mitt. Grenzg. Med. u. Chir.*, t. 20, f. 4, p. 650, 1908.

Magnus-Lévy, A.—Der Stoffwechsel bei Erkrankungen einiger Drüsen ohne Ausführungsgang. *Handb. d. Path. d. Stoffw.*, Berl., t. 2, p. 325, 1907.

Mikulicz und Reinbach, G.—Ueber Thyroidismus bei einfachem Kropf. *Mitt. Grenzg. Med. u. Chir.*, t. 8, f. 3, p. 247, 1896.

Oswald, A.—Die Schilddrüse in Physiologie und Pathologie. Leipzig, 1916.

Plummer, H. S.—Functions of the normal and abnormal thyroid gland. *Oxf. Med. N. Y.*, t. 3, p. 839, 1921.

— The clinical and pathological relationship of hyperplastic and non-hyperplastic goitre. *Jour. Am. Med. Ass. Chgo.*, t. 61, 650, 1913.

— The function of the thyroid, normal and abnormal. *Tr. Ass. Am. Phys.*, t. 31, p. 129, 1916.

de Quervain, F.—Zur pathologischen Physiologie der verschiedenen Kropfarten und ihrer Einwirkung auf das biologische Verhalten des Blutes. *Schw. med. W.*, t. 4, No. 1, 1923.

Salis, H. v., und Vogel, A.—Die Beziehungen der Iodbehandlung zum lymphoiden Gewebe und zur Blutlymphozytose bei einigen Fällen von Basedow, Hypothyreose und Struma ohne Funktionsstörung. *Mitt. Grenzg. Med. u. Chir.*, t. 27, f. 2, p. 275, 1913.

Staemmler, M.—Ueber Struma congenita und ihre Beziehungen zu Störungen der inneren Sekretion. *Virch. Arch.*, t. 219, f. 2, p. 226, 1915.

Wegelin, C., und Abelin, J.—Ueber die Wirksamkeit der menschlichen Schilddrüse im Froschlarvenversuch. *Arch. f. experim. Path. u. Pharm.*, t. 89, f. 5, u. 6, 1921.

(6) Normal and Pathological Metabolism (see also 14 and 15).

Aub, J. C. — The relation of the internal secretions to metabolism. *Jour. Am. Med. Ass. Chgo.*, t. 79, p. 95, 1922.

Baldoni, A.—Lo scambio gassoso polmonare nei cani tiroidectomizzati. *Bull. della R. Acad. Med. di Roma*, t. 25, f. 4, 1898-1899.

Benedict, F. G.—Ein Universalrespirationsapparat. *D. Arch. f. klin. Med.*, t. 107, p. 160, 1912.

— The measurements and standards of basal metabolism. *Jour. Am. med. Ass.*, t. 77, p. 247, 1921.

Benedict, F. G., and Hendry, M. F.—The energy requirements of girls from 12 to 17 years of age. *Boston Med. and Surg. Jour.*, t. 184, March and April, 1921.

Benedict, F. G., and Talbot, F. B.—Metabolism and Growth from Birth to Puberty. *Carnegie Inst. Washington Publ.*, No. 302, 1912.

Boothby, W. M.—The basal metabolic rate in hyperthyroidism. *Jour. Am. Med. Ass. Chgo.*, t. 77, p. 232, 1921.

Boothby, W. M. and Sandiford, I.—A laboratory manual of the technic of basal metabolic rate determinations. Phila., W. B. Saunders Co., 1920.

— Nomographic charts for the calculations of the metabolic rate by the gasometer method. *Boston Med. and Surg. Jour.*, t. 185, p. 337, 1921.

— A comparison of the Du Bois and the Harris and Benedict normal standards for the estimation of the basal metabolic rate. *Jour. of Biol. Chem.*, t. 54, f. 4, 1922.

— Summary of the basal metabolism data on 8,614 subjects with especial reference to the normal standards for the estimation of the basal metabolic rate. *Jour. of Biol. Chem.*, t. 54, f. 4, 1922.

Doubler, Fr. H.—Ueber den respiratorischen Gaswechsel bei der Struma vasculosa im Kindesalter und nach Implantation von Kropfgewebe bei Kretinen. *Schw. med W.*, t. 3, No. 38, 1922.

Dreyer, G.—Normal basal metabolism in man and its relation to the size of the body and age. Expressed in simple formulæ. *Lancet*, t. 2, p. 289, 1920.

Du Bois, D., and Du Bois, E. F.—A formula to estimate the approximate surface area if height and weight be known. *Arch. Int. Med. Chgo.*, t. 17, p. 863, 1916.

Else, J. E.—The interpretation of the basal metabolic rate in toxic goitre. *North-west med. Seattle*, t. 20, p. 118, 1921.

Gephart, F. C., and Du Bois, E. F.—The basal metabolism of normal adults with special reference to surface area. *Arch. Int. med.*, t. 17, p. 902, 1916.

Hauri, O.—Das Verhalten der Kohlensaüre- und Wasserausscheidung des schilddrüsen- und milzlosen Kaninchens bei normaler und erhöhter Aussentemperatur. *Biochem. Ztschr.*, t. 98, f. 1-3, 1919.

Krogh, A.—The respiratory exchange of animals and man. Longmans, Green and Co., London, 1916.

McCaskey, G. W.—The basal metabolism and hyperglycemic tests of hyperthyroidism with special reference to mild and latent cases. *Jour. Am. med. Ass. Chgo.*, t. 73, p. 243, 1919.

Magnus-Levy, A. — Gaswechsel und Fettumsatz bei Myxoedem und Schilddrüsenfütterung. *Kongr. f. inn. Med.*, t. 137, 1896.

— Ueber den respiratorischen Gaswechsel unter dem Einfluss der Thyreoidea, sowie unter verschiedenen pathologischen Zuständen. *Berl. klin. W.*, t. 32, p. 650, 1895.

Means, J. H.—Determination of the basal metabolism as a method of diagnosis and as a guide to treatmeut. *Jour. Am. med. Ass. Chgo.*, t. 77, p. 347, 1921.

Means, J. H., and Aub, J. C.—The basal metabolism in exophthalmic goitre. *Arch. Int. Med. Chgo.*, t. 24, p. 645, 1919.

Nyffenegger, W.—Die Reaktion von schilddrüsenlosen und thymuslosen Kaninchen auf den Wärmestich. *Biochem. Ztschr.*, t. 121, f. 1-4, 1921.

Olmstead, W. H., Barr, D. P., and Du Bois, E. F.—Metabolism of boys 12 to 14 years old. *Arch. Int. Med.*, t. 21, p. 621, 1918.

de Quervain, F.—Ueber den respiratorischen Gaswechsel bei der Struma vasculosa im Kindesalter und nach Implantation von Kropfgewebe bei Kretinen. *Schw. med. W.*, t. 3, No. 38, 1922.

Roth, P.—Clinical observations with Benedict's new portable respiration apparatus. *Boston Med. and Surg. Jour.*, t. 184, p. 222, 1921,

Sanborn Editors.—Basal metabolism, its determination and application. Sanborn Co., Boston, 1922.

Sandiford, I.—The basal metabolic rate in exophthalmic goiter, with a brief description of the technic used at the Mayo Clinic. *Endocrin.*, t. 4, p. 71, 1920.

(7) Etiology and Epidemiology (see also 1.)

Bayard, O.—Beiträge zur Schilddrüsenfrage. B. Schwabe, Basel, 1919.

Bircher, E.—Zur experimentellen Erzeugung der Struma, zugleich ein Beitrag zu deren Histogenese. *D. Ztsch. f. Chir.*, t. 103, p. 276, 1910.

— Weitere Beiträge zur experimentellen Erzeugung des Kropfes. Die Kropfätiologie, ein colloid-chemisches Problem. *Ztschr. f. exp. Path. u. Ther.*, t. 9, f. 1, 1911.

— Weitere histologische Befunde bei durch Wasser erzeugten Rattenstrumen und Kropfherzen. *D. Ztschr. f. Chir.*, t. 112, p. 368, 1911.

— Mitteilungen über das Kropfproblem. *Beitr. z. klin. Chir.*, t. 89, f. 1, p. 1, 1914.

Blauel.—Versuche über künstliche Kropferzeugung. *Beitr. z. klin. Chir.*, t. 83, p. 225, 1913.

Depage.—Du goitre en Belgique. *Ann. de la Soc. belge de chir.*, f. 9, 1897.

Dieterle, Hirschfeld und Klinger.—Epidemiologische Untersuchungen über den endemischen Kropf. *Arch. f. Hyg.*, t. 81, p. 128, 1913.

— Zum Kropfproblem. *Corr. Bl. f. Schw. Ae.*, t. 44, f. 20, 1914.

Galli-Valério.—Infection à bacterium pseudopestis murium chez les rats et goitre. *Ztbl. f. Bakt. u. Paras.*, t. 70, p. 278, 1913.

Hedinger, E.—Ueber das Kropfproblem. Compte rendu de la Soc. suisse des Sc. nat. Congr. de Neuchâtel, 1920.

Hirschfeld, L. und Klinger, R.—Experimentelle Untersuchungen über den endemischen Kropf. *Arch. f. Hyg.*, t. 85, f. 4, 1917.

— Studien über den endemischen Kropf. *Münch. med. W.*, t. 61, p. 246, 1914.

Hunziker, H.—Der Kropf, eine Anpassung an iodarme Nahrung. Aprioristische Gedanken über Wesen und Verhütung des Kropfes. Francke, Bern, 1915.

Isenschmid, R. Die Ursache des endemischen Kropfes. *Med. Klin.*, f. 42, 1917.

Kerzmann, H. Vergleichende Untersuchungen über die Häufigkeit des Kropfes in kindlichem Alter im Neuenburger Jura und in der Stadt Bern. Diss., Bern, 1921.

Klinger, R. und Montigel, Th.—Weitere epidemiologische Untersuchungen über den endemischen Kropf. *Corr. Bl. f. Schw. Ae.*, t. 45, No. 17, 1915.

Klinger, R.—Experimentelle Untersuchungen über den menschlichen Kropf. *Arch. f. Hyg.*, t. 86, f. 4 u, 5, 1917.

Kocher, Th.—Vorkommen und Verteilung des Kropfes im Kanton Bern. Ein Beitrag zur Kenntnis der Ursachen der Kropfbildung. Bern, 1889.

Kolle, W.—Ueber Ziele und Wege und Probleme der Erforschung des endemischen Kropfes. Jahresversamml. d. schw. Ae. in Bern. *Corr. Bl. f. Schw. Ae.*, t. 39, No. 17, 1909.

Kutschera, A. von Aichbergen.—Die Uebertragung des Kretinismus vom Menschen auf das Tier. *Wien. klin. W.*, No. 45, 1910.

— Weitere Beiträge zur Aetiologie des Kropfes und des Kretinismus. *Prag. med. W.*, t. 39, p. 141, 1914.

Landsteiner, Schlagenhaufer und Wagner von Jauregg.—Experimentelle Untersuchungen über die Aetiologie des Kropfes. Hölder, Wien, 1915.

Langhans, Th. und Wegelin, C.—Der Kropf der weissen Ratte. Bern, 1919.

Lobenhoffer, W.—Die Verbreitung des Kropfes in Unterfranken. *Mitt. Grenzg. Med. u. Chir.*, t. 24, p. 475, 1912.

MacCarrison, E.—Fats in relation to the genesis of goitre. *Brit. M. J. Lond.*, f. 1, p. 178, 1922.

Marine, D.—Further observations and experiments in goitre (so-called thyroid carcinoma) in brook trout. III. Its prevention and cure. *Jour. of exp. med.*, t. 19, p. 70, 1911.

Marine, D. and Lenhard.—Colloid glands (goiters). Their etiology and physiological significance. *Bull. of the Johns Hopkins Hosp.*, May, 1909.

— On the occurrence of goiter (active thyroid hyperplasia in fish). *Bull. of the Johns Hopkins Hosp.*, April, 1910.

Messerli, F.—Contribution à l'étude du goitre endémique. Le goitre dans la vallée de Tavannes (Jura bernois). *Schw. Rundschau f. Med.*, t. 14, p. 481, 1914.

— Le goitre endémique. Contribution à son étiologie et à son traitement. Lausanne, 1916.

— Le problème de l'étiologie du goitre endémique. *Schw. med. W.*, t. 3, 1922.

— La fréquence du goitre dans une région du Jura bernois. *Rev. méd. de la Suisse Rom.*, f. 1, 1922.

Répin, Ch.—Goitre expérimental. *Compte rendu de la Soc. de Biol.*, t. 71, 1911.

Roussy, G.—De l'étiologie du goitre. *Presse méd.*, p. 765, 1912.

Saint-Lager, J.—Etudes sur les causes du crétinisme et du goitre endémique. Baillière et Fils, Paris, 1867.

Sasaki, J.—Zur experimentellen Erzeugung der Struma. *D. Ztschr. f. Chir.*, t. 119, p. 229, 1912.

Schittenhelm und Weichardt.—Der endemische Kropf mit besonderer Berücksichtigung des Vorkommens im Königreich Bayern. Springer, Berlin, 1912.

Taussig, S.—Ueber Kropf und Kretinismus in Bosnien. *Wien. klin. W.*, t. 24, p. 1717, 1911.

— Kropf und Kretinismus. Eine epidemiologische Studie. Fischer, Jena, 1912.

Wegelin, C.—Die experimentelle Kropfforschung. Wyss Erben, Bern, 1917.

Wilms, M.—Experimentelle Erzeugung und Ursache des Kropfes. *D. med. W.*, No. 36, p. 604, 1910.

Woelz, E.—Vergleichende Untersuchungen über die Häufigkeit der verschiedenen Kropfformen in Basel und in Bern. *Schw. med. W.*, t. 2, No. 27, 1921.

(8) Prophylaxis (see also 1, 7).

Fritzche, E.—Radikale Kropfoperation und Kropfprophylaxie. *Schw. med. W.*, t. 2, No. 44, 1921.

Galli-Valerio.—Pour la lutte contre le goitre et le crétinisme. *Corr. Bl. f. Schw. Ae.*, t. 48, No. 18, 1918.

Hunziker, H. und von Wyss, M.—Ueber systematische Kropftherapie und Prophylaxe. *Schw. med. W.*, t. 3, 1922.

Klinger, R.—Zur Prophylaxe des endemischen Kropfes. *Corr. Bl. f. Schw. Ae.*, t. 48, f. 17, 1918, t. 49, f. 17, 1919, und *Schw. med. W.*, t. 2, No. 1, 1921.

Kocher, Th.—Zur Verhütung des Kretinismus und cretinoider Zustände nach neuen Forschungen. *D. Ztschr. f. Chir.*, t. 34, p. 156, 1892.

Marine, D. and Kimball, O. P.—The prevention of simple goiter in man. *Jour. Lab. and Clin. Med. St. Louis*, t. 3, p. 40, 1917; *Arch. Int. Med. Chgo.*, t. 22, p. 41, 1918; *Jour. Am. Med. Ass. Chgo.*, t. 73, p. 1873, 1919; *Arch. Int. Med. Chgo.*, t. 25, p. 661, 1920.

Oswald, A.—Zur Kropfprophylaxe. *Schw. med. W.*, t. 3, No. 13, 1922.

de Quervain, F.—Schilddrüse und Iod mit Rücksicht auf die Kropfprophylaxe. *Schw. med. W.*, t. 3, No. 35, 1922.

— La prophylaxie du goitre. *Rev. suisse d'Hyg.*, 1922.

Roux, C.—Prophylaxie du goitre. *Rev. méd. de la Suisse rom.*, No. 5, 1918.

Weith.—Goitre et iode à l'école. *Corr. Bl. f. Schw. Ae.*, t. 49, No. 39, 1919.

(9) Clinical Studies of Goitre (see also 1).

Asch, R.—Die Zungenstruma gleichzeitig ein casuistischer Beitrag zum postoperativen Myxoedem und zur Frage der Tetania parathyreopriva. *D. Ztschr. f. Chir.*, *f.* 130, f. 5 u. 6, 1914.

Bigler, W.—Ueber Herzstörungen bei endemischen Kropf. *Beitr. z. klin. Chir.*, t. 89, p. 158, 1914.

Bircher, E.—Experimenteller Beitrag zum Kropfherz. *Med. Klin.*, t. 6, No. 10, 1910.

Blauel, O., Müller und Schlayer.—Ueber das Verhalten des Herzens bei Struma. *Beitr. z. klin. Chir.*, t. 62, f. 1, p. 119, 1909.

Brüning.—Ueber Kropfblutungen. *Arch. f. klin. Chir.*, t. 91, f. 3, p. 614.

v. Burg, K.—Die subkutane traumatische Kropfruptur. Intrastrumöse, sog. Spontanblutungen. *Beitr. z. klin. Chir.*, t. 78, p. 564, 1912.

Cadet, L.—Contribution à l'étude des goitres intra-thoraciques. Storck et Cie., Lyon, 1905.

Chvostek.—Kropfherz, Gesellsch. d. Ae. Wien, 10, III, 1917. *D. med. W.*, t. 43, p. 864, 1917.

Enthoven, T. H.—Thyrogene haartstoornessen. *Nederl. Tijdschr. v. Geneesk. Amsterdam*, t. 61, p. 1461, 1917.

Fahr, Th.—Histologische Befunde am Kropfherzen. *Ztbl. f. allg. Path. u. path. Anat.*, t. 27, p. 1, 1916.

Heller, E.—Ueber den Ablauf der Ossifikation in kropfendemischen und kropffreien Gebieten. *Beitr. z. klin. Chir.*, t. 94, p. 334, 1914.

Hunziker, H.—Kropf und Längenwachstum. *Schw. med. W.*, t. 1, No. 11, 1920.

Kraus.—Ueber Kropfherz. *Berlin. klin. W.*, t. 43, p. 1412, 1906.

Kreuzfuchs, S.—Die intrathoracische Struma in klinischer und radiologischer Beleuchtung. *Würzb. Abhandl.*, t. 12, f. 4, p. 125, 1912.

Lanz, O.—Beiträge zur Schilddrüsenfrage. Sallmann, Basel u. Leipzig, 1895.

Minnich, W.—Das Kropfherz und die Beziehungen der Schilddrüsenerkrankungen zu dem Kreislaufapparat. Leipzig und Wien. 1904.

Reichbach, G.—Ueber accessorische retroviscerale Strumen. *Beitr. z. klin. Chir.*, t. 21, f. 2, 1898.

Richard, E.—Le goitre chez le nouveau-né. Thèse de Lyon, 1906-07.

Wuhrmann.—Die Struma intrathoracica. *D. Ztschr. f. Chir.*, t. 43, f. 1, 1896.

(10) Diagnosis of Simple Goitre (see also 1).

Baradoulin, G.—Die morphologische Zusammensetzung des Blutes bei Kropf und Basedow und die Veränderungen derselben nach Operation. *Chir. Arch. Weljaminova*, t. 29, p. 689, 1913 (Russ.), *Ztbl. f. Chir.*, t. 41, No. 15, p. 660, 1914.

Bauer, J. und Hinteregger, J.—Ueber das Blutbild bei endemischen Kropf und seine Beeinflussung durch Schilddrüsen- und Ioddarreichung. *Ztschr. f. klin. Med.*, t. 76, p. 115, 1912.

Carpi, U.—Ueber morphologische Blutveränderungen bei Struma und Morbus Basedowii. *Berl. klin. W.*, p. 209, No. 45, 1910.

Guntz, J. H. Th.—Die Trachealstenose bei Struma im Röntgenbilde. Diss. Freiburg i. Br. S. S., 1912.

Holmgren, J.—Ueber die Leucocytenformen bei Kropf. Verein der inn. Med. Stockholm, 1914. *Ztbl. f. inn. Med.*, t. 36, p. 220, 1915.

Hunziker, H.—Drei Jahre Schilddrüsenmessungen. *Schw. med. W.*, t. 1, No. 45, 1920.

— Kropfmessungen am Lebenden. *Schw. med. W.*, t. 1, No. 5, 1920.

Jastram, M.—Ueber das Blutbild bei Strumen und seine operative Beeinflussung. *Mitt. Grenzg. Med. u. Chir.*, t. 29, f. 2, p. 228, 1917.

Kocher, Th.—Die Trachea im Röntgenbilde bei Struma. *Verh. d. D. Ges. f. Chir.*, p. 108, 1906.

Maranon, G. — Der Status thymico-lymphaticus, die Kocher'sche Formel und die endocrinen Affektionen. *Bol. de la soc. espan. de biol.*, Mai, 1911.

Matschawarianu, A. G.—Ueber die Gerinnung, Viskosität und einige andere Eigenschaften des Blutes bei den verschiedenen Kropfformen. *Russki Wratsch*, t. 12, p. 1091, 1913.

Müller, C.—Ueber morphologische Blutveränderungen bei Struma. *Med. Klin.*, No. 34, 1910.

Naegeli, O.—Blutkrankheiten und Blutdiagnostik. Verein Wissensch. Verl. Berlin und Leipzig, 1919, 3 Aufl.

Nägelsbach, E.—Blutbild bei Strumen und seine Beeinflussung durch die Strumektomie. *Beitr. z. klin. Chir.* t. 83, f. 3, p. 489, 1913.

Oppikofer, E.—Paraffin-Wachsausgüsse von Larynx und Trachea bei strumöser Bevölkerung. *Arch. Laryng. u. Rhin.*, t. 26, p. 399, 1912.

— Demonstration von in situ der Organe hergestellten Wachsausgüssen der Trachea und Hauptbronchien. 20. Tagung des Ver. D. Laryng., Stuttgart, Mai 1913. *Ztbl. f. Laryng.*, t. 24, p. 396, 1913.

Pfeiffer, C.—Die Darstellung der Trachea im Röntgenbild, besonders bei Struma. *Beitr. z. klin. Chir.*, t. 45, f. 3, p. 716, 1905.

de Quervain, F.—Clinical Surgical Diagnosis, Bale, 3rd., 1920.

Sandelin, T.—Blood changes in thyroid diseases. *Finska Läkares. Handl. Helsingfors* t. 58, p. 1076, 1916.

Sgalitzer.—Die röntgengraphische Darstellung der Luftröhre mit besonderer Berücksichtigung ihrer Veränderungen bei Kropfkranken. *Arch. f. klin. Chir.*, t. 110, f. 2.

Turin, M.—Blutveränderungen unter dem Einfluss der Schilddrüse und Schilddrüsensubstanz. *D. Ztschr. f. Chir.*, t. 107, p. 343, 1910.

Wild, O.—Die Untersuchung der Luftröhre und die Verwendung der Tracheoskopie bei Struma. *Beitr. z. klin. Chir.*, t. 45, f. 1, 1905.

(11) Non-operative Treatment of Simple Goitre (see also 15).

Aikins, W. H. B.—Radium in goiter. *Am. J. Roentgenol. Detroit.*, t. 7, p. 404.

Belot, J.—Traitement radiothérapique de la maladie de Basedow. *Bull. méd.*, t. 34, p. 1063, 1920.

Bingham, G. H. and Richards, G. E.—Correlation of results of treatment by surgical and X-ray methods. *Canad. M. Ass. J. Toronto*, t. 10, p. 988, 1920.

Bruns, P.—Beobachtungen und Untersuchungen über die Schilddrüsenbehandlung des Kropfes. *Beitr. z. klin. Chir.*, t. 16, f. 2, 1896.

Demoor, J. et van Lint, A.—Le sérum antithyroïdien et son mode d'action. Hayez, Bruxelles, 1903.

Gilmer.—Die Röntgenbehandlung bei Struma und Basedow. Kongr. f. inn. Med. in München, 1906.

Grumme.—Zur Ioddarreichung bei Kropf. *Corr. Bl. f. Schw. Ae.*, t. 46, No. 16-18, 1916.

Hutten, v. d.—Experimenteller Beitrag zur Frage der Verwachsungen nach Strumenbestrahlung. *Giessen Med. Ges. D. med. W.*, p. 284, 1921.

Kocher, A.—Ueber die Wirkung von Schilddrüsenpräparaten auf Schilddrüsenkranke. *Mitt. Grenzg. Med. u. Chir.*, t. 29, f. 2, p. 309, 1917.

Kocher, Th.—Die Therapie des Kropfes. *D. Klin.*, t. 8, 1904.

Kocher, Th.—Ueber Kropf and Kropfbehandlung. *D. med. W.*, t. 38, p. 1265 u. 1313, 1912.

Krehl, L.—Rat zur Vorsicht bei Gebrauch von Iod. *Münch. med. W.*, t. 57, p. 2449, 1910.

Messerli, F.—Contribution à l'étude de l'étiologie du goitre endémique. Le traitement du goitre par la désinfection intestinale continue au benzonaphtol. *Rev. méd. de la Suisse rom.*, f. 4, 1918.

Oswald, A.—Zur Klärung der Ioddarreichung bei Kroft. *Corr. Bl. f. Schw. Ae.*, t. 46, No. 16-18, 1916.

Pfeiffer.—Die Röntgenbehandlung des Kropfes. *Beitr. z. klin. Chir.*, t. 48, p. 367, 1906.

Pineles, F.—Ueber Empfindlichkeit des Kropfes gegen Iod. *Wien. klin. W.*, t. 33, p. 253, 1910.

Porter.—Injection of boiling water in the treatment of hyperthyreoidism. *Jour. of the Am. Med. Ass.*, t. 61, f. 2, 1913.

Romheld.—Gefahren der Iodmedikation. Iodempfindlichkeit und Iodbasedow. *Med. Klin.*, p. 1930, 1910.

Wyeth, J. A.—The cure of goiter by injection of boiling water into the substance of the enlarged thyroid. *Med. Rec.*, t. 87, f. 22, 1915.

(12) Operative Treatment of Simple Goitre (see also 15).

Ach, A.—Ueber die Technik bei Kropfoperationen. *Beitr. z. klin. Chir.*, t. 93, p. 269, 1914.

Alamartine, H.—La technique actuelle des opérations pour goitres. *Rev. de chir.*, t. 47, f. 4, p. 512, 1913.

Allen, L.—Contribution à l'étude de l'isthmectomie et de l'isthmotomie dans le traitement des goitres parenchymateux. Thèse de Paris, 1906.

Arnd, C.—Technik der Kropfdislokation. *Ztbl. f. Chir.*, t. 38, No. 22, 1910.

Bérard, L.—A propos de mille opérations pour goitres. *Bull. de l'Acad. de Méd. Paris*, t. 83, No. 17, 1920.

— Les paralysies transitoires du récurrent après les opérations pour goitres. *Lyon chirurg.*, t. 19, f. 1, 1922.

Bossart, A.—Ueber 1400 Strumaoperationen der Krankenanstalt Aarau. *Beitr. z. klin. Chir.*, t. 99, f. 1, 1914.

Brunner, C.—Ueber Kropfrecidive und Recidivoperationen. *Beitr. z. klin. Chir.*, t. 26, f. 1, 1900.

Bruns, P.—Die Entwicklung der modernen Behandlungen des Kropfes. *Berl. klin. W.*, t. 33, No. 22, 1896.

Claessen, M.—Erleichterung schwieriger Strumektomien durch Anwendung grosser Umstechung und Zügel. *Ztbl. f. Chir.*, t. 47, f. 1, 1920.

Du Clot, H.—De l'énucléation massive des goitres (Opération de A. Poncet,) Thèse de Lyon, 1901.

Dumont, F. L.—Rekurrensläsionen bei Strumaoperationen. *D. Ztschr. f. Chir.*, t. 104, 386, 1910.

Eicken, v. C.—Strumaoperationen bei eingeführtem Tracheoskop. *Ztschr. f. Chir.*, t. 46, p. 369, 1919.

Germanier, A.—Les récidives après l'opération du goitre à l'hôpital cantonal de Lausanne, Sion, Aymon, 1917.

Hackenbruch.—Kropfexcision unter Lokalanaesthesie. *D. med. W.*, No. 39, 1909.

Halsted, W. S.—The operative story of goiter. *Johns Hopkins Hosp. Rep.*, t. 19.

— The preliminary ligation of the thyroid arteries and of the inferior in preference to the superior artery. *Tr. of the Am. Surg. Ass.*, 1913.

Hildebrand.—Erfahrungen über den Kropf und seine Behandlung.

Hoessly, H.—Ueber Störungen der Larynxinnervation im Anschluss an 250 Kropf operationen. *D. Ztschr. f. Chir.*, t. 134, p. 521, 1915.

Hotz, G.—Beiträge zur Kropfoperation. *Schw. med. W.*, t. 1, No. 1, 1920.

Jehn, W.—Die operative Entfernung grosser intrathoracaler Strumen. *D. Ztschr. f. Chir.*, t. 133, p. 25, 1914.

Kaelin, W.—Ueber Störungen des Halssympathicus bei einfacher Struma im Anschluss an deren operative Behandlung. *D. Ztschr. f. Chir.*, t. 134, p. 395, 1915.

Kausch, W.—Beidseitige Resection oder einseitige Exstirpation des Kropfes? *Arch. f. klin. Chir.*, t. 93, f. 4, 1910.

Klose, H. und Hellwig, A.—Ueber Kropfrezidive. *Klin. W.*, No. 38, 1922.

Kocher, Th.—Ueber Kropfexstirpation und ihre Folgen. *Arch. f. klin. Chir.*, t. 29, p. 593, 1883.

— Bericht über ein zweites Tausend Kropfexcisionen. *Verh. D. Ges. f. Chir.*, t. 30, No. 10, p. I. 25, 32, II. 344, 1901.

— Einige Schlussfolgerungen aus einem dritten Tausend Kropfexcisionen. *Verh. D. Ges. f. Chir.*, t. 35, No. 10, p. I. 41, p. II. 24, 1906.

— Chirurgische Operationslehre. 5 Aufl. G. Fischer, Jena, 1907.

— Ueber Kropfoperation bei gewöhnlichen Kröpfen, nebst Bemerkungen zur Kropf prophylaxe. Verh. d. Schw. Ges. f. Chir. *Corr. Bl. f. Schw. Ae.*, t. 47, No. 49, 1917

Krönlein, R. U.—Klinische Untersuchungen über Kropf, Kropfoperation und Kropftod. *Beit. z. klin. Chir.*, t. 9, f. 3, 1892.

Lardy, E.—Contribution à l'histoire de la cachexie thyréoprive.

Leischner.—Postoperative Stimmlippenschädigungen nach Kropfoperationen. *Mitt. Grenzg. Med. u. Chir.*, t. 19, p. 304, 1909.

Matti, H.—Normalmethode für die Operation der Zungenstruma. *Arch. f. klin. Chir.*, t. 103, p. 241, 1913.

Mayo, C. H.—The treatment of goiter. *Monthly Cyclop. Am. Med. Bull*, t. 17, p. 16, 1914.

Mitrovitch, P.—Contribution à l'étude de l'énucleation et de l'extirpation partielle du goitre. Thèse de Genève, 1894.

Monnier, E.—Klinische Studien über die Strumektomie an der Hand von 670 Kropfoperationen. *Beit. z. klin. Chir.* t. 54, f. 1, 1907.

Nägeli, Th.—Ueber 1000 Kropfkranke aus der Garrè'schen Klinik 1907-1918. *Beitr. z. klin. Chir.*, t. 115, f. 1, 1919.

Oberst.—Der Kropf und seine Behandlung. *Berl. Fischers med. Hd.*, 1910.

Pamperl, R.—Ueber die nach Kropfoperationen auftretenden Funktionsstörungen der Nachbarorgane. *Beitr. z. klin. Chir.*, t. 87, p. 413, 1913.

de Quervain, F.—Zur Technik der Kropfoperation. *D. Ztschr. f. Chir.*, t. 116, p. 574, 1912.

— Weiteres zur Technik Kropfoperation. *D. Ztschr. f. Chir.*, t. 134, p. 475, 1915.

— Preliminary hemostasis in goiter operations. *Surg. Gynec. Obst.*, Oct., 1916.

— Verhn. der Schweiz. Ges. f. Chir. *Corr. Bl. f. Schw. Ae.*, No. 49, 1917.

— Evoluzione e stato attuale della operazione del gozzo. *Rif. med.*, f. 9, 1922.

Reinbach, G.—Ueber das Verhalten der Temperatur nach Kropfoperationen. *Mitt. Grenzg. Med. u. Chir.*, t. 4, p. 606, 1899.

Reverdin, J. L.—Rapport sur sur le traitement chirurgical du goitre. Congr. français de chirurgie 1898. Alcan, Paris.

— Some remarks on the intraglandular enucleation of goitre. *Surg. Gynec. Obst.*, March, 1908.

Rose, E.—Der Kropftod. Ueber die Radikalkur der Kröpfe. Hirschwald, Berlin, 1878.

Roux, C.—Rapport sur lach irurgie du goitre. Compte rendu de la Soc. Suisse de chir., 1917, *Corr. Bl. f. Schw. Ae.*, t. 47, f. 49, 1917.

Schloffer.—Kropfoperation und Rekurrensstörung *Verh. d. D. Ges. f. Chir.*, No. 20, p. I. 82, t. 39, 1910.

Schultze, K.—Experimentelle Untersuchungen über das Fieber nach Kropfoperationen. *Mitt. Grenzg. Med. u. Chir.*, t. 47, f. 5, p. 613.

Steinegger, A.—Ueber Wundbehandlung, Wundverlauf und Wundfieber bei 400 Kropfoperationen. *Beitr. z. klin. Chir.*, t. 94, p. 431, 1914.

Steinmann, Fr.—Beitrag zur Kropfverlagerung. *Arch. f. klin. Chir.*, t. 74, f. 4, 1904.

Stierlin, R.—Nervus recurrens und Kropfoperationen. *D. Ztschir. f. Chir.*, t. 89, p. 78, 1907.

Tietze, A.—Beiderseitige Resektion oder einseitige Exstirpation des Kropfes. *Berl. klin. W.*, t. 50, p. 99, 1913.

Wölfler, A.—Die chirurgische Behandlung des Kropfes. Berlin, 1887-91.

(13) Thyroid Transplantation.

Borowsky, D.—De l'hypertrophie fonctionnelle des greffes thyroïdiennes. Thèse de Genève, 1906.

Cristiani, H.—Effets thérapeutiques de la greffe thyroïdienne chez l'homme. Congr. internat. Lisbonne, 1906.

Cristiani, H. et Kummer, E.—Ueber functionnelle Hypertrophie überpflanzter Schilddrüsenstückchen beim Menschen. *Münch. med. W.*, t. 53, p. 2377, 1906.

Guthrie, C. C.—The survival of engrafted Thyroid and renal tissue. *Proc. of the Soc. f. exp. Biol. and Med.*, t. 7, f. 2, 1909.

Kocher, Th.—Die Schilddrüsentransplantation. *Arch. f. klin. Chir.*, t. 87, p. 1, 1908.

— Ueber die Bedingungen erfolgreicher Schilddrüsentransplantation beim Menschen. *Arch. f. klin. Chir.*, t. 105, f. 4, 1914.

— Dauerresultate der Schilddrüsentransplantation beim Menschen. *Verh. D. Ges. f. Chir.*, t. 43, No. 8, p. 175, 1914.

Kummer, E.—The relation of the nerve supply of thyroid grafts to their endocrin activity. *Endocrin.*, t. 1, p. 222, 1917.

Paschoud, H.—Contribution à l'étude des greffes thyroïdiennes. *Lyon chirurg.*, t. 10, p. 474, 1913.

Payr.—Experimentelle Untersuchungen über die Schilddrüsentransplantation bei Hunden, Katzen und Kaninchen. *Verh. d. D. Ges. f. Chir.*, No. 34, t. 35, p. I. 155. II. 503, 1906.

Serman, C.—Ueber eine neue Methode der Transplantation des Schilddrüsengewebes, *D. Ztschr. f. Chir.*, t. 96, p. 440, 1908.

(14) Hypothyroidism (see also 1, 5, 6).

Baillarger et Krishaber.—Crétin, crétinisme et goitre endémique. *Dictionnaire encyclopédique des sc. méd.*, Paris, juin, 1879.

Bayon, P. G.—Beitrag zur Diagnose und Lehre vom Kretinismus unter besonderer Berücksichtigung der Differentialdiagnose mit andern Formen von Zwergwuchs und Schwachsinn. Kabitsch, Würzburg, 1903.

— Ueber die Aetiologie des Schilddrüsenshwunds bei Kretinismus und Myxoedem, *Nerol. Ztbl.*, p. 792, 1904.

Bertrand.—Infantilism dysthyroïdien. Thèse de Paris, 1902.

Bircher, E.—Entwicklung und Bau des Kretinenskeletts. *Arch. u. Atlas d. norm. pathol. Anat.*, t. 21, Hamburg, 1909.

— Die kretin. Degeneration (Kropf, endem. Kretinismus und Taubstummheit) in ihrer Beziehung zu anderen Wissensgebieten. Wien, Urban und Schwarzenberg, 1911.

— Beitrag zur Kenntnis der Schilddrüse und Nebenschilddrüse bei kretinoiden Kretinen und endemisch Taubstummen, *Frankf. Ztschr. f. Pathol.*, t. 11, p. 262, 1912.

Bircher, H.—Das Myxoedem und die cretinische Degeneration. No. 357, Chir. No. 110, 1889-90. *Volkm. klin. Vortr.*

Bolten, G. C.—Over hypothyreoide (Minor thyroid insufficiency). *Psychiat. en neurol. Amsterdam*, t. 22, p. 135, 1918.

Buschan, G.—Myxoedem und verwandte Zustände, zugleich ein Beitrag zur Schilddrüsenphysiologie und Schilddrüsentherapie. Leipzig u. Wien, Deuticke, 1896.

Charrière, L.—Contribution à l'étude de l'absence congénitale du corps thyroïde et de ses conséquences dans l'arrêt du développement physique et intellectual. Thèse de Paris, 1907.

Relazione della commissione nominata d'ordine di S. M. il Re di Sardegna per studiare il cretinismo. *Stamperia Reale, Torino*, 1848.

Del cretinismo in Lombardia. Relazione della commissione nominata dal R. Istituto lombardo di scienze e lettere. G. Bernardoni, Milano, 1864.

Committee of Clinical Society of London : Report on myxoedema. *Tr. Clin. Soc. London*, t. 21, suppl. 1, p. 299, 1888.

Coulon, de W.—Ueber Thyreoidea und Hypophysis der Cretinen, sowie über die Thyreoideareste bei Struma nodosa. *Virch. Arch.*, t. 147, f. 1, p. 53, 1897.

Crookshank, F. G.—Nervous cretinism. *The Lancet*, p. 604, Oct., 1917.

Dieterle, Th.—Die Athyreosis unter besonderer Berucksichtigung der dabei auftretenden Skelettveränderungen sowie der differential diagnostischen vornehmlich in Betracht kommenden Störungen des Knochenwachstums. Untersuchungen über Thyreoplasie, Chondrodystrophia foetalis. Osteogenesis imperfecta. *Virch. Arch.*, t. 184, f. 1, 1906.

Getzowa, S.—Ueber die Thyreoidea von Kretinin und Idioten. *G. Reimer*, Berlin, 1905.

Goett, M. E. L. G.—Contribution à l'étude de l'hypothyroïdie en particulier la céphalée thyroidienne. Thèse de Bordeaux, 1909.

Grundler, R.—Zur Cachexia strumipriva. H. Laupp, Tübingen, 1885.

Hellwig, A., und Neuscholz, S. M.—Zur funktionellen Schilddrüsendiagnostic. *Klin. W.*, No. 40, 1922.

Hertoghe, E.—Die Rolle der Schilddrüse bei Stillstand und Hemmung des Wachstums und der Entwicklung und der chronische gutartige Hypothyreoidismus (ins Deutsche übertragen von Spiegelberg), München, 1900.

— Throid insufficiency. *Practitioner*, London, t. 94, f. 26, 1915, *Med. Rec. N. Y.*, t. 86, p. 489, 1914.

Horsley, V.—Report of the myxoedema committee of the Clin. Soc., 1889.

Jeandelize.—Insuffisance thyroïdienne et parathyroidienne. Thèse de Nancy, 1902.

Kirmse, K.—Ueber infantiles Myxoedem. B. Georgi, Leipzig, 1903.

Kocher, Th.—Krankheitserscheinungen bei Schilddrüsenerkrankungen geringen Grades. Stockholm, 1910.

— Das Blutbild bei Cachexia strumithyreopriva (Myxoedem, cretinoide Zustände), *Arch. f. klin. Chir.*, t. 99, p. 210, 1912.

Kutschera, A. von Aichbergen.—Der endemische Kretinismus, seine Ursachen und seine Behandlung. Beilage von "*Das österr. Sanitätswesen*," 1911, No. 7, *D. med. W.*, p. 2151, 1911.

Langhans, Th.—Ueber Veränderungen in den peripheren Nerven bei Cachexia thyreopriva des Menschen und Affen, sowie bei Kretinismus. *Virch. Arch.*, t. 128, p. 318, 1892.

Magnus-Levy.—Ueber Myxoedem. *Ztschr. f. klin. Med.*, t. 52, f. 3 u. 4, p. 201, 1904.

Michel, M. L.—Le sourcil dans ses rapports avec le corps thyroïde. Thèse de Paris, 1912

Osborne, O.—Some common types of hyposecretion of the thyroid. *Jour. of the Am. Med. Ass.*, t. 59, p. 1618, 1912.

Peterson, F.—Results of thyroid treatment in sporadic cretinism. *Pediatri*, t. 1, f. 10, 1896.

Pineles, F.—Sporadischer und endemischer Kretinismus in ihrem pathogenetischen Gegensatz. Ges. f. Ae. in Wien, 14. Nov. 1902. *Wien. klin. W.*, p. 1265, 1902.

de Quervain, F.—Ueber die Veränderung des Centralnervensystems bei experimenteller Cachexia thyreopriva der Thiere. *Virch. Arch.*, t. 133, 1893.

Rothmann, M.—Ueber familiäres Vorkommen von Friedreichscher Ataxie, Myxoedem und Zwergwuchs. *Berl. klin. W.*, No. 2, 1915.

Scholz, W.—Klinische und anatomische Untersuchungen über den Cretinismus. Hirschwald, Berlin, 1906.

Scholz und Zingerle—Ueber Gehirnveränderungen bei Kretinismus. *Ztschr. f. Erk. jugendl. Schwachs.*, t. 2, p. 337, 1909.

v. Siebenthal, K.—Ueber einen Fall von Thyreoaplasie (kongenitales Myxoedem) unter spezieller Berücksichtigung über mikroskopisch-histologischen Verhältnisse der Halsorgane und sämtlicher innersekretorischen Drüsen. Diss. Zurich, 1921.

Soderbergh, G.—Symptômes cérébelleux dans le myxoedème. *Nordisk. Med. Ark.*, f. 3, No. 11, 1912.

Springer, M.—Traitement des arrêts de croissance. Baillière, Paris, 1920.

Stépanoff, G.—Sur les rapports des auto-infections avec l'hypothyroïdie. Maloine, Paris, 1908.

Stoccada, F.—Untersuchungen über die Synchondrosis sphenooccipitalis und den Ossifikationsprozess bei Kretinismus und Athyreosis. *Beitr. z. path. Anat. u. z. allg. Path.*, t. 61, 1915.

Villard, J.—Des ptoses viscérales par insuffisance thyroïdienne. Thèse de Lyon, 1912-13.

Wagner, v. Jauregg—Ueber Behandlung des endemischen Kretinismus mit Schilddrüsensubstanz. *Wien. Klin. W.*, p. 835, 1904.

— Myxoedem und Kretinismus. *Deuticke*, Wien, 1912.

Weygandt, W.—Der heutige Stand der Leher vom Kretinismus. Marhold, Halle a. S., 1904.

— Schwachsinn und Hirnkrankheiten mit Zwergwuchs. *Monatsschr. f. Psych. u. Neurol.*, t. 35, p. 25, 1914.

Wieland, E.—Ueber hypothyreotische Konstitution und über frühzeitig erworbene. Athyreose. *Ztschr. f. Kinderheilk.*, t. 4, f. 4, 1912.

(15) Hyperthyroidism (see also 1, 5, 6).

Abadie.—Section du sympathique cervical dans le goitre exophtalmique. 10e congr. franc. de chir., Paris, 21 oct. 1896. *Sem. méd.*, p. 421, 1896.

Achard, Ch.—Le syndrome basedowien. Publications du Prog. Méd., 1922.

Alamartine, H.—Les lésions thyroïdiennes de la malaidie de Basedow primitive et du goitre basedowifiant. *Lyon chirurg.*, t. 4, p. 116, 1910.

— Le goitre exophtalmique. Maloine, Paris, 1910.

Alamartine, H. et Perrin, E.—Les résultats éloignés des interventions thyroïdiennes dans la maladie de Basedow. *Lyon chirurg.*, t. 6, p. 461, 1911.

Askanazy, M.—Contribution anatomo-pathologique à la connaissance de la maladie de Basedow. *D. Arch. f. klin. Med.*, t. 61, 1898.

Ballet et Enriquez.—Congrès des médecins aliénistes et neurologistes. Bordeaux 1895. *Sem. méd.*, p. 329, 1895.

Baruch.—Zur experimentellen Erzeugung des Morbus Basedowii. *Ztbl. f. Chir.*, t. 39, No. 21, p. 316, 1912.

Baum, H. L.—Die experimentelle Erzeugung der Basedowkrankheit. *Beitr. z. klin. Chir.*, t. 88, p. 647, 1914.

Béclère, A.—La radiothérapie dans la maladie de Basedow. *Jour. méd. franç.*, juillet, 1920.

Beebe, P. et Wallace, J.—Reveridge thyroid disease. *N. Y. Med. Jour.*, 25, 12, 1915. *N. Y. Med. Rec.*, t. 32, p. 55, 1916.

Beebe, P. et Rogers.—La sérothérapie du goitre exophtalmique. *Sem. méd.*, p. 436, 1906, et 57e réunion annuelle de l'Ass. méd. à Boston, juin, 1906. *Med. Rec.*, p. 995, 1906.

Bialokur.—Basedowsymptome als Zeichen tuberkulöser Infektion. *Ztschr. f. Tuberk.*, t. 16, No. 6, 1910.

Bircher, E.—Zur experimentellen Erzeugung des Morbus Basedow. *Ztbl. f. Chir.*, t. 39, p. 138, 1912.

Bodolec, E.—Traitement du goitre exophtalmique par la thyroïdectomie. Thèse de Paris, 1909.

Boggs, R. H.—Röntgen rays in goiter. *Interstate M. J. St. Louis*, t. 24, p. 362, 1917.

v. Boltenstein.—Ueber Iodbasedow. *Ztschr f. arztl. Fortbldg.*, No. 9, 1912.

Boothby, W. M.—Adenoma of the thyroid with hyperthyroidism. History of the recognition of this disease as a clinical entity. A study of the symptomatology with basal metabolic rates. *Endocrin.*, t. 5, f. 1, 1921.

Bouchut.—Rôle du rhumatisme articulaire aigu et subaigu dans l'étiologie de la maladie de Basedow et dans la terminaison par l'asystolie. Lyon, 1908.

Bram, J.—Diagnostic methods in exophthalmic goiter with special reference to quinine. *Med. Rec., N. Y.*, t. 98, p. 888, 1920.

— Exophthalmic goiter and its non-surgical treatment. *C. B Mosby Co.*, St. Louis, 1920.

— The rational therapeusis of exophthalmic goiter. *Endocrin.*, t. 3, p. 467, 1919.

Bühler.—Lymphocytose bei Basedow'scher Krankheit und bei Basedowoid. Diss., Tübingen, 1910.

Burghart und Blumenthal.—Ueber die spezifische Behandlung des Morbus Basedowii. Die Therapie der Gegenwart, 1903.

Buschan, G.—Die Basedow'sche Krankheit. *Leipzig u. Wien*, 1894 (Deuticke).

Cannon, W. B., Binger, C. A. L. and Fitz, R.—Experimental hyperthyroidism. *Am. Jour. Physiol. Balt.*, t. 36, p. 363, 1914-15.

Capelle, W. und Bayer—Thymus und Schilddrüse in ihren wechselseitigen Beziehungen. *Ztschr. f. klin. Chir.*, t. 86, p. 509, 1913.

Capelle, W.—Die Behandlung des Morbus Basedowii. *Ztschr. f. ärztl. Fortbldg.*, f. 2., 1918.

Caro, L.—Blutbefunde bei Morbus Basedowii und beim Thyreodismus, *Berl. klin. W.*, t. 45, p. 1755, 1908.

Carpi, U.—A proposito del reporto ematologico nel morbo di Bas. e nel tiroidismo. *Gaz. med. ital.*, f. 50, 1908.

Chalier, A.—Le traitement de la maladie de Basedow par les opérations dirigées sur le sympathique cervical. Masson, Paris, 1912.

Chiari, R.—Ueber Herzerscheinungen bei Morbus Basedowii. Ges. f. inn. Med. u. Kinderheilk. Wien, 1914. *Wien. klin. W.*, t. 27, p. 352, 1914.

Chvostek, F.—Morbus Basedowii und die Hyperthyreosen. *Enzyklopaedie der klin. Med. Inn. Secret.*, Berl., 1917.

Claggett, A. N.—The treatment of goiter with radium. *Ill. med. Jour.*, Oak Park, t. 37, p. 318, 1920; see also: *Radium therapy of the thyroid, J. Radiol*, Iowa City, t. 1, p. 121, 1920.

Ciuffini, P.—Ulteriore contributo alle ematologia del morbo di Flaiani-Basedow. *Policl. sez. med.*, t. 16, Nos. 8-9, 1909.

Crile, G. W.—The kinetic theory of Graves' Disease. *Am. Jour. of the Med. Sc.*, t. 145, No. 1, 1913.

Dayton.—Treatment of exophthalmic goiter with thyreoidectin. *Jour. of the Am. Med. Ass.*, t. 56, No. 16, 1911.

Delgado, H. F—Mecanismo de la acción terapeutica del yoduro en los estados de hipertiroidismo. *Cronméd. Lima* (Pérou), t. 36, p. 155, 1919.

Delore, X. et Alamartine, H.—La ligature des artères thyroïdiennes principalement dans la maladie de Basedow. *Rev. de Chir.*, t. 44 (année 31), juillet, 1911.

Dor, H. et Dor, L.—Du traitement de la maladie de Basedow par le thymus. *Lyon méd.*, t. 108, p. 19, 1907.

Edmunds, W.—Observations and experiments on the pathology of Graves' disease.

Eulenburg, A.—Basedow'sche Krankheit und Schilddrüse. *D. med. W.*, 1894.

Farner, E.—Beiträge zur pathologischen Anatomie des Morbus Basedowii mit besonderer Berücksichtigung der Struma. Diss. Bern, 1896. *Virch. Arch.*, t. 143, p. 509, 1896.

Fisher, M. K.—The X-ray treatment of exophthalmic goiter. *N. Y. Med. Jour.*, f. 10, p. 455, 1915.

Fonio, A.—Ueber vergleichende Blutplättchenuntersuchungen (auch bei Basedowkranken). *Corr. Bl. f. Schw. Ae.*, t. 45, No. 48, 1915.

Froment, J.—Cardiopathies valvulaires compliquées de Basedowisme. Thèse de Lyon, 1906.

Gayme, L.—Essai sur la maladie de Basedow. Etude clinique et pathogénique. Thèse de Paris, 1898.

Geyser, A. C.—The treatment of exophthalmic goiter. *Am. Med. Jour.*, N. Y., t. 25, p. 278, 1919.

Gley, E.—Recherches sur la pathogénie du goitre exophtalmique. *J. de Physiol. et de Pathol. gén.*, No. 6, p. 955, 1911.

Goetsch, E. — Functional significance of mitochondria in toxic thyroid adenomata. Preliminary report. *The Johns Hopkins Hosp. Bull.*, t. 27, f. 303, May, 1916.

— The diagnosis and treatment of hyperthyroidism. *N. Y. Med. Jour.*, March, 1921.

— The early diagnosis and treatment of hyperthyroidism. *N. Y. Med. Jour.*, March, 1922.

Guillebeau, A.—Die pathologische Anatomie des Morbus Basedowii. *Virch. Arch.*, t. 126, p. 271.

v. Haberer, H.—Weitere Erfahrungen über Thymusreduktion bei Basedow und Struma. *Arch. f. klin. Chir.*, t. 105, f. 2, p. 296, 1914.

— Thymusreduktion und ihre Erfolge. *Mitt. Grenzg. Med. u. Chir.*, t. 27, p. 199, 1914.

Haemig, G. — Anatomische Untersuchungen über Morbus Basedowii. Diss., Zürich, L. Schumacher, Berlin, 1897.

Hallion.—Du traitement sérothérapique de la maladie de Basedow suivant la méthode de Ballet et Enriquez. Congr. de Bruxelles, août, 1913.

Halsted, W. S.—The excision of both lobes of the thyroid gland for the cure of Graves' disease. *Tr. of the Am. Surg. Ass.*, 1913.

— The results of the X-ray treatment of the thymus gland on Graves' disease. *Johns Hopkins Hosp. Bull.*, Balt., t. 26, p. 55, 1915.

Haskovec, L. — Der Exophthalmus bei der Basedow'schen Krankheit. *Wien. klin. Rundschau*, No. 39-40, 1906.

Hatiegan, J.—Ueber das Blutbild bei Struma u. Morbus Basedowii. *Wien. klin. W.*, t. 25, p. 1419, 1912.

Haudek, M. und Kriser, A.—Röntgenbehandlung der Basedow'schen Krankheit. *Berl. klin. W.*, No. 1, p. 271, 1922.

Hellwig, A.—Die Hyperthyreosen leichteren Grades. Eine vergleichend klinische und pathologisch-anatomische Studie. *Beitr. z. klin. Chir.*, t. 125, f. 1, 1922.

— Die Hyperthyreosen. *D. med. W.*, No. 13, 1922.

Holland, M.—Ueber Iodbasedow. Diss. Tübingen, 1916.

Holmgren.—Ueber den Einfluss der Basedow'schen Krankheit und verwandter Zustände auf das Längenwachstum nebst einigen Gesetzen der Ossifikation. *Nord. med. Ark.*, Abt. II, t. 42, No. 5-8, t. 43, No. 1-3, 1909.

— Ueber die Leucocytenformel bei Kropf und die Behandlung von Morbus Basedowii mit Leucocyten erregende Stoffe. Ver. d. inn. Med. in Stockholm. Febr. 1914. *Ztbl. f. inn. Med.*, t. 36, p. 220, 1915.

Horaud, R.—Lésions du sympathique cervical dans le goitre exophtalmique. *Rev. neurol.*, t. 18, p. 343, 1910.

Hubeny, M. J.—X-ray treatment of exophthalmic goiter. *Ill. Med. Jour.*, Oak Park, t. 37, p. 383, 1920.

Jaboulay, M.—Interventions sur le sympathétique cervical et sur le corps thyroïde dans la maladie de Basedow. *Lyon chir.*, t. 4, p. 225, 1910.

Jacobson.—The thyrogenic origin of Basedow disease. *Ann. of Surg.*, 1913.

Kaess, W. — Untersuchungen über die Viskosität des Blutes bei Morbus Basedowii. *Beitr. z. klin. Chir.*, t. 82, p. 253, 1912.

Kappis, M.—Ueber Lymphocytose des Blutes bei Basedow und Struma. *Mitt. Grenzg. Med. u. Chir.*, t. 21, p. 729, 1910.

Klose, H.—Die pathologisch-anatomischen Grundlagen der Basedowkrankheit. *Beitr. z. klin. Chir.*, t. 102, p. 1, 1916.

Klose, H., Lampe, A. R. und Liesegang, R. E.—Die Basedow'sche Krankheit, eine chirurgisch-experimentelle und biologische Studie. *Beitr. z. klin. Chir.*, t. 77, p. 601, 1912.

Knox, R.—X-ray therapy. *Lancet*, London, t. 11, p. 183, 1919.

Kocher, A.—Ueber Morbus Basedowii. *Mitt. Grenzg. Med. u. Chir.*, t. 9, p. 1, 1902.

— Die histologische und chemische Veränderung der Schilddrüse bei Morbus Basedowii und ihre Beziehung zur Funktion der Drüse. *Virch. Arch.*, t. 208, p. 86, 1912.

— Ueber Basedow-Krankheit und Thymus. *Arch. f. klin. Chir.*, t. 105, p. 944, 1914.

Kocher, A.— Dauerfolge des operativ behandelten Morbus Basedowii. *Verh. d. D. Ges. f. Chir.*, t. 34, No. 31, p. 136, 1905.

— Blutuntersuchungen bei Basedow. *Verh. d.D. Ges. f. Chir.*, t. 37, No. 43, p. 118, 1908.

— Blutuntersuchungen bei Moebus Basedowii mit Beiträgen zur Frühdiagnose und Theorie der Krankheit. *Arch. f. klin. Chir.*, t. 87, 1908.

— Zur Frühdiagnose der Basedow'schen Krankheit. *Corr. Bl. f. Schw. Ae.*, t. 40, No. 7, 1910.

— Ueber Iodbasedow. *Verh. d. D. Ges. f. Chir.*, t. 39, No. 18, p. 82 u. 396, 1910.

— The surgical treatment of Graves' disease. *Brit. Med. Jour.*, Oct., 1910.

— Morbus Basedow. *Arch. f. klin. Chir.*, t. 96, p. 403, 1911.

Kraus, O.—Ueber Altersthyreoidismus (Spätthyreoidismus). 31. Deutscher Kongr. f. inn. Med., Wiesbaden, 1914. *Wien. klin. W.*, No. 27, 1914.

Labouré, J.—Le gros thymus dans la maladie de Basedow. *Arch. de chir.*, No. 12, 1912.

Laignel-Lavastine. — Troubles psychiques par perturbations des glandes à sécrétion interne. Masson, Paris, 1908.

Lampé, A. E. — Die Blutveränderungen bei Morbus Basedowii im Lichte neuerer Forschung. *D. med. W.*, t. 38, p. 1127, 1912.

Landström, J.—Morbus Basedowii nach moderner Anschauung. *Allm. svenska läkartidn.*, p. 847, 1908.

Lanz, O.—Ueber Schilddrüsenfieber und Schilddrüsenintoxikation. Ein Beitrag zur Basedowfrage. *Mitt. Grenzg. Med. u. Chir.*, t. 8, f. 1-2, 1901.

Ledoux.—La lymphocytose des Thyréotoxicoses. *Prov. méd.*, f. 2, 1912.

Ledoux, Lebard.—La radiothérapie du goitre exophtalmique. *Arch. d'électr. méd.*, S. S. 330.

Ledoux et Tisserand.—Le Basedowisme iodique. *Prog. méd.*, f. 15, 1913.

Lévy, J.—L'hémato-thérapie de la maladie de Basedow. Thèse de Paris, 1907.

Lian, C.—Le signe de l'hyperesthésie de la région thyroïdienne et le diagnostic du basedowisme fruste. *Presse méd.*, t. 26, p. 665, 1918.

Liek, E.—Die Frühoperation des Morbus Basedow. *Arch. f. klin. Chir.*, t. 104, f. 1.

Lier, E.-H. van.—Blutuntersuchung nach Strumektomie bei Morbus Basedowii. *Ned. Tijdsch. v. Geneesk.*, t. 1, p. 823, 1911.

Lüdin, M. — Die Behandlung der Strumen und des Morbus Basedowii mit Röntgenstrahlen. *Zentrbl. f. d. Grenzg. d. Med. u. Chir.*, t. 18, No. 3, p. 205, 1914.

MacCallum. — On the production of specific cytolytic sera for thyroid and parathyroid, with observations on the physiology and pathology of the parathyroid gland, especially in its relation to exophthalmic goiter. *The Med. News*, Oct., 1903.

Maranon, G. — Le facteur émotionnel dans la pathogénie des états hyperthyroïdiens. *Ann. de Méd.*, t. 9, f. 2, 1921.

— Observaciones experimentales sobre el exoftalmos hypertiroideo. Congr. Asoc. espagnola para el Prog. de las Ciencias, Valladolid, 19 Oct., 1915.

Masson, G.—Le goitre exophtalmique, sa pathogénie, son traitement. Thèse de Genève, 1918.

Matti, H.—Die Beziehungen der Thymus zum Basedow (Referat). *Berl. klin. W.*, t. 51, No. 28, p 1310, No. 29, p. 1365, 1914.

Mayo, Ch.—Ligation and partial thyroidectomy for hyperthyroidism. *Surg. Gynec. Obst.*, p. 562, Dec., 1910.

Mayor, A.—Causerie sur la question de l'iodisme constitutionnel. Communication à la Soc. méd. de Genève, 1895. *Rev. Méd. de la Suisse rom.*, p. 332, 1895.

Means, J. H., and Aub, J. C.—The basal metabolism in exophthalmic goiter. *Arch. Int. Med.*, Chgo., t. 24, p. 645, 1919.

Melchior.—Die Basedow'sche Krankheit. *Ergeb. d. Chir. u. Orthop.*, t. 1, 1911.

Michailow, W. N.—Ueber die Veränderungen des Blutes bei Basedow'scher Krankheit. *Praktischeskij Wratsch*, No. 40-41, 1909.

Möbius, P. J.—Die Basedow'sche Krankheit. 2. Aufl. Holder, Wien, 1906.

Neisser, E.—Ueber Iodbehandlung bei Thyreotoxicose. *Berl. klin. M.*, t. 57, p. 461, 1920.

Nordentoft.—Ueber die Behandlung des Morbus Basedowii. *Ugeskrift for Laeger*, t. 81, No. 29, p. 1169, 1919.

Ochsner, A. J.—Exophthalmic goiter. *Ann. Surg.*, Phila., t. 64, p. 385, 1916.

Oswald, A.—Ueber den Morbus Basedowii. *Corr. Bl. f. Schw. Ae.*, t. 42, No. 30, 1912.

— Zur Theorie des Basedow. *Münch. med. W.*, t. 62, p. 907, 1915.

— De l'iodisme constitutionnel et de ses rapports avec le goitre exophtalmique. *Rev. méd. de la Suisse romande*, No. 9, 1915.

—Kommt Hyperthyreoidismus bei vorher völlig Gesunden vor? *Münch. me W.*, t. 63, No. 18, 1916.

Parhon, C. J., et Stocker, A.—Syndrome de Basedow et trophoedème. *Rev. neurol.*, Par., t. 27, p. 1020, 1920.

Pettavel, C. A.—Beitrag zur pathologischen Anatomie des Morbus Basedowii. *D. Ztschr. f. Chir.*, t. 116, p. 488, 1912.

— Weiterer Beitrag zur pathologischen Anatomie des Morbus Basedowii. *Mitt. Grenzg. Med. u. Chir.*, t. 27, f. 4, 1914.

Pfahler, G. E.—A summary of the results obtained by the X-ray treatment of exophthalmic goiter. *N. Y. Med. Jour.*, 24 Oct. 1908.

Pfahler, G. E., et Zulick, J. D.—Roentgen treatment of Exophthalmic goiter. *Penn. Med. Jour.*, Athens, t. 19, p. 661, 1915-16 ; ibid., *Am. Jour. Roentgenol.*, Detroit, t. 3, p. 63, 1916.

Pfender, C. A.—The application of Roentgen rays as an effective measure in exophthalmic goitre. *Med. Counc. Phila.*, t. 20, p. 36, 1917.

Pisanté, B.—Traitement de la maladie de Basedow par les humeurs d'animaux éthyroïdes. Thèse de Paris, 1904.

Plummer, H. S.—The Clinical and pathological relationship of simple and exophthalmic goiter. *Am. Jour. of the Med. Sc.*, t. 146, f. 6, p. 790, 1913.

Plummer, W. A.—The blood picture in exophthalmic goiter. *Minnesota Med.*, t. 2, p. 330, 1919.

Porter, M. F.—The thyroid with special reference to hyperthroidism and a new method of treatment. *Journal of the Am. Med. Ass.*, t. 57, 1911.

Rehn, L.—Exstirpation des Kropfes bei M. Basedowii. *Berl. klin. W.*, t. 21, p. 163 1884.

Riche, P.—Le goitre exophtalmique. Interprétation nouvelle. *Biblioth. gén. de Med.*, Paris, 1897.

Rogers, J.—Exophthalmic goiter and its treatment. *N. Y. State Jour. of Med.*, Jan. 15, 1915.

— Organ Therapy in thyroid and allied disorders. *Med. Rec. N. Y.*, t. 98, p. 631, 1920.

Roth, N.—Blutuntersuchungen bei Morbus Basedowii. *D. Med. W.*, t. 36, p. 258, 1910.

Roussy, J., et Clunet.—Lésions du corps thyroïde dans la maladie de Basedow. *Rev. neurol.*, No. 13, 1913.

Sainton.—Pathogénie et traitement du goitre exophtalmique. 9e Congr. franc. de. méd. Paris 1907.

Sattler.—Die Basedow'sche Krankheit. 2. Aufl. Engelmann, Leipzig, 1909-10.

Schmidt, O.—Ueber den Morbus Basedow. *Mitt. Grenz. Med. u. Chir.*, Jena, t. 33, p. 512, 1921.

Schuler-Rosenberg.—Röntgentiefenbestrahlung der Schildddrüse bei Basedowkrankheit. *Med. Klin.*, t. 8, p. 1986, 1912.

Selenew.—Die Basedow'sche Krankheit in syphilitischen Familien. *Russ. Ztschr. f. Haut u. vener. Krankheiten*, t. 31, 1916.

Sergent, E.—Syndrome de Basedow et Tuberculose. *Paris méd.*, f. 30, 1920.

Sermensan, P.—Les sels de quinine dans le traitement de la maladie de Basedow. Thèse de Paris, 1912.

Söllung, H. A.—Untersuchungen über die Blutveränderungen bei Morbus Basedowii. *Nord. Med. Ark.*, Abt. I, t. 49, No. 7, p. 1, Stockholm, 1906.

Sonne, C.—Uebt das Antithyreoidin eine spezifische Wirkung gegenüber dem Morbus Basedowii aus? *Ztschr. f. klin. Med.*, t. 80, f. 3 u. 4, p. 229, 1914.

Souques.—Goitre exophtalmique et rheumatisme aigu. *Soc. méd. des. hôp. Par.*, 1910. *Sem. méd.*, p. 47, 1910.

Stern, R.—Differentialdiagnose und Verlauf des Morbus Basedowii und seiner unvollkommenen Formen. *Jahrb. f. Psych. u. Neurol.*, t. 29, f. 2 u. 3. Deuticke, Wien, 1909.

Sudeck, P.—Die Behandlung des Morbus Basedowii und der Struma maligna mit Röntgenstrahlen. *D. med. W.*, No. 40, t. 44, 1918.

— Ueber die chirurgische Behandlung des Morbus Basedow. *D. med. W.*, No. 47, p. 1224, 1921; u. *Berl. klin. W.*, t. 58, p. 1050, 1921.

Swan, J. M.—An analysis of fifty cases of dysthyroidism. *Internat. Clin. Phila.*, t. 1, p. 777, 1916.

Tschikste, A.—Ueber die Wirkung des im Schilddrüsenkolloid enthaltenen Nukleoproteides bei Morbus Basedowii. *D. med. W.*, No. 48, t. 37, 1911.

Undeutsch, W.—Experimentelle Gaswechseluntersuchungen bei Morbus Basedowii. Grundumsatz und Umsatz nach Aufnahme von animalischem und vegetabilischem Eiweiss. Diss., Leipzig, 1913.

Vincent, H.—Le Signe thyroïdien dans le rhumatisme aigu. *Bull. et. mém. de la Soc. méd. des hôp. Paris*, séance 8, VI, 1906, p. 599.

— Rapport de la maladie de Basedow avec le rhumatisme aigu. *Bull. soc. méd. hôp.*, 1907.

Waters, C. J.—Roentgenization of the thymus gland in Graves' disease. *J. A. M. A.*, Chgo., t. 66, p. 1392, 1915; id. Further observations on Roentgenization of thymus in Graves' disease. *Am. J. Roentgenol.*, N. Y., t. 4, p. 574, 1917.

Watson, L. F.—Quinine and urea injections in hyperthyroidism. *Jour of Am. Med. Ass.*, t. 65, No. 13, 1915.

— A method of controlling hyperthroidism. *Endocrin.*, t. 1, p. 178, 1917.

Wilson, L. B.—The pathology of the thyroid gland in exophthalmic goiter. *Am. Journ. of the Med. Sc.*, t. 146, No. 6, p. 781, 1913.

— A study of the pathology of the thyroid from cases of toxic non-exophthalmic goiter. *Am. Journ. of the Med. Sc.*, t. 147, p. 344, 1914.

— Relation of the pathology and the clinical symptoms of simple and exophthalmic goiter. *Jour. of the Am. Med. Ass.*, t. 62, p. 111, 1914.

— Veränderungen der sympathischen Ganglien bei Morbus Basedow. *Am. Jour. of the Med. Sc.*, Dec., 1916.

Zander, P.—Zur Histologie der Basedow Struma. *Mitt. Grenzg. Med. u. Chir.*, t. 25, p. 682, 1913.

(16) Inflammatory Conditions (see also 4).

Coissard, A.—L'infection éberthienne et la glande thyroïde. Thèse de Lyon, 1902.

Costa, C. A.—Tuberculose inflammatoire. Goitres d'origine tuberculeuse. Thèse de Lyon, 1905.

Coulon.—Thyroïdite syphilitique tertiare. *Ann. de Mal. vénér.*, t. 7, p. 200.

Gebele.—Ueber Schilddrüsentuberkulose. (3. Vers. d. Ver. bayr. Chir., München) 1913, *Beitr. z. klin. Chir.*, t. 88, p. 652, 1914.

Hedinger, E.—Zur Lehre der Schilddrüsentuberkulose. *D. Ztschr. f. Chir.*, t. 116, p. 125, 1912.

Jesionek.—Syphilis der Schilddrüse. *Handb. d. Geschl. Krankh.*, Wien. u. Leipzig, t. 3, 1 partie.

Küttner, H.—Struma syphilitica. *Beitr. z. klin. Chir.*, t. 22, f. 2, 1898.

Lenormand.—La tuberculose du corps thyroïde. *Rev. internat. de la Tuberc.*, t. 22, f. 2, mars, 1913.

Mygind, H.—Thyreoiditis simplex. *Jour. of Laryngol., Rhinol. and Otol.*, t. 9, No. 3, 1895.

Pauchet, V.—La pratique chirurgicale illustrée. Traitement des goitres. Doin, Paris, 1922.

Payr.—Ueber Kropffisteln. *Arch. f. klin. Chir.*, t. 71, 1903.

Pollag, S.—Ueber die Tuberculose der Schilddrüse. Diss., Zürich, 1913. Kabitzsch, Würzburg.

Poncet, A. et Leriche, R.—Syphilis du corps thyroïde. *Bull. et mém. de la soc. de chir.*, Paris, t. 38, f. 21, p. 783, 1912.

de Quervain, F.—Die akute nicht eiterige Thyreoditis und die Beteiligung der Schilddrüse an Infektionen überhaupt. *Mitt. Grenzg. Med. u. Chir.*, 2. Suppl. Bd., 1904

— Thyreoditis simplex und toxische Reaktion der Schilddrüse. *Mitt. Grenzg. d. Med. u. Chir.*, Jena, t. 15, f. 3 u. 4, 1905.

Reist, A.—Ueber chronische Thyreoiditis. *Frankf. Ztschr. f. Path.*, t. 28, f. 1-2, 1922.

Ruppanner, E.—Ueber tuberkulöse Strumen. Ein Beitrag zur Kenntnis der Schilddrüsentuberkulose. *Frankf. Ztschr. f. Path.*, t. 2, f. 4, 1909.

Shimodaira. — Experimentelle Untersuchungen über die Tuberkuloseinfektion der Schilddrüse. *D. Ztschr. f. Chir.*, t. 109, f. 5-6, p. 443, 1911.

Shunji Uemura. — Ueber Tuberkulose der Schilddrüse mit besonderer Berücksichtigung der Tuberkulose in Basedowschilddrüsen. *D. Ztschr. f. Chir.*, t. 140, f. 3 u. 4, p. 242.

Tavel, E.—Ueber die Aetiologie der Strumitis. Ein Beitrag zur Lehre von den haematogenen Infektionen. Sallmann, Basel, 1892.

Thompson, L.—Syphilis of the thyroid. *Am. Jour. Syphil.*, St. Louis, t. 1, p. 179, 1917.

Tixler, L. et Savy, P. — Tuberculose thyroïdienne folliculaire à forme de thyroïdite ligneuse. *Lyon chirurg.*, t. 9, p. 367, 1913.

Vogel, R. — Ein Fall von rezidivierender Strumitis mit Bildung eines Kropfsteines mit Durchbruch in den Sinus pyriformis und Oesophagus. *Ztbl. f. Chir.*, t. 39, p. 909, 1912.

Zoeller, C.—Contribution à l'étude de la syphilis de la glande thyroïde. Un cas de syphilis thyroïdienne à la période tertiaire. Thèse de Lyon, 1911.

(17) Malignant Goitre.

Bérard, L. et Dunet.—Le goitre métastatique existe-t-il? *Rev. de Chir.*, t. 59, p. 521, 1921.

Carrel, A.—Le goitre cancéreux. Baillière, Paris, 1901.

Felsenstein, E.—Zur Kenntnis der Struma postbranchialis (Getzowa). Diss., Heidelberg, 1915.

Gaylord and Marsh.—Carcinoma of the thyroid in the salmonoid fishes. State Inst. for the Study of Malignant Disease. Serial No. 99, Apr., 1914.

Hedinger, E. — Zur Lehre der Struma sarcomatosa. 1. Die Blutgefässendotheliome der Struma. *Frankf. Ztschr. f. Path.*, t. 3, f. 3, 1909.

Honsell.—Ueber gutartige metastasierende Strumen. *Beitr. z. klin. Chir.*, t. 24, f. 1. 1899.

Jäger, W.—Ueber die Parastruma. Diss., Zürich, 1913.

Kocher, Th.—Zur klinischen Beurteilung der bösartigen Geschwülste der Schilddrüse. *D. Ztschr. f. Chir.*, t. 91, f. 3 u. 4, 1907.

Kocher, Th., jun.—Ueber glykogenhaltige Strumen. Diss., Bern, 1899.

Langhans, Th.—Ueber die epithelialen Formen der malignen Struma. *Virch. Arch.*, t. 189, 1907.

— Epitheliale Struma maligna. *Virch. Arch.*, t. 206, f. 3, 1911.

Maisonneuve, J.—Du cancer ligneux de la glande thyroïde. Thèse de Lyon, 1902.

de Quervain, F.—Parastruma maligna aberrata. *D. Ztschr. f. Chir.*, t. 100, p. 334, 1909.

Rocher, H.—Des métastases du goitre. Thèse de Lyon, 1903.

Simmonds, M. — Ueber das Carcinoma sarcomatodes, insbesondere der Schilddrüse. *Ztschr. f. Krebsforschung*, t. 13, p. 307, 1913.

Simpson, B. T. — Pathology of goiter based upon specimens received at the State Institute for study of malignant disease, Buffalo. *New York Surg. Gyn. Obst.*, t. 28, p. 153, 1919.

Trotter, W.—Early clinical types of certain diseases. 3. Malignant disease of the thyroid. *Clin. Jour.*, t. 32, p. 399, 1908.

Wilson, L. B —Malignant tumors of the thyroid. *Ann. of Surg.*, Aug., 1921.

Wolff, G. — Wuchernde Struma, ein Beitrag zur Lehre von den epithelial bösartigen Geschwülsten der Schilddrüse. *Beitr. z. klin. Chir.*, t. 121, p. 56, 1920.

Zehbe, M.—Zur Frage der bösartigen Epithelgeschwülste der Schilddrüse. *Virch. Arch.*, t. 197, p. 240, 1909.

(18) Parathyroid Glands. Tetany. (See also 1, 3, 5, 12.)

Bérard, L. et Alamartine, H.—Les goitres d'origine parathyroïdienne. *Lyon chirurg.*, févr., 1909.

— Les glandules parathyroïdes et leurs tumeurs. *Lyon chirurg.*, mai, 1909.

Boothby, W. — The parathyroid glands. A review of the literature. *Endocrin.*, t. 5, f. 4, p. 403, 1921.

Delore, X. et Alamartine, H.—La tétanie parathyréoprive post-opératoire et la technique des thyroïdectomies principalement dans la maladie de Basedow. *Rev. de Chir.*, 30e année, f. 9.

v. Eiselsberg, A.—Zur Frage der dauernden Einheilung verpflanzter Schilddrüsen und Nebenschilddrüsen, zugleich ein Beitrag zur postoperativen Tetania parathyreopriva. *Arch. f. klin. Chir.*, t. 106, f. 1, 1915.

— Zur Behandlung der Tetania parathyreopriva. *Arch. f. klin. Chir.*, t. 118, 1921.

Farner, E. et Klinger, R.—Experimentelle Studien über Tetanie. II. Untersuchungen über die Tetanie der Katzen. *Mitt. Grenzg. u. Med. Chir.*, t. 32, f. 4. 1920.

Guleke. — Chirurgie der Nebenschilddrüsen (Epithelkörperchen). *Neue. d. Chir.*, t. 9, Enke, Stuttgart, 1913.

Hagenbach, E. — Experimentelle Studie über die Funktion der Schilddrüse und der Epithelkörperchen. *Mitt. Grenzg. Med. u. Chir.*, t. 18, f. 329, 1908.

Halsted, W. S. — Hypoparathyreosis, status parathyreoprivus and transplantation of the parathyroid glands. *Am. Jour. of the Med. Sc.*, t. 134, f. 1, July, 1907.

— The parathyroid glandules, their blood supply, and their preservation in operation upon the thyroid gland. *Ann. of Surg.*, t. 46, f. 4, Oct., 1907.

— Transplantation of the parathyroid glands. *Pathol. Soc. of Phila.*, New Series, t. 11, f. 4-5, 1908.

— Auto and isotransplantation in dogs, of the parathyroid glandules. *Journ. of Exper. Med.*, t. 11. f. 1, 1909.

Hammett, F. S.—Studies of the thyroid apparatus. V. Significance of the comparative mortality of parathyroidectomized wild Norway rats and excitable and non-excitable albino rats. *Endocrin.*, t. 6, f. 2, 1922.

Harvier, P.—Recherches sur la tétanie et les glandes parathyroïdes. Thèse de Paris, 1909.

Iselin, H.—Tetanie jugendlicher Ratten nach Parathyreoidektomie. Steigerung der tetanischen Reaktionsfähigkeit jugendlicher Ratten bei Nachkommen parathyreoidektomierter Ratten. *D. Ztschr. f. Chir.*, t. 93, p. 397, 1908.

— Wachstumshemmung infolge von Parathyreoidektomie bei Ratten. Ein Beitrag zur Kenntnis der Epithelkörperchenfunktion bei jungen Ratten. *D. Ztschr. f. Chir.*, t. 93, p. 494, 1908.

— Untersuchungen über die Folgen der operativen Entfernung der Epithelkörperchen bei jugendlichen Tieren und über die Leistungsfähigkeit der Epithelkörperchenverflanzung bei bereits ausgebildeter Tetanie. *Neurolog. Centralblatt*, Leipzig, 1911, XXX, 220-233.

Iversen, T.—Das Verhältnis der Glandulae parathyroideae bei Struma und Morbus Basedowii. *Arch. Internat. de Chir.*, p. 154, et 255, 1913.

Lenormant, Ch.—Goitres et parathyroïdes. *Presse méd.*, t. 21, p. 148, 1913.

McCallum and Voegtlin, C.—On the relation of tetany to the parathyroid glands and to calcium metabolism. *Jour. of Experim. Med.*, t. 11, f. 1, 1909.

McCallum, W. G.—The function of the parathyroid glands. *Journ. of the Am. Med. Ass.*, t. 59, p. 319, 1912.

Mayo, Ch. and McGrath, B. F.—Parathyroids and their surgical relation to goiter. *Ann. of Surg.*, t. 55, p. 185, 1912.

Nicolaysen, J.—Transplantation von Parathyreoidea bei postoperativer Tetanie. *Nord. Tijdsskrift for Terapi.*, t. 12, f. 2.

Pepere, Alb.—Le ghiandole paratirodiee. Torino, 1906.

Pineles, F.—Ueber die Funktion der Epithelkörperchen. Aus den Sitzungsberichten der kaiserl. Akad. d. Wissensch. Wien. *Mathem. naturw. Klasse*, t. 113, Abt. III, 1904.

de Quervain, F.—Ueber den Schutz der Epithelkörperchen. *Beitr. z. klin. Chir.*, t. 128, f. 1, 1923.

v. Saar.—Zur Technik der Epithelkörperchentransplantation. *Mitt. d. Vereins der Ae. in Steiermark*, No. 5, 1911.

(19) Polyglandular Disturbances.

Claude et Gougerot.—Sur l'insuffisance simultanée de plusieurs glandes, secrétion interne (insuffisance pluriglandulaire). *Soc. de Biol.*, 28. déc., 1907, p. 785. *Jour. de Physiol. et Patho. gén.*, 15 mai 1908, pp. 409 et 505. *Rev. de Méd.*, 1908.

Faure, Beaulieu, Villaret, M. et Sourdel, M.—Syndrome pluriglandulaire. Etude clinique et anatomique d'un type à prédominance thyroïdienne et pancréatique. *Presse méd.*, p. 691, 1911. *Arch. de Méd. expér.*, 1912.

Laignel-Lavastine.—La corrélation des glandes à sécrétion interne et leurs syndromes pluriglandulaires. *Gaz. Hóp.*, 1908.

Rol, L.—Contribution à l'étude des syndromes pluriglandulaires. Vigot, Paris, 1911.

Sourdel, M.—Contribution à l'étude anatomo-clinique des syndromes pluriglandulaires. Vigot, Paris, 1912.

INDEX.

John Bale, Sons and Danielsson, Ltd., 83-91, Great Titchfield Street, London, W. 1.